Vascular Angiotensin II Receptors in SHR

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SUMMARY We investigated the density (B, max) of angiotensin II (ANG II) receptors in the mesenteric vascular bed of spontaneously hypertensive rats (SHR) and age-matched Wistar-Kyoto (WKY) control rats. In 12-week-old SHR, the B, max and the dissociation constant (K_d) of ANG II binding sites were not different from those of WKY rats in the sodium replete state or after sodium depletion. In prehypertensive (4- and 6-week-old) SHR, the B, max of the vascular ANG II receptors was significantly higher (p < 0.05) than in age-matched WKY rats. This result could not be attributed entirely to differences in the circulating renin-angiotensin-aldosterone system in 4-week-old rats. In 6-week-old WKY rats, the plasma renin activity was significantly higher (p < 0.05), which may account in part for the higher density of ANG II binding sites in SHR. There was an age-related decrease in the number of ANG II receptors in SHR. The increased density of vascular ANG II receptors in young SHR may play a role in the development of high blood pressure in this model of spontaneous hypertension. The higher number of ANG II binding sites in young SHR is not selective for ANG II receptors, since an increased density of α1-adrenergic receptors was also found in the mesenteric arteries of 4-week-old SHR. (Hypertension 6: 682-688, 1984)

KEY WORDS • genetic hypertension • vascular reactivity • mesenteric artery • renin-angiotensin-aldosterone system

THE mechanisms involved in the elevation of blood pressure in the spontaneously hypertensive rat (SHR) of the Okamoto strain are as yet uncertain. An increase in the peripheral resistance appears to play a primary role. This increase in vascular resistance has been attributed to structural alterations in blood vessels of SHR (increased wall/lumen ratio), to enhanced vascular reactivity, or to increased activity of the sympathetic nervous system. The greater reactivity of blood vessels from SHR may be a genetic defect or the result of vascular alterations produced by elevated blood pressure. Increased vascular response to angiotensin II (ANG II), norepinephrine, serotonin, and vasopressin has been demonstrated early in the life of SHR. The abnormal response of blood vessels from SHR may be nonspecific, the result of a change in the availability of calcium to trigger contraction, of other ionic transport phenomena, or changes at the level of contractile proteins. However, the differences between SHR and WKY are not identical for all vasoactive substances, which suggests that postreceptor events may not be the only mechanism involved in the increased responsiveness observed.

Plasma renin activity (PRA) is normal in SHR, although there are reports of increased renin. Treatment with angiotensin I (ANG I)-converting-enzyme inhibitors may lower the blood pressure of SHR, which indicates that the renin system may play a role in blood pressure elevation even in this model of normal renin hypertension. Together with the evidence suggesting increased response to ANG II, these results have prompted us to examine the possibility of a specific increase in the density of ANG II receptors in the vascular smooth muscle of SHR.

One way to distinguish between the contribution of receptor and that of postreceptor mechanisms to increased vascular reactivity is to perform radioligand-binding studies to determine the density and affinity of vascular receptors. We have therefore examined the binding of 125I-ANG II to a particulate fraction obtained from a resistance vascular bed, the mesenteric blood vessels, from SHR and age-matched Wisk...
Materials and Methods

Animal Experiments

Male SHR and age-matched WKY control rats were obtained from Taconic Farms (Germantown, New York), and age-matched SD rats were obtained from Charles River, Canada (St-Constant, Quebec). The SD rats were investigated simultaneously as internal controls of the experiments and were not intended for comparison with SHR or WKY rats. All rats were maintained on a normal sodium diet (Purina, St. Louis, Missouri) and had free access to tap water unless otherwise stated. Blood pressure was measured in conscious 12-week-old rats by the tail-cuff method. Blood pressure was measured in 4-week-old SHR and WKY intraarterially under ether anesthesia. A PE-50 polyethylene catheter filled with 0.9% NaCl containing 100 U of heparin per ml was introduced into the left carotid artery. Blood pressure was monitored via a Statham P23ID transducer (Gould, Oxnard, California) and recorded on a Grass Model 7 polygraph (Grass Instruments, Quincy, Massachusetts). Heart rate was measured with a cardiotachograph from the arterial blood pressure waveform. Catheterized rats were not used for binding studies.

Sodium depletion was achieved by feeding the rats a sodium-deficient diet (Hartroft Test Diet, ICN Nutritional Biochemicals, Cleveland, Ohio; sodium content less than 5 mmol/kg diet) for 10 days and by injecting furosemide 10 mg/kg intraperitoneally on the first 2 days. These rats drank deionized water. Sodium replete and -depleted SHR, WKY, and SD rats were studied simultaneously.

Rats were killed by decapitation at between 8:00 and 9:00. During the next 5 seconds, blood was collected from all of the rats from the trunk into chilled vacuutainer tubes containing ethylenediaminetetraacetic acid (EDTA). Proteins were measured by the Coomassie blue method.

Preparation of Mesenteric Artery Particulate Fraction

A modification of the technique of Wei et al. was employed, similar to that used by Gunther et al., as we have previously described. Briefly, rats were sacrificed by decapitation. Three to six rats per group were used in each individual experiment to obtain enough material for the saturation binding curves. To examine the 4- and 6-week-old rats, eight rats were killed per group per experiment. The mesenteric artery was sectioned from the aorta at its origin, and the mesentery was dissected from the mesenteric border of the intestine and immersed in cold phosphate-buffered saline. Adipose tissue was removed by blunt dissection, and the cleaned arteries were transferred to a 0.25 M sucrose solution. Arteries were resuspended in new 0.25 M sucrose solution, finely minced with scissors, then homogenized twice for 10 seconds each in a Polytron (Kinematica, Luzern, Switzerland, setting 8). The homogenate was centrifuged at 1500 g for 10 minutes at 4°C, and the supernatant was decanted and recentrifuged. The final supernatant was filtered through cheesecloth, then centrifuged at 104,000 g for 30 minutes. Electron microscopy of the pellet showed a preparation that contained vesicles exclusively. The pellet was resuspended in a 0.05 M Tris-HCl buffer, pH 7.4, containing 120 mM NaCl, 2 mM MgCl₂, and 1 mM EDTA. Proteins were measured by the Coomassie blue method. After this, bovine serum albumin was added at a concentration of 0.2%, and the membranes were diluted to a protein concentration of 1 mg/ml in the Tris-HCl buffer containing 0.2% albumin ("assay buffer").

¹²⁵I-Angiotensin-II-Binding Assay

The binding assay was performed at 22°C for 45 minutes, since a plateau is achieved after 30 minutes. Saturation binding curves were constructed by incubating 100 µg of receptor protein per tube with increasing concentrations of ¹²⁵I-ANG II (0.06–2 nM). Nonspecific binding was determined by incubation in the presence of 1 µM unlabeled ANG II for each point of the saturation binding curves. All assays were performed in duplicate. Separation of bound and free radioactivities was achieved by rapid filtration through Whatman GF/C filters soaked with 0.5 ml of assay buffer. The filters were washed twice with 3 ml of 0.9% NaCl, then allowed to dry, and counted in a Rackgamma LKB counter (Wallac, Turku, Finland) with 85% efficiency. Total binding to membranes was approximately 5% of total radioactivity in the presence of 0.1 nM ¹²⁵I-ANG II. Specific binding (total binding minus nonspecific binding, in the presence of 1 µM unlabeled ANG II) was 90% to 95% of the total binding. Binding to filters in the absence of membranes was 0.1% to 0.2% of the total radioactivity. We have already demonstrated the specificity of the binding sites for ANG II detected with this technique.

³H-Prazosin-Binding Assay

This assay was performed identically to the ¹²⁵I-ANG II-binding assay except that the ligand used was...


Biochemical Determinations

The PRA was measured by RIA of the ANG I generated during a 2-hour incubation at 37°C, as previously described. Within-assay coefficient of variation for 20 samples with low PRA (1.7 ± 0.1 ng ANG I. ml⁻¹.hr⁻¹) was 2.4%. Interassay coefficient of variation was 13.5% in 10 successive determinations. Plasma ANG II was measured by RIA, as described previously. Within-assay coefficient of variation for low ANG II concentrations was 8.5%, and the between-assay variation was 5.5%. Recovery of added ANG II (100 pg/ml) was 82.2% ± 4.9% (n = 10). Cross-reactivity of the anti-ANG II antibody with ANG I was 0.27%, and with ANG III, 100%. Plasma aldosterone was measured by RIA. Within-assay coefficient of variation was 1.5% and interassay variation was 7.3%.

Analysis of Data

Results are means ± se. The B_max and the apparent K_d were calculated from Scatchard plots. The correlation coefficient for all reported Scatchard plots was between 0.93 and 1.00. Statistical analysis was performed by one-way or two-way analysis of variance (ANOVA) followed by Student’s t test. Paired comparisons were done for binding data from groups examined on the same day. Differences were considered statistically significant when p < 0.05.

Results

In SHR at 12 weeks of age, the B_max of the binding sites for I²S-I-ANGII in the mesenteric vascular bed was not different from that of age-matched WKY rats (Figure 1 and Table 1). The apparent K_d was also similar. PRA was slightly lower in SHR than in WKY (Table 2). After sodium depletion, PRA and plasma aldosterone concentration increased significantly in all groups, without change in blood pressure. The binding capacity for ANG II was at least 10% lower in five of six experiments in SHR, and in four of six experiments in WKY and in SD rats (Figure 1 and Table 1). Two-way ANOVA showed that the binding capacity decreased significantly after sodium depletion. There was, however, no significant difference in the change in the B_max between the hypertensive and normotensive strains after sodium depletion. The increase in PRA or plasma aldosterone after sodium depletion was not significantly different in SHR or WKY (Table 2).

![Figure 1](http://hyper.ahajournals.org/)

**Figure 1.** Scatchard analysis of data from saturating binding isotherms (0.06–2 nM I²S-I-angiotensin II) of a representative experiment performed simultaneously on receptor protein obtained from the mesenteric arterial bed of 12-week-old spontaneously hypertensive rats (SHR), Wistar-Kyoto (WKY), and Sprague-Dawley (SD) rats on a normal sodium balance and after sodium depletion. Filtration for separation ofBound from bound radioactivity was performed within a 90-minute period from the first to the last group. The order in which the different groups were assayed in each individual experiment was changed at random.
TABLE 2. Plasma Renin Activity, Plasma Aldosterone Concentration, and Systolic Blood Pressure of 12-Week-Old Spontaneously-Hypertensive Rats (SHR), Wistar-Kyoto (WKY), and Sprague-Dawley (SD) Rats

<table>
<thead>
<tr>
<th>Rat strain</th>
<th>PRA (ng ANG I•ml⁻¹•hr⁻¹)</th>
<th>Plasma aldosterone (ng/dl)</th>
<th>Blood pressure (mm Hg)</th>
<th>PRA (ng ANG I•ml⁻¹•hr⁻¹)</th>
<th>Plasma aldosterone (ng/dl)</th>
<th>Blood pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHR</td>
<td>1.3 ± 0.1 *</td>
<td>15.3 ± 2.9</td>
<td>170 ± 3†</td>
<td>8.3 ± 1.5†</td>
<td>181.7 ± 26.4†</td>
<td>170 ± 3†</td>
</tr>
<tr>
<td>WKY</td>
<td>2.1 ± 0.5</td>
<td>20.2 ± 3.1</td>
<td>108 ± 3 (27)</td>
<td>12.4 ± 2.4</td>
<td>185.7 ± 23.8†</td>
<td>117 ± 2 (24)</td>
</tr>
<tr>
<td>SD</td>
<td>1.8 ± 0.3</td>
<td>11.1 ± 2.1</td>
<td>117 ± 5 (24)</td>
<td>8.9 ± 1.7†</td>
<td>181.6 ± 33.2†</td>
<td>112 ± 4 (26)</td>
</tr>
</tbody>
</table>

Results are means ± SEM. The number of rats is in parentheses. *p < 0.05, as compared with WKY. †p < 0.01, as compared with WKY. ‡p < 0.01, as compared with Na replete rats.

We also examined young SHR and WKY rats at 4 and 6 weeks in the sodium-replete state. This is the prehypertensive period for SHR, whose blood pressure rises in the 7th to 8th week of life. However, already at 4 weeks the mean blood pressure of SHR was 115 ± 4 mm Hg (n = 5), significantly higher than that of WKY (99 ± 2 mm Hg, p < 0.05). The heart rate of SHR was 336 ± 10 bpm, significantly lower (p < 0.05) than the heart rate of the 4-week-old WKY (420 ± 12 bpm). In these young rats, the B_max for ANG II was higher in the mesenteric vascular bed of SHR than in WKY, both at 4 and 6 weeks of age (Figures 2 and 3 and Table 3). The PRA was not significantly different in both strains at 4 weeks, but was slightly higher (p < 0.05) in WKY rats at 6 weeks. Plasma aldosterone concentration was similar in young 4- and 6-week-old SHR and WKY rats.

When the binding data of 12-week-old SHR, WKY, and SD rats (from Table 1), as well as those of 4- and 6-week-old WKY rats (from Table 3), were plotted against the logarithm of PRA, a significant inverse correlation was found (r = 0.66, p < 0.05) (Figure 4). The binding data from 4- and 6-week-old SHR (open circles in Figure 4) were evidently not in an inverse correlation with the logarithm of PRA. If these data are indeed included, the correlation is no longer significant (r = -0.49).

Although the PRA was similar in 4-week-old SHR and WKY rats, the higher density of binding sites might be caused by a lower concentration of circulating ANG II in young SHR than in age-matched WKY. Furthermore, it was important to determine whether sites for other ligands were increased in young SHR. Table 4 shows data obtained from examination of addi-

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**Figure 2.** Scatchard analysis of data from saturation binding isotherms (0.06-2 nM [125I]-angiotensin II) of a representative experiment performed simultaneously on receptor protein obtained from the mesenteric arterial bed of 4-week-old SHR and WKY on a normal sodium diet.

**Figure 3.** Scatchard analysis of data from saturation binding isotherms (0.06-2 nM [125I]-angiotensin II) of a representative experiment performed simultaneously on receptor protein obtained from the mesenteric arterial bed of 6-week-old SHR and WKY on a normal sodium diet.
TABLE 3. Angiotensin II Receptors in the Mesenteric Artery of Prehypertensive Spontaneously Hypertensive Rats (SHR) and of Wistar-Kyoto (WKY) Rats

<table>
<thead>
<tr>
<th>Rat group</th>
<th>Bmax (fmol/mg)</th>
<th>Kd (nM)</th>
<th>PRA (ng ANG I·ml⁻¹·hr⁻¹)</th>
<th>Plasma aldosterone (ng/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-week-old SHR (24)</td>
<td>180 ± 9*†</td>
<td>1.0 ± 0.1</td>
<td>2.1 ± 0.2</td>
<td>13.8 ± 7.7</td>
</tr>
<tr>
<td>4-week-old WKY (24)</td>
<td>100 ± 25</td>
<td>1.0 ± 0.3</td>
<td>2.7 ± 0.3</td>
<td>13.5 ± 4.0</td>
</tr>
<tr>
<td>6-week-old SHR (25)</td>
<td>139 ± 13*†</td>
<td>1.0 ± 0.1</td>
<td>2.1 ± 0.2*</td>
<td>14.4 ± 3.1</td>
</tr>
<tr>
<td>6-week-old WKY (25)</td>
<td>84 ± 18</td>
<td>1.3 ± 0.1</td>
<td>3.6 ± 0.4</td>
<td>11.9 ± 1.9</td>
</tr>
</tbody>
</table>

Results are means ± SEM. Three to five experiments were performed. Number of rats is in parentheses.

*p < 0.05, as compared with WKY.

†p < 0.05, compared with 6-week-old rats.

TABLE 4. ¹²⁵I-Angiotensin II (ANG II) and ³H-Prazosin Binding to Mesenteric Artery Membranes, Plasma Renin Activity (PRA), and Plasma ANG II Concentration in 4-Week-Old Spontaneously Hypertensive Rats (SHR) and Wistar-Kyoto (WKY) Rats

<table>
<thead>
<tr>
<th>¹²⁵I-ANG II bound (fmol/mg protein)</th>
<th>³H-Prazosin bound (fmol/mg protein)</th>
<th>PRA (ng ANG I·ml⁻¹·hr⁻¹)</th>
<th>Plasma ANG II (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHR 62 ± 6*</td>
<td>24 ± 4*</td>
<td>1.9 ± 0.3</td>
<td>30 ± 13</td>
</tr>
<tr>
<td>WKY 27 ± 7</td>
<td>14 ± 3</td>
<td>2.1 ± 0.3</td>
<td>12 ± 5</td>
</tr>
</tbody>
</table>

Values are means ± SEM. Four to six experiments were performed. ¹²⁵I-ANG II bound = specifically bound in the presence of 0.3 nM ¹²⁵I-ANG II. ³H-prazosin bound = specifically bound in the presence of 1 nM ³H-prazosin.

FIGURE 4. Correlation of the density of angiotensin II binding sites in the mesenteric artery of SHR, WKY, and SD rats from Tables I and 3 and plasma renin activity (PRA) values from the same groups. The regression line includes 12-week-old SHR, WKY, and SD rats as well as 4- and 6-week-old WKY (closed circles), but not 4- and 6-week-old SHR (open circles).
sodium depletion did not demonstrate a significantly different behaviour of receptor regulation in the hypertensive rats.

SHR have a reduced number of ANG II receptors in the adrenal glomerulosa. We would have expected a reduced aldosterone response to sodium depletion since the renin-angiotensin system is known to be the main mediator of the adrenal response to a negative sodium balance. Plasma aldosterone was, however, similar in the three strains of rats after sodium depletion. These results are in contrast to those of Williams et al. who demonstrated increased PRA and ANG II concentration but reduced plasma aldosterone in 12-week-old female SHR in response to sodium depletion. The difference may be due to the sex of the animals examined or to heterogeneity in SHR from different breeders.

Treatment of 4-week-old SHR with captopril, an ANG I-converting enzyme inhibitor, prevents the development of hypertension. These young rats already have at 4 weeks a higher mean blood pressure than 4-week-old WKY. In this context, it is of interest that we found the density of the binding sites for ANG II to be increased in young SHR. These differences cannot be adequately explained in the 4-week-old rats by the main regulatory mechanism for ANG II vascular receptors, that is, plasma renin (Figure 4) via ANG II, or by differences in plasma aldosterone (which we have found may modulate the regulatory effects of ANG II on its vascular receptors).

In 6-week-old SHR, PRA was significantly lower than in WKY. The physiopathological significance of this difference is obscure. Although our PRA assay is sensitive and precise at low PRA (see Methods), normal values in our laboratory vary between 1.5 and 4 ng ANG 1·ml⁻¹·hr⁻¹ for normal rats. In successive series of WKY we have found the PRA to be similar to that of SHR (Table 4 and unpublished observations). Furthermore, larger differences in PRA appear to explain smaller changes in Bmax in other normotensive rats. It is therefore difficult to attribute the differences in receptor density in 6-week-old SHR and WKY entirely to the differences found in PRA (Figure 4).

Since differences in ANG II concentration could hypothetically occur in the absence of differences in PRA, we reexamined the binding of ANG II to membranes from 4-week-old SHR (Table 4). We found that the binding capacity was increased, as was found in our initial experiments in prehypertensive SHR. Plasma renin and circulating levels of ANG II were similar in 4-week-old SHR and WKY and could not therefore explain our results. Although the ANG II assay is reasonably precise, values within the normal range have a low correlation with prevailing PRA. There is a higher correlation with plasma ANG II concentration when a wide range of PRA is examined. We do not therefore think that the absence of a difference in measured values of plasma ANG II is a definitive proof that, indeed, circulating ANG II levels are identical in young SHR and WKY. However, the tendency was for SHR to have higher values. For ANG II levels to explain the increased density of the ANG II of the binding sites in SHR, the opposite would have been expected. We have no evidence of differences in the ANG II concentration at the level of the receptor, which might explain our findings in these prehypertensive SHR.

Berecek et al. have demonstrated in SHR at this early age an increased renal blood vessel reactivity to norepinephrine and ANG II. Interestingly, in 4-week-old SHR, the density of α1-adrenergic binding sites is also increased (Table 4). This suggests that the differences in the number of binding sites is not unique for ANG II in young SHR. A more generalized abnormality of the smooth muscle cell membrane of SHR may be implicated.

A reduced lumen and enlarged media have been demonstrated histologically by Mulvany et al. at 6 weeks of age in the mesenteric arterioles of SHR. In the renal afferent arteriole of 6-week-old SHR, on the other hand, Gattone et al. showed a smaller lumen than in WKY, but the wall thickness/radius ratio was similar in both strains. This suggested increased vascular constriction or hypoplasic vessels in SHR rather than increased wall thickness. Thus, intrinsic smooth muscle abnormalities may be the basis for the increased density of ANG II and α1-adrenergic receptors in mesenteric blood vessels of prehypertensive SHR.

The finding of an increased number of ANG II and α1-adrenergic receptors in the vasculature of SHR before the development of hypertension agrees with the increased reactivity to ANG II and norepinephrine. In the established phase of hypertension, the enhanced responsiveness to ANG II is of less magnitude than to norepinephrine. We have found that at 12 weeks the Bmax of binding sites for ANG II is normalized. However, we have found an increased density of α1-adrenergic receptors persisting into this phase in SHR (E. Schiffrin, unpublished observations). It may be speculated that early in the life of SHR, an increased density of the adrenergic and ANG II receptors (genetically determined?) is involved in the enhanced vascular responsiveness. This does not necessarily exclude a role for postreceptor events. During the phase of established hypertension, probably in part due to structural abnormalities, increased reactivity persists, although ANG II-receptor density is normalized. However, at this date, vascular hyperresponsiveness to norepinephrine is more marked than for ANG II because an increased number of α1-adrenergic receptors is still present.

In conclusion, we find that vascular ANG II receptors in a resistance vessel are increased in young prehypertensive SHR (4 and 6 weeks old). This result can be explained only in part by differences in the circulating renin-angiotensin-aldosterone system. We also find that α1-adrenergic binding sites are higher in 4-week-old SHR than in age-matched WKY. In 12-week-old SHR, which are markedly hypertensive, the number of the binding sites for ANG II in the mesenteric blood vessels is not different in SHR and WKY in the sodi-
um-replete state. There is an age-related decrease in the binding capacity for ANG II in resistance vessels in SHR. We conclude that the increased density of the vascular ANG II receptors in young SHR may be part of a generalized vascular smooth muscle abnormality that includes increased α₁-adrenergic receptors and that this abnormality may play a role in the development of high blood pressure in this model of spontaneous hypertension.

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