Angiotensinogen Genotype Affects Renal and Adrenal Responses to Angiotensin II in Essential Hypertension

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Background—Renovascular and adrenal responses to infused angiotensin II (Ang II) are intermediate phenotypes that may indirectly reflect tissue renin-angiotensin system activity. We examine herein angiotensinogen (AGT) as a candidate gene to help elucidate potential mechanisms for previously reported AGT linkage and association studies.

Methods and Results—Renal plasma flow and plasma aldosterone were measured before and after a 45-minute infusion of Ang II (3 ng · kg⁻¹ · min⁻¹) in 190 hypertensive patients who were on carefully controlled high- and low-salt diets. Reduced renal vascular (P = 0.0002) and adrenal (P = 0.002) responses to infused exogenous Ang II were associated with the AGT -6A allele. In multiple logistic regression, greater body mass index, lower basal renal plasma flow, and higher diastolic blood pressure together with AGT -6A genotype were associated with lower renal vascular response. In contrast, only male sex and AGT -6A genotype were associated with lower adrenal response. When both the renal and adrenal responses to Ang II were in the lowest tertile, the AGT -6AA genotype was present in 55.6%; in contrast, when both responses were in the upper 2 tertiles, the -6AA genotype was present in only 17.8% (P = 0.001).

Conclusions—A clear association between AGT genotype and response to infused Ang II was demonstrated for both the renal vasculature and the adrenal, consistent with the hypothesis that the AGT -6A genotype results in increased tissue expression of angiotensinogen and Ang II. (Circulation. 2002;105:1921-1927.)

Key Words: angiotensin • genetics • hypertension • kidney • renin

Activity of tissue renin-angiotensin-aldosterone systems (RAAS), particularly within the kidney, appears to have importance beyond what is apparent from measures of the circulating RAAS in relation to hypertension, diabetic and other nephropathy, congestive heart failure, and stroke. Results from our group provide clear evidence of increased renovascular tone supported by higher intrarenal angiotensin II (Ang II) that was not reflected by differences in plasma aldosterone, Ang II, or plasma renin activity. Increases in renal plasma flow varied widely between individuals after renin or ACE inhibition, but responses to the 2 drugs were highly correlated. A more indirect measure of intrarenal RAAS activity, change in renal plasma flow after infused Ang II, also correlated with the response to pharmacological RAAS inhibition. These findings are consistent with the hypothesis that high baseline intrarenal Ang II predicts both a greater increase in renal plasma flow in response to a RAAS-blocking drug and a blunted response (less of a decrease) to infused Ang II, presumably because of down-regulation of renovascular Ang II type I (AT₁) receptors in the face of high tissue Ang II. With its apparent strong familial component, renovascular response to exogenous Ang II infusion during a high-salt diet (when responses are normally maximal) is an attractive intermediate phenotype in the study of the genetics of human hypertension. For similar reasons, adrenal responses during a low-salt diet and atrial natriuretic peptide responses to infused Ang II have been suggested as intermediate phenotypes of considerable interest.

One of our major goals has been to identify genetic contributions to the expression of these intermediate phenotypes. Initial candidate genes of interest have been elements of the RAAS, particularly angiotensinogen (AGT), given the generally positive linkage and association of certain AGT polymorphisms with hypertension. Examination of genotypic association, however, is complicated by the recognition that additional factors blunt renal or adrenal responses to infused Ang II, including male sex, black race, diabetes, acute hyperglycemia, obesity, and insulin resistance. We considered these issues in a previous multivariate analysis and found an independent association with the AGT235T polymorphism and reduced renal vasoconstriction in response to infused Ang II. That study was limited by inclusion of few hypertensive subjects (most subjects were normotensive rel-
ative of hypertensives) and performance of infusions only during a high-salt diet.

The completion of Ang II infusions in an unprecedented number of hypertensive subjects studied during both carefully controlled high- and low-salt diets afforded us the opportunity to examine genotypic effects on adrenal and renal vascular responses to infused Ang II. Specific new questions include whether AGT genotype is associated with both renal and adrenal response to Ang II and whether influences from other factors differentially affect the genotypic associations.

Methods

Subjects and Protocol

Subjects in this report were studied by the international HyperPath (Hypertensive Pathotype) group. Included in this report are a total of 190 hypertensive patients with AGT genotypes who completed renal plasma flow studies on a high-salt diet and plasma aldosterone measurements on a low-salt diet. Patients were studied at the General Clinical Research Centers (GCRCs) of the Brigham and Women’s Hospital in Boston (n=101) or at the University of Utah Medical Center in Salt Lake City (n=89). Details of these protocols have been reported previously.

Hypertension diagnosis before age 60 years in the patient and ≥1 other sibling and current age 18 to 65 years were the major inclusion criteria. Relatively severe hypertension was required to be present in ≥1 sibling, defined as diastolic blood pressure ≥100 mm Hg off medication on ≥3 occasions, diastolic blood pressure ≥90 mm Hg while taking ≥1 antihypertensive medication on ≥3 occasions, or treatment with ≥2 antihypertensive medications. Less severely affected siblings had to have a diastolic blood pressure of ≥90 mm Hg off medication on ≥3 occasions or diastolic blood pressure of ≥80 mm Hg on 1 antihypertensive medication on ≥3 occasions. Exclusion criteria included substantial obesity (body mass index [BMI] >33 kg/m² for men, >31 kg/m² for women), diabetes mellitus (use of hypoglycemic drugs or serum glucose >126 mg/dL), renal insufficiency (serum creatinine >1.9 mg/dL), secondary forms of hypertension (based on history, physical examination, and multichannel serum chemistry screening), or any other significant medical problem. All subjects had a screening history and physical and laboratory examinations. Antihypertensive medications, if used, were withdrawn gradually such that all subjects were off medication for ≥2 weeks before the Ang II infusion studies. ACE inhibitors and angiotensin receptor blockers were discontinued 3 months before the study. The Institutional Review Board of each center approved the study, and all patients gave informed written consent before enrollment. There were 80 patients studied with no other sibling included, 98 patients from affected sibling pairs (49 sibships), and 12 studied from affected trios (4 sibships).

All subjects received high-salt (≥200 mmol sodium/d) and low-salt (10 mmol sodium/d) foods from the GCRC research kitchen to be consumed as outpatients. Subjects were admitted to the GCRC the night before studies. They received Ang II infusions at 3 ng·kg⁻¹·min⁻¹ on day 7 of high- and low-salt diets after overnight bed rest in the GCRC. Effective renal plasma flow (as p-aminoinhippuric acid clearance) was calculated from steady-state plasma p-aminoinhippuric acid concentrations at baseline and at the end of the Ang II infusion period as previously described. Effective renal plasma flow was normalized to a BSA of 1.73 m² by the equation BSA=0.048 × H⁰.⁶⁶ × 0.007184, where BSA is body surface area in square meters, W is weight in kilograms, and H is height in centimeters. Baseline blood pressure for this study refers to the mean of 3 consecutive readings (by Dinamap) separated by 5 minutes each measured at bed rest on the morning of the high- or low-salt studies in the GCRC obtained 30 minutes before initiation of the Ang II infusion.

Details of all laboratory assays and genotyping have been described previously. Low-renin patients were defined as having a plasma renin activity of <2.4 ng Ang I·mL⁻¹·h⁻¹ after 2 hours of upright posture when in balance on a 10 mmol/d sodium diet as in previous studies. The posture study was performed the day before hospital admission for the Ang II infusion during the low-salt diet. Plasma renin activity was measured in blood drawn at baseline just before the Ang II infusions on both high- and low-salt diet after patients had remained supine overnight in the GCRC.

Protocols were carefully standardized at each site through start-up and periodic visits between clinic sites, regular conference calls, and use of common written protocols and clinical data collection forms. All assays were performed at a central laboratory. Importantly, there were no consistent differences in key performance variables between the centers, including 24-hour urinary sodium excretions, renal plasma flow and aldosterone responses to infused Ang II, or blood pressure responses except for systolic blood pressure response on the low-salt diet (14.8±11.9 mm Hg, Boston; 19.8±13.1 mm Hg, Salt Lake City; P=0.008).

Statistical Analysis

All statistical analyses were performed with the SAS 8.0 statistical analysis package for the PC (SAS Institute Inc). The primary response variables were examined by comparing the lowest tertile with the upper 2 tertiles of change in response to Ang II infusion. This approach does not require any assumption about distribution of the outcome variable or the nature of its relationship to dependent variables. It allows us to focus on effects that lower response (the primary response of interest) without giving undue weight to factors that may be associated with large responses. Indeed, entirely different genetic or other correlates may be associated with increased as opposed to blunted response. Generalized estimating equations (PROC GENMOD using family number as the repeated variable) were used to correct for potential inflation of significance estimates caused by inclusion of family members (with potential nonindependence of observations). Previous studies suggest that this is a conservative method to correct for potential inflation of probability value and that for most situations, no special method of adjustment because of family dependencies is, in fact, necessary.

Results

The major phenotypes of interest in this study were renal vascular response to infused Ang II on a high-salt diet and adrenal response to infused Ang II on a low-salt diet. Reduced renal vascular response was defined as the lowest tertile of change for renal plasma flow on a high-salt diet (decrement <71 mL/min for this population). Reduced adrenal response was defined as the lowest tertile of change for plasma aldosterone (a <416 pmol/L [15 ng/dL] increment in plasma aldosterone). Clinical characteristics, renal plasma flow measurements, plasma aldosterone levels, and AGT genotypes are compared in those with reduced (lowest tertile) or normal (upper 2 tertiles) renal and adrenal responses in Table 1.

As shown in Table 1, AGT genotype was the only factor tested that consistently associated with both a reduced renal vasculature and reduced adrenal response to Ang II infusion. Older age, higher BMI, more severe hypertension, and lower baseline renal plasma flow associated with a smaller decrement of renal plasma flow on a high-salt diet. Other than AGT genotype, male sex, black race, and higher urinary sodium (borderline) were associated with a smaller adrenal response. There was no relationship between serum potassium concentrations during the high- or low-salt diet and either adrenal or renovascular responses to infused Ang II.

Association of the −6A allele with renal or adrenal unresponsiveness (and concordance for both) was tested further in several subgroups (Figure 1). In general, odds ratios
were in the direction expected and showed little heterogeneity. Too few blacks were tested to confirm AGT genotypic associations separately. The association of AGT genotype with reduced renal or adrenal responses after simultaneous control for other factors was confirmed in multiple logistic regression (Table 2). All of the factors listed in Table 2 were found to be independently associated with renal or adrenal response. As suggested by Table 1 and confirmed in the logistic regression analysis, the renal phenotype was influenced by more factors, the most significant being baseline renal plasma flow and BMI. Importantly, even after adjustment for other correlates, AGT genotype remained independently associated with both renal and adrenal response. AGT genotype was not significantly associated with any of the other factors listed in Table 1 except race. Multiple logistic regression stratified by race (to avoid colinearity issues between race and genotype) yielded results similar to those shown in Figure 1.

We also examined the association of AGT genotype with phenotype defined as concordant unresponsive, concordant responsive, or discordant as shown in Figure 2. The chi-squared value for AGT association was 18.6, with \( P = 0.0010 \) (2 degrees of freedom). When patients were defined as concordantly responsive or unresponsive by both criteria, AGT genotype remained highly and independently associated (Figure 1, Table 2).

The discordant patients were then examined separately to provide insights as to why some patients would have only renal or adrenal unresponsiveness. The same variables as in Table 1 were examined for differences between these 2 discordant groups. As shown in Table 3, patients with reduced renal but not adrenal responses had significantly
greater BMI and diastolic blood pressure, but lower baseline renal plasma flow. The other differences shown in Table 3 were expected, on the basis of the respective definitions of the phenotypes. When age, sex, BMI, baseline diastolic blood pressure, serum creatinine, creatinine clearance, baseline renal plasma flow, and AGT genotype were entered into multiple logistic regression with backward stepping, only BMI ($P=0.03$) and baseline renal plasma flow ($P=0.003$) remained in the model. In discriminant function analysis, BMI and baseline renal plasma flow correctly classified 76% of the discordant patients (Wilks $\lambda=0.671$, $P=0.0001$ for both BMI and baseline renal plasma flow). Thus, much of the difference in phenotypic expression could be explained by greater BMI and lower baseline renal plasma flow in those with a reduced renal vascular response to Ang II but a normal adrenal response.

**Discussion**

We have found a strong association between reduced renal vascular and adrenal responses to infused Ang II and the AGT $-6A$ genotype among a large group of hypertensive patients. This is the first report of such an association with assessment of both renal vascular (on high salt) and adrenal (on low salt) phenotypes in all subjects. The strong association of higher BMI and lower baseline renal plasma flow with blunted renal vascular response but not blunted adrenal response was responsible for much of the difference in phenotypic expression between individuals not explained by genotype and provided additional insights into the complexity of these phenotypes.

**Table 2. Results of Multiple Logistic Regression to Examine Independent Associations of AGT Genotype With Renal and Adrenal Responses to Infused Ang II (Lowest vs Upper 2 Tertiles)**

<table>
<thead>
<tr>
<th>Dependent Variable</th>
<th>Standardized Parameter Estimate</th>
<th>Odds Ratio (95% CI)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowest tertile of renal blood flow response (on high-salt diet)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>0.321</td>
<td>1.13 (1.02–1.25)</td>
<td>0.0164</td>
</tr>
<tr>
<td>Baseline diastolic BP</td>
<td>0.362</td>
<td>1.059 (1.016–1.093)</td>
<td>0.0061</td>
</tr>
<tr>
<td>Baseline RPF</td>
<td>-0.657</td>
<td>0.988 (0.983–0.993)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AGT genotype</td>
<td>0.292</td>
<td>1.98 (1.16–3.35)</td>
<td>0.0106</td>
</tr>
<tr>
<td>Lowest tertile of aldosterone response (on low-salt diet)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>0.260</td>
<td>2.59 (1.30–5.16)</td>
<td>0.0067</td>
</tr>
<tr>
<td>AGT genotype</td>
<td>0.237</td>
<td>1.74 (1.13–2.67)</td>
<td>0.0113</td>
</tr>
<tr>
<td>Concordant by both criteria*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline RPF</td>
<td>-0.613</td>
<td>0.988 (0.981–0.994)</td>
<td>0.0018</td>
</tr>
<tr>
<td>AGT genotype</td>
<td>0.521</td>
<td>3.31 (1.66–6.60)</td>
<td>0.0011</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; RPF, renal plasma flow. Backward stepping was used ($P=0.05$ to keep) with the following initial independent variables: age, sex, BMI, urinary sodium on low-salt diet, baseline diastolic BP on high-salt diet, baseline RPF on high-salt diet, and AGT $-6$ genotype. AGT $-6$ genotype was coded as 1, GG; 2, GA; and 3, AA. Generalized estimating equations using family number as a repeated variable were used to determine the $P$ value shown.

*Includes 27 concordant lowest-tertile responders and 90 concordant more responsive patients.

**Figure 1.** Stratified analysis of AGT $-6A$ allele association with lower tertile responses to infused Ang II. Error bars are 95% confidence intervals. Concordant group refers to those who were either responsive or unresponsive by both renal and adrenal measures ($n=27$ concordant unresponsive, 90 concordant responsive in total).

**Figure 2.** AGT genotype (%) in hypertensive patients categorized as concordant unresponsive to infused Ang II (by both renal vascular and adrenal criteria), concordant responsive, and discordant patients (either unresponsive by renal vascular criteria but not adrenal criteria or vice versa). Excess of AGT $-6A$ genotypes among unresponsive patients is readily apparent. Association was significant, with $\chi^2=18.6$ and $P=0.0010$. 
How might variants of the AGT gene promote blunted renal and adrenal responses to infused Ang II, and how might such changes be related to hypertension? For the renal response, we may hypothesize that an increase in intrarenal production of angiotensinogen associated with the AGT 6A variant would be expected to lead to increased tissue Ang II, 1 which, in expression of angiotensin associated with the AGT 6A variant in the promoter region of AGT, would be expected to lead to increased tissue Ang II, 1 although without any apparent functional significance itself, would be expected to lead to increased Ang II, 1 and adrenal responses to infused Ang II. These changes would be expected to lead to modest changes in renal hemodynamics and salt handling favoring hypertension. Data in support of this hypothesis are indirect and not without some negative findings or controversy. However, a recent meta-analysis of 69 association studies with 27,906 subjects concluded that the AGT 235TT genotype conferred 31% greater risk for hypertension (P=0.001), whereas those with the MT genotype had 11% greater risk (P=0.03). 12 The AGT 235T polymorphism, although without any apparent functional significance itself, is in almost complete linkage disequilibrium with the −6A variant in the promoter region of AGT, which, in expression studies, was found to result in an increase in function compared with the −6G allele (hence the use of this variant in the present study). 22 Potentially relevant are findings in transgenic animal models that suggest a dose-dependent effect of renal angiotensinogen production on hypertension development. 1,23 Several groups have reported other vascular disease associations with the AGT −6A (or 235T) variant, including increased left ventricular mass index, 24 brain infarctions, 25 and more rapid progression of immunoglobulin A nephropathy. 26,27 One group 28 reported more rapid progression to end-stage renal disease in diabetics with the 235T variant, and another did not. 29 These and the present findings would suggest that effects caused by common AGT gene variants are likely to be modest in absolute terms, even when statistically apparent.

Explaining the blunted adrenal response in those with the AGT −6A variant may be less straightforward. In rats and mice, increased exposure to Ang II, including low-salt diet, actually upregulated both AT1a, and AT1b receptors in the adrenal glomerulosa. 30 Other mammals have a single AT1 receptor gene, which appears to undergo ligand-mediated downregulation in the adrenal, similar to the response in vascular and other smooth muscle cells. 31 In nonrodent

### Table 3. Variables Examined in Persons Discordant for Response Status (Renal Unresponsive vs Renal Responsive)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Renal Unresponsive, Adrenal Responsive (n=37), Mean±SD</th>
<th>Renal Responsive, Adrenal Unresponsive (n=36), Mean±SD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>48.9±7.6</td>
<td>46.8±12.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Male, %</td>
<td>65</td>
<td>75</td>
<td>0.4</td>
</tr>
<tr>
<td>BMI</td>
<td>31.0±3.9</td>
<td>27.6±3.4</td>
<td>0.0002</td>
</tr>
<tr>
<td>Systolic BP, high salt, mm Hg</td>
<td>151.5±17.9</td>
<td>136.1±16.8</td>
<td>0.0004</td>
</tr>
<tr>
<td>Diastolic BP, high salt, mm Hg</td>
<td>90.9±12.0</td>
<td>83.0±11.4</td>
<td>0.0059</td>
</tr>
<tr>
<td>Systolic BP change, mm Hg</td>
<td>19.9±17.5</td>
<td>13.4±10.6</td>
<td>0.065</td>
</tr>
<tr>
<td>Diastolic BP change, mm Hg</td>
<td>8.7±9.1</td>
<td>6.9±7.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>1.05±0.37</td>
<td>1.01±0.35</td>
<td>0.6</td>
</tr>
<tr>
<td>RPF baseline, high salt, mL/min</td>
<td>418.9±76.0</td>
<td>522.1±92.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RPF response, high salt, mL/min</td>
<td>48.1±21.1</td>
<td>117.0±42.6</td>
<td>NR</td>
</tr>
<tr>
<td>RPF baseline, low salt, mL/min*</td>
<td>389.4±68.4</td>
<td>485.7±77.5</td>
<td>0.0002</td>
</tr>
<tr>
<td>RPF response, low salt, mL/min*</td>
<td>55.5±20.2</td>
<td>70.1±36.0</td>
<td>0.12</td>
</tr>
<tr>
<td>RPF change, low to high salt, mL/min*</td>
<td>3.4±20.7</td>
<td>35.3±54.8</td>
<td>0.016</td>
</tr>
<tr>
<td>Aldosterone baseline, high salt, ng/dL</td>
<td>6.80±5.09</td>
<td>4.98±3.94</td>
<td>0.092</td>
</tr>
<tr>
<td>Aldosterone response, high salt, ng/dL</td>
<td>11.87±6.87</td>
<td>6.87±6.66</td>
<td>0.0027</td>
</tr>
<tr>
<td>Aldosterone baseline, low salt, ng/dL</td>
<td>18.19±8.73</td>
<td>20.09±15.12</td>
<td>0.51</td>
</tr>
<tr>
<td>Aldosterone response, low salt, ng/dL</td>
<td>30.44±24.31</td>
<td>8.64±4.14</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Low renin, %</td>
<td>22</td>
<td>14</td>
<td>0.40</td>
</tr>
<tr>
<td>AGT −6 genotype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GG, %</td>
<td>19</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>GA, %</td>
<td>51</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>AA, %</td>
<td>30</td>
<td>33</td>
<td>0.4†</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; RPF, renal plasma flow; and NR, not relevant (for variables that were used to define tertiles). As in Table 1, “change” refers to change from low- to high-salt diet; “response” refers to response to Ang II infusion.

*Data available for only 40 patients.
†By $\chi^2$ 2×3 table.
mammals, virtually all of the increased sensitivity of adrenal aldosterone production to Ang II during a low-salt diet appears to be mediated by increased activity of enzymes in the synthetic pathway of aldosterone or other postreceptor effects, effects that are highly sensitive to salt balance.32 Therefore, blunted adrenal response to infused Ang II in subjects with AGT −6A may reflect increased local RAAS activity and downregulation of AT1 receptors and/or other factors that increase salt balance (including renal effects).

The major effects of BMI and baseline renal plasma flow are consistent with our previous observations.17 Recently, renal norepinephrine spillover was shown to be increased in both normotensive and hypertensive obese subjects.33 Others have also reported interactions between body fat, blood pressure, and AGT genotype.34 The lack of sympathetic nervous system effects on adrenal aldosterone production may explain the absence of an association between BMI and adrenal response. Although multiple factors affected renal vascular response, AGT genotype and sex were associated primarily with adrenal response in our study. The effect of race could not be statistically separated from the genotypic effect for the adrenal response. We therefore cannot exclude an additional, independent effect of black race on adrenal response. The powerful effect of sex on adrenal response has been reported previously.13

In previous studies in our group, among 18 mostly male hypertensives, age 18 to 45 years, renal (on high salt) and adrenal (on low salt) responses to infused Ang II appeared to highly correlated.35 In the present series, just 42.2% of patients in the lower tertile of renal plasma flow decrement also had lower-tertile aldosterone increment (odds ratio 1.82, \( P=0.059 \)). The wider ranges in age, blood pressure, baseline renal vascular blood flow, and BMI and inclusion of 2 racial groups in the present study may explain the blurring of expected correlation between renal and adrenal responses to infused Ang II, as illustrated in Figure 3. Examining the correlation in the subgroup with lower BMI (42 patients had BMI <25), 15 subjects had lower-tertile adrenal responses, but just 5 had lower-tertile renal responses to infused Ang II; 4 of these 5 also had lower-tertile adrenal responses (odds ratio 9.5, \( P=0.028 \)). Thus, higher BMI appeared to have been a major factor obscuring the expected correlation between renal and adrenal responses.

In conclusion, we have observed a significant association between AGT genotype and response to infused Ang II in hypertensive subjects on both high- and low-salt diets. The renal findings are consistent with the hypothesis that the AGT −6A genotype results in a modest increase in local Ang II production, leading to downregulation of AT1 receptors and relative insensitivity to infused, exogenous Ang II. The basis for the adrenal findings may be more complex. Our findings indicate that phenotypic expression of genetic variation can be influenced by factors such as race, sex, obesity, and severity of hypertension but not necessarily equivalently in all target tissues.

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