Renal Alpha-Adrenergic Receptor Abnormality in the Spontaneously Hypertensive Rat

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SUMMARY Activation of renal α-adrenergic receptors induces vasoconstriction, proximal tubular reabsorption of sodium, and inhibition of renin release. Excesses of these effects are present in varying degrees in animal models of, and in patients with, "essential" hypertension. Since essential hypertension is genetically determined, we sought abnormalities of renal α-adrenergic receptors in the Oka-moto-Aoki strain of spontaneously hypertensive rats (sr-SHR) and their stroke-prone variant (sp-SHR). Total α-adrenergic receptor concentrations were determined by Scatchard analysis of [3H]dihydroergocryptine binding to a renal membrane fraction and were found to be increased (p < 0.02) in male sr-SHR at 4, 16, and 32 weeks of age and in female sr-SHR at 16 weeks of age as compared to age- and sex-matched Wistar-Kyoto controls. They were also increased in 9-week-old sp-SHR renal membranes (p < 0.005). Further studies revealed that this increase in renal α-adrenergic receptors was due entirely to an increase in α2-receptors as measured by [3H]yohimbine binding rather than to an increase in α1-receptors as quantitated by [3H]prazosin binding. No difference in binding affinities of the various radioligands could be demonstrated between any of the hypertensive and normotensive groups of rats. Plasma norepinephrine levels were elevated (p < 0.01) in the 4-, 9- and 16-week-old SHR, but not in the 32-week-old hypertensive rats. Thus, high renal α2-adrenergic receptor number is coupled with a significant increase in plasma norepinephrine concentrations during the development of hypertension in SHR. By mediating an enhanced receptor-coupled response, such as increased proximal tubular sodium reabsorption, this abnormality of renal α-adrenergic receptors may contribute to some or all of the pathophysiologic derangements leading to hypertension in SHR. (Hypertension 4: 881-887, 1982)

KEY WORDS • renal • α-receptor • SHR • hypertension • radioligand

THE kidney contributes fundamentally to genetically determined hypertension in rats. For example, transplantation of normotensive rat kidneys to hypertensive rats prevents or reverses their hypertension.1,4 Alternatively, transplantation of hypertensive kidneys to normotensive rats induces high blood pressure. Two renal functional abnormalities are common to genetically hypertensive rats and, interestingly, to patients with essential hypertension. These abnormalities are increased renal tubular reabsorption of sodium at any given perfusion pressure,4,5 and increased renal vascular resistance and increased vasoconstrictor responsiveness to norepinephrine and angiotensin.6-8 As renal vasoconstriction in rat kidneys is mediated by α-receptors,10 an increase in affinity or number of this receptor type could mediate enhanced renal vascular resistance as a result of increased responsiveness to norepinephrine. Similar enhancement of angiotensin vasoconstriction is observed however, in spontaneously hypertensive rat (SHR) kidneys,7 indicating a lack of receptor specificity for this phenomenon. Tobian et al.11 and Steele and Underwood12 demonstrated that, at equivalent perfusion pressure, kidneys from SHR manifested a degree of natriuresis similar to that of kidneys from normotensive animals. In the latter study, however, the addition of norepinephrine to the perfusate markedly attenuated the natriuretic response of the hypertensive kidneys. This differential effect is consistent with increased α-recep-
tor functioning, because of either higher affinity or receptor number. Since α₁-receptors may be concentrated on proximal tubules,\(^\text{12}\) the site at which norepinephrine mediates enhanced renal reabsorption of sodium,\(^\text{14, 15}\) we looked for a biochemical abnormality of renal α₁-adrenergic receptors in SHR of the Okamoto-Aoki strain (sr-SHR)\(^\text{16}\) and their stroke-prone variant (sp-SHR).\(^\text{17}\)

**Methods**

We used male (4, 16, and 32 weeks old) and female (12 weeks old) sr-SHR (Taconic Farms, Germantown, New York), and male (9 weeks old) sp-SHR (NIH, Bethesda, Maryland) of the Okamoto-Aoki strain, and age- and sex-matched normotensive Wistar-Kyoto rats (NCR) (Taconic Farms, Germantown, New York, and NIH, Bethesda, Maryland) of the same stock from which the SHR were derived. The rats were housed in groups of five to 10 per cage and exposed to light by an automated system from 0600 to 1800. The animals were maintained on a standard Purina rat chow diet containing 150 mEq Na+/kg and 220 mEq K+/kg and tap water ad libitum. The rats were weighed 2 to 3 days below the origin of the renal arteries.\(^\text{19}\) After surgery, the abdominal aorta so that the tip of the catheter was placed in the abdominal aorta so that the tip of the catheter was below the origin of the renal arteries.\(^\text{19}\) After surgery, the animals were housed in individual cages. On the day of the study, the rats were placed in a quiet room and allowed to move freely in their own cages. The aortic catheter was used to record the arterial blood pressure and heart rate via a Narco RP-1500 pressure transducer (Narco Scientific Industries, Inc., Fort Washington, Pennsylvania) and a Grass Model-7 polygraph (Grass Instrument Company, Quincy, Massachusetts), and also for collection of a blood sample for determination of plasma norepinephrine concentration.

After a 60-minute stabilization period, mean arterial blood pressure and heart rate were recorded and a blood sample (1.0 ml) collected into a syringe containing ethylene-glycol-bis (β-amino-ethyl ether) N, N', tetra acetic acid (EGTA) (10 μl 0.24 M/0.2 M glutathione).\(^\text{20}\) In all cases blood was sampled and hemodynamic measurements made between 0800 and 1000 hours to avoid diurnal variation. Blood samples were placed immediately into a plastic tube kept on ice and within 10 minutes were centrifuged at 2000 × g for 20 minutes at 4°C. The plasma was then separated at 4°C and stored at −80°C until assayed for norepinephrine. The animals were then sacrificed by decapitation and both kidneys immediately removed for determination of α₁-adrenergic receptors.

**Plasma Norepinephrine**

Plasma norepinephrine concentration was determined by a radioenzymatic procedure.\(^\text{21, 22}\) The catecholamines were converted to their O-methylated derivatives by enzymatic O-methylation using S-adenosyl-L-[³H]methionine (40 Ci/mmoles, Arlington, Arlington Heights, Illinois). After extraction, the [³H]-normetanephrine was separated by thin-layer chromatography, eluted with 0.05 M ammonium hydroxide, and the labeled derivative converted to [³H]vanillin with 50 μl 4% w/v sodium metaperiodate, acidified with 1.0 ml of 0.1 M acetic acid, and the tritium assayed by liquid scintillation spectrometry. The method was linear over a range extending up to 10 ng norepinephrine and was sufficiently sensitive to assay of about 25 pg norepinephrine per milliliter of plasma. Interassay variability was 12.3% and intraassay 11.8%.

**Alpha Receptor Assay**

Total α₁-adrenergic receptors were determined in the rat kidneys using the ergot alkaloid, [³H]dihydroergocryptine, a potent α₁-adrenergic antagonist. To determine α₁-receptors, [³H]prazosin was used, and to determine α₂-receptors, [³H]yohimbine was used.\(^\text{10}\) Renal plasma membranes were prepared from both kidneys of each animal according to the procedure of Williams et al.\(^\text{23}\) After removal, the kidneys were placed into ice-cold buffer (0.25 M sucrose, 1mM MgCl₂, 5 mM Tris, pH 7.4). The capsule was removed, and the kidneys weighed, minced, and homogenized in 10 ml of ice-cold buffer using a Brinkman Model PT-20 Polytron (Kinematica Gmbt, Lucerne, Switzerland). The homogenate was filtered through two layers of cheesecloth, centrifuged at 400 g for 10 minutes at 4°C, and the supernatant recentrifuged at 28,000 g for 10 minutes at 4°C. The resulting pellet was washed twice by resuspension in ice-cold incubation buffer (10 mM MgCl₂, 50 mM Tris, pH 7.5) using a Potter-Elvehjem homogenizer (Bodine Electric Company, Chicago, Illinois) and recentrifuged at 28,000 g for 10 minutes at 4°C. The final pellet was suspended in sufficient incubation buffer to provide a protein concentration of 2.0 to 3.0 mg membrane protein/ml. Membrane protein was determined according to the procedure of Lowry et al.,\(^\text{24}\) using bovine serum albumin as the standard. To avoid interassay variability, the protein determinations for each SHR and matched NCR group were performed in one assay.

The binding of [³H]ligands to the rat renal membranes was determined as described by Williams et al.\(^\text{25}\) with the following modifications: increasing concentrations of [³H]ligand and rat renal membranes (100 μl) were incubated with constant shaking for 30 minutes at 25°C in 50 mM Tris, pH 7.5, containing 10 mM MgCl₂ in a final volume of 150 μl. For the binding of [³H]yohimbine, a 50 mM sodium-phosphate buffer, pH 7.4, was used. At the end of the incubation, samples were diluted with 5 ml of incubation buffer at 4°C and rapidly filtered through Whatman GF/C filters (Whatman, England). The filters were then rapidly washed with three additional 5-ml aliquots of the incubation buffer (4°C), dried, placed in scintillation vials, and counted in 10 ml of Triton/toluene aqueous scintillation mixture at a counting efficiency of 41%. All results were expressed in terms of specific binding, which was defined at the binding that was inhibitable by 10 μM phentolamine. All determinations were per-
formed in duplicate. In each experiment the specific binding of [3H]dihydroergocryptine was measured at nine different concentrations (0.1 to 40 nM) of the radioligand. To reduce interassay variability, an SHR and its matched NCR were assayed on the same day. The binding determined at each concentration was used to construct a Scatchard plot by linear regression analysis for each experiment. This plot allowed the calculation of binding-site concentration at saturation from the intercept with the abscissa, and the calculation of the dissociation constant from the negative reciprocal of the slope of the line. The results thus obtained from each experiment were averaged, and mean values of each group compared by unpaired Student's t test for single comparisons and analysis of variance for multiple comparisons.

Results

Mean arterial pressure, heart rate, plasma norepinephrine concentration, and body and kidney weights of the hypertensive and normotensive rats are shown in table 1. To minimize artifacts due to anesthesia and handling blood sampling for determination of plasma norepinephrine concentration and hemodynamic measurements were performed while the animals were conscious, resting, and unrestrained. As shown in table 1, mean arterial pressure was already significantly higher in the 4-week-old sr-SHR than in the respective group of NCR. This difference increased with age in the sr-SHR and was greatest in magnitude in the sp-SHR. Heart rate and plasma norepinephrine concentration, indices of sympathetic nerve activity, were also higher in the SHR. In keeping with previous reports, the difference between the plasma norepinephrine concentrations in the adult (32 weeks old) animals was not significant. With the exception of the 4-week-old groups, the SHR weighed less than the matched NCR. The combined weight of the left and right kidneys (table 1) was significantly lower in all groups of sr-SHR.

As shown for the 32-week-old rats (fig. 1, left), the binding of dihydroergocryptine to renal α-adrenergic receptors was significantly increased in the membranes derived from the spontaneously hypertensive animals. Scatchard analysis (fig. 1, right) revealed this increase in binding was due to an increase in the number of binding sites and not to an increased affinity for dihydroergocryptine. A similar increase in the number of binding sites, with no change in affinity, was also observed in the renal membranes of the 4- and 16-week-old sr-SHR and 9-week-old sp-SHR (table 2). Although the number of binding sites in the renal membranes of the 12-week-old female rats was somewhat lower than in the older male rats, a significant increase in renal α-adrenergic receptors was also noted in the female sr-SHR (table 2). These increases in the number of binding sites could not be attributed to differences in the yield of membrane protein, as the amount of membrane protein obtained per gram of wet kidney weight was similar for the hypertensive and normotensive animals (table 2). Moreover, the number of α-receptors, determined by the binding of [3H]prazosin (0.1–6.0 nM) to renal membranes from a separate group of sr-SHR and NCR at 16 weeks of age (table 3), was similar in both the hypertensive and normotensive animals. In contrast, these additional studies revealed that the increase in total renal α-adrenergic receptors ([3H]dihydroergocryptine binding) was entirely due to an increase in α, as measured by the binding of [3H]yohimbine (0.5–40.0 nM) (table 3).

In the male sr-SHR and their matched NCR groups, significant negative correlations were observed be-

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**Table 1. Mean Arterial Pressure (MAP), Heart Rate (HR), Plasma Norepinephrine Concentration (PNE) and Body and Kidney Weights of Normotensive Control Rats (NCR) and Spontaneously Hypertensive Rats (SHR)**

<table>
<thead>
<tr>
<th>Rat group</th>
<th>Age (wks)</th>
<th>MAP (mm Hg)</th>
<th>HR (bpm)</th>
<th>PNE (pg/ml)</th>
<th>Body weight (g)</th>
<th>Kidney weight (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Males</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCR</td>
<td>4</td>
<td>76 ± 4(7)†</td>
<td>427 ± 15(7)†</td>
<td>192 ± 17(7)†</td>
<td>89.4 ± 4.6(8)†</td>
<td>1.1 ± 0.03(8)†</td>
</tr>
<tr>
<td>sr-SHR</td>
<td>4</td>
<td>95 ± 3(5)</td>
<td>494 ± 9(5)</td>
<td>370 ± 56(5)</td>
<td>86.6 ± 4.2(9)</td>
<td>0.98 ± 0.03(8)</td>
</tr>
<tr>
<td>NCR</td>
<td>16</td>
<td>112 ± 2(7)*</td>
<td>336 ± 20(7)†</td>
<td>236 ± 35(7)‡</td>
<td>316.8 ± 4.1(7)*</td>
<td>2.9 ± 0.04(7)‡</td>
</tr>
<tr>
<td>sr-SHR</td>
<td>16</td>
<td>140 ± 5(6)</td>
<td>407 ± 20(6)</td>
<td>442 ± 51(5)</td>
<td>275.3 ± 5.1(7)</td>
<td>2.4 ± 0.13(7)</td>
</tr>
<tr>
<td>NCR</td>
<td>32</td>
<td>102 ± 3(10)*</td>
<td>317 ± 3(10)†</td>
<td>246 ± 31(9)‡</td>
<td>357.2 ± 14.2(10)</td>
<td>3.7 ± 0.11(7)</td>
</tr>
<tr>
<td>sr-SHR</td>
<td>32</td>
<td>138 ± 3(8)</td>
<td>352 ± 6(8)</td>
<td>295 ± 54(7)</td>
<td>312.5 ± 10.6(8)</td>
<td>2.8 ± 0.15(7)</td>
</tr>
<tr>
<td>NCR</td>
<td>9</td>
<td>115 ± 4(8)*</td>
<td>301 ± 10(8)†</td>
<td>331 ± 59(7)§</td>
<td>292.3 ± 7.3(8)§</td>
<td>2.2 ± 0.06(9)§</td>
</tr>
<tr>
<td>sp-SHR</td>
<td>9</td>
<td>166 ± 4(8)</td>
<td>345 ± 7(8)</td>
<td>723 ± 138(7)</td>
<td>261.8 ± 5.4(8)</td>
<td>2.3 ± 0.06(10)</td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCR</td>
<td>12</td>
<td>105 ± 3(8)*</td>
<td>339 ± 5(8)*</td>
<td>201 ± 17(8)†</td>
<td>192.7 ± 4.9(8)§</td>
<td>1.7 ± 0.03(8)‡</td>
</tr>
<tr>
<td>sr-SHR</td>
<td>12</td>
<td>138 ± 5(8)</td>
<td>392 ± 13(7)</td>
<td>273 ± 106(6)</td>
<td>176.3 ± 5.6(8)</td>
<td>1.6 ± 0.05(8)</td>
</tr>
</tbody>
</table>

Number in brackets indicates number of animals per group. Results are expressed as the means ± se. sr-SHR = stroke-resistant spontaneously hypertensive rat (SHR); sp-SHR = stroke-prone SHR.

Significance of difference between NCR and age- and sex-matched SHR groups: *p < 0.001; †p < 0.005; ‡p < 0.01; §p < 0.025; ‖p < 0.05; ‡‡p < 0.1, not significant.
FIGURE 1.  Left: Specific binding of $^3$H)dihydroergocryptine (DHE) to renal membranes from 32-week-old male stroke-resistant spontaneously hypertensive rats (SHR) and age- and sex-matched normotensive Wistar-Kyoto controls (NCR). Each value is the mean ± se of the results obtained in seven animals per group. Binding was assessed in duplicate in each experiment at each concentration of DHE examined.  Right: Scatchard plots of the data shown in the left graph. The points represent the mean values of the results obtained in seven animals per group. The number of binding sites at saturation ($n$) for each group was determined from the intercept of each line with the ordinate. The dissociation constant ($K_D$) was calculated from the negative reciprocal of the slope of each line. Correlation coefficients ($r$) for the regression lines are shown.

TABLE 2.  Binding of $^3$H)dihydroergocryptine (DHE) to Renal Alpha-Receptors and Yield of Membrane Protein per Gram of Wet Kidney Weight in Normotensive Control Rats (NCR) and Spontaneously Hypertensive Rats (SHR)

<table>
<thead>
<tr>
<th>Rat group</th>
<th>No. of binding sites (fmole/mg protein)</th>
<th>$K_D$ (nM)</th>
<th>Membrane yield (mg membrane protein/g kidney)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCR</td>
<td>4</td>
<td>186 ± 12*</td>
<td>12 ± 2</td>
</tr>
<tr>
<td>NCR</td>
<td>7</td>
<td>16</td>
<td>146 ± 10*</td>
</tr>
<tr>
<td>NCR</td>
<td>9</td>
<td>9</td>
<td>199 ± 13*</td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCR</td>
<td>8</td>
<td>12</td>
<td>169 ± 6†</td>
</tr>
<tr>
<td>NCR</td>
<td>8</td>
<td>12</td>
<td>199 ± 10</td>
</tr>
</tbody>
</table>

Number in brackets is number of animals per group; results are expressed as the means ± se. Abbreviations: sr-SHR = stroke-resistant SHR; sp-SHR = stroke-prone SHR.

Significance of differences between NCR and age- and sex-matched SHR groups: *p < 0.005; †p < 0.02; §p < 0.025; ¶ Differences between SHR and respective NCR group: p < 0.2, not significant.

FIGURE 2.  Age-related changes in the number of renal $\alpha$-adrenergic receptors in the male stroke-resistant spontaneously hypertensive rats (SHR) and age- and sex-matched normotensive Wistar-Kyoto controls (NCR). Each value is the mean ± se of the results obtained in each group at each age. Significant correlation between age and number of $\alpha$-adrenergic receptors ($\alpha$-receptor concentration) was observed in both the hypertensive and normotensive animals. With all 22 data points used, analysis of covariance revealed that the elevations ($F = 595$, $p < 0.0001$) but not the slopes ($F = 0.16$, NS) of the regression lines differed significantly.
renal α-receptors in SHR/Graham et al.

Table 3. α₁ ([3H]Prazosin), α₂ ([3H]Yohimbine), and α₁ + α₂ ([3H]Dihydroergocryptine) (DHE) Receptor Number (B_max) and Affinity Constants (K_D) for Binding to Renal Plasma Membranes from Spontaneously Hypertensive Rats (SHR) and Normotensive Controls (NCR) at 16 Weeks of Age

<table>
<thead>
<tr>
<th>Rat group</th>
<th>[3H]DHE</th>
<th>[3H]Prazosin</th>
<th>[3H]Yohimbine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B_max (fmole/mg protein)</td>
<td>K_D (nM)</td>
<td>B_max (fmole/mg protein)</td>
</tr>
<tr>
<td>SHR</td>
<td>296 ± 12</td>
<td>12 ± 2.1</td>
<td>62 ± 11</td>
</tr>
<tr>
<td>NCR</td>
<td>201 ± 9</td>
<td>9 ± 1.2</td>
<td>61 ± 12</td>
</tr>
<tr>
<td>p &lt; 0.02</td>
<td>NS</td>
<td>NS</td>
<td>p &lt; 0.02</td>
</tr>
</tbody>
</table>

Data are means ± se; from 11 rats per group.

Discussion

The sympathetic nervous system can produce long-term effects on blood pressure through sodium-retaining mechanisms. One site is the β-adrenergic receptor stimulating renin release and causing aldosterone synthesis, which mediates sodium and water retention by an effect on the distal renal tubule. This sodium-retaining mechanism is linked with excretion of potassium and hydrogen ions. Because of this linkage, excesses of this mechanism leading to hypertension are usually associated with hypokalemic alkalosis. Thus, the normal blood pH and potassium of essential hypertension suggests another site of enhanced sodium reabsorption in response to sympathetic nerve stimulation. However, the less selective antagonists, phenoxybenzamine and phentolamine, are also effective in this regard, while the blocking potential of α₂-selective antagonists, such as yohimbine, has yet to be examined.

Evidence that renal α₁-receptors can stimulate proximal tubular sodium reabsorption of sodium. The link has been unclear, however, between this effect of α-receptors and the enhanced renal tubular sodium reabsorption of the spontaneously hypertensive and Dahl salt-sensitive rat. Using an artificial perfusate, Steele and Underwood were unable to demonstrate enhanced sodium reabsorption in isolated perfused SHR kidneys. With the addition of norepinephrine to the perfusate, however, the tubular reabsorption of sodium was augmented far more in the SHR than in the normotensive rat kidneys. Similarly, Tobian et al. demonstrated enhanced sodium reabsorption in isolated kidneys from Dahl hypertensive rats perfused with arterial blood from a normotensive rat donor. Assuming the general applicability of Steele and Underwood’s observations to genetically hypertensive rats, one would conclude that circulating catecholamines are capable of activating renal α-receptors which enhance renal tubular reabsorption of sodium. Thus, the increase in renal α₂-receptors in SHR observed in the present study may be of particular interest if renal α₂-adrenergic receptors are indeed located on proximal tubules and mediate sodium reabsorption. Enhanced sodium reabsorption at this site would not be expected to cause hypokalemia and alkalosis as occurs with mineralocorticoid excess. Thus, normalcy of body pH and potassium and increased proximal tubular α-receptor mediated sodium reabsorption constitute an attractive mechanism to explain the general Guyton thesis of inappropriate renal retention of sodium in hypertensive man and animals.

Nevertheless, the role of renal α₂-receptors remains unclear, and further studies aimed at elucidating the location and function of these receptors are in progress. DiBona and coworkers (personal communication, Dallas, Texas, 1981) have demonstrated that the α₁-selective antagonist, prazosin, blocks tubular sodium reabsorption in response to sympathetic nerve stimulation. However, the less selective antagonists, phenoxybenzamine and phenotolamine, are also effective in this regard, while the blocking potential of α₂-selective antagonists, such as yohimbine, has yet to be examined. Evidence that renal α₂-receptors may be linked to sympathetically mediated tubular sodium reabsorption is the finding that in isolated tubules from rat kidney cortex, α-adrenergic stimulation reduces the rate of cyclic AMP production; a response generally linked to α₂-receptors. Furthermore, infusion of dibutyryl cyclic AMP into the renal artery of hypophysectomized dogs causes a diuresis due to a decrease in tubular sodium reabsorption.

Other explanations for the observed increase in renal α₂-adrenergic receptors in SHR, and the consequences of their proposed proximal tubular location, must also be considered. For example, α₂-receptors located prejunctionally on postsynaptic sympathetic nerve terminals have been identified, on the basis of pharmacologic studies, in most tissues including the kidney. It is unlikely, however, that the α₂-receptors identified in the present study are the prejunctional α₂-receptors that inhibit stimulus-induced norepinephrine release, as we and others have been unable to identify prejunctional α₂-receptors on the basis of radioligand binding studies. In this regard, it should be noted that Robbie found no evidence that prejunctional α₂-receptors are functionally significant in the dog kidney. It is also unlikely that [3H]yohimbine is binding to vascular α₂-
receptors, which mediate predominantly venoconstriction, as postjunctional vascular $\alpha_1$-receptors have not been identified in the kidney. U’Pritchard et al. have reported that renal $\alpha_1$-adrenergic receptors are not increased in SHR. It is possible, however, that their use of [H]$\beta$-epinephrine to identify $\alpha_1$-receptors may have masked a difference in $\alpha$-receptor numbers, as this radioligand binds with high affinity to $\alpha_1$, as well as $\alpha$-receptors. For this and other reasons discussed in detail by Starke and Docherty, it is now apparent that agonists are of lesser utility in subclassifying $\alpha$-receptors than $\alpha_1$-specific antagonists, such as [H]$\beta$-yohimbine. Along the same lines, with the availability of this $\alpha_2$-specific agonist, we and other investigators have found that the predominant $\alpha$-receptor in the rat kidney is the $\alpha_2$-receptor rather than the $\alpha_1$-receptor as previously reported from studies using a non-specific tritiated agonist. The mechanisms responsible for the increased number of renal $\alpha$-adrenergic receptors in SHR compared to NCR are presently uncertain. It has become apparent, however, that plasma-membrane receptors may be dynamically regulated by the neurotransmitters with which they interact. In the present study, the concentration of plasma norepinephrine was significantly higher in the younger sr-SHR and in the sp-SHR than in the matched NCR (table 1). One might anticipate, therefore, that the number of renal $\alpha$-adrenergic receptors should have been depressed in the SHR. The findings of significantly increased renal $\alpha$-receptors may thus be due to a failure of the normal "feedback suppression mechanism." In the studies demonstrating homologous receptor regulation, however, high agonist concentrations ($>10^{-7} \text{M}$) were required to show a decrease in receptor binding and functioning. As the increases in plasma norepinephrine levels observed in the SHR were only small, and cannot be directly related to changes in the intrasynaptic concentration of norepinephrine to which the receptors are exposed, the possibility that a defect in homologous receptor regulation is involved in the increased number of renal $\alpha$-receptors in SHR must remain speculative. Nevertheless, an enhanced receptor-mediated response is likely to result from the combination of increased $\alpha_1$-receptors and high agonist concentrations, unless the receptors are indeed vascular receptors with an extrasynaptic location, which are not responsive to changes in sympathetic nerve activity.

In addition to suggesting a unique role for receptors in the control of tissue sensitivity to hormonal stimulation, radioligand-binding studies have provided evidence for changes in hormonal receptors during adulthood and senescence, which may constitute a common manifestation of the aging process. In most of these studies receptor concentrations were found to decrease with increasing age, either during senescence or earlier in adulthood. Despite investigations in a wide variety of tissues in which age-related changes were found in a number of different hormone receptors, the effect of aging on $\alpha$-receptors has not been examined. It is of interest, therefore, that a parallel decrease in renal $\alpha$-receptors with age, was observed in both the hypertensive and normotensive animals (fig. 2).

In conclusion, the present study demonstrates that renal $\alpha$-adrenergic receptors, particularly those of the $\alpha_2$-type, are increased in SHR of the Okamoto-Aoki strain, as compared to age- and sex-matched Wistar-Kyoto NCR. In addition, this increase in $\alpha$-adrenergic receptors appears to be independent of the age and sex of the animals and is present in both the stroke-prone and stroke-resistant strains of SHR. This receptor abnormality may play a primary role in the development of hypertension in SHR by contributing to enhanced renal tubular reabsorption of sodium with secondary effects on volume, vascular resistance, and sensitivity to vasoconstrictor mechanisms.

Acknowledgments

We thank Dr. Walter Lovenberg (NIH, Bethesda, Maryland) for the generous gift of the stroke-prone, spontaneously hypertensive rats; Dr. Michael J. Davey (Pitzer, Sandwich, Kent, UK) for the generous gift of [H]$\beta$-prazosin; and Tina Murphy and William H. Stephensen for expert technical assistance.

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_Hypertension_. 1982;4:881-887
doi: 10.1161/01.HYP.4.6.881
_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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