Regulation of Vascular Angiotensin II Receptors in the Rat during Altered Sodium Intake

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SUMMARY Changes in sodium intake exert well-defined and opposite effects on adrenal and vascular responsiveness to angiotensin II (All). Whereas the adrenal glomerulosa zone becomes more sensitive to All during sodium restriction, vascular sensitivity to All is decreased during sodium restriction and increased by sodium loading. The extent to which regulation of smooth muscle All receptors is involved in such altered vascular responsiveness was examined by assay of $^{125}$I-All binding in the mesenteric artery and urinary bladder of rats during low and high sodium intake. The All receptors of vascular smooth muscle were found to be similar to those of the mesenteric artery in terms of their binding properties and regulation by altered sodium intake. During sodium restriction, blood All was elevated and All receptor concentration was significantly decreased (by 40%) in both tissues. Conversely, sodium loading was accompanied by decreased blood All and an increase in smooth muscle All receptors. The changes in All binding during sodium restriction were not attributable to occupancy of receptors by endogenous All, and no effect on receptor affinity was observed at either extreme of sodium intake. Elevation of the circulating All concentration within the physiological range by infusion of the octapeptide for 2-4 days decreased All receptor concentration in urinary bladder particles. These findings demonstrate that smooth muscle All receptors are regulated during altered sodium intake, at least partially via changes in the circulating All concentration, in a manner reciprocal to the adrenal glomerulosa receptors. Such modulation of vascular All receptors by the renin-angiotensin system could be responsible both for the altered pressor responses that accompany changes in sodium balance and for the reduced vascular reactivity that occurs in patients with high levels of circulating All.


THE vascular and adrenal responses to angiotensin II are influenced by variations in sodium balance. Vascular reactivity to exogenous angiotensin II is attenuated by sodium restriction and is increased during sodium loading. These effects of sodium balance on vascular responses to angiotensin II are opposite to those exhibited by the adrenal zona glomerulosa, where the aldosterone response is potentiated during sodium restriction and decreased by sodium loading. The sensitizing action of sodium restriction on the adrenal gland is accompanied by trophic changes in the glomerulosa cells, including increased angiotensin II receptors and enhanced activity of enzymes in the aldosterone biosynthetic pathway. We have demonstrated recently that the development of these adrenal changes depends on the elevated levels of angiotensin II that accompany sodium restriction and exert a trophic action on the glomerulosa cell (Aguilera and Catt, 1978; Aguilera et al., 1980).

In vascular tissues, where sodium deficiency causes decreased pressor responsiveness to angiotensin II, altered sodium balance has little effect on the pressor responses to other vasoactive hormones, such as catecholamines or vasopressin (Reid and Laragh, 1965; Stewler et al., 1972). The selectivity of this effect suggests that a specific mechanism, possibly receptor-mediated, is responsible for the changing sensitivity to angiotensin II. This concept was implicit in earlier in vivo studies which suggested that the decreased pressor effects of angiotensin II during sodium restriction were due to reduced receptor affinity and/or prior occupancy of vascular angiotensin II receptors by the endogenous peptide (Brunner et al., 1972; Thurston and Laragh, 1975).

The characterization of angiotensin II receptors in vorta (Baudouin et al., 1971; LeMorvan and Palaic, 1975) and other major vessels has been complicated by the small amount of smooth muscle in such tissues, and by the difficulty of obtaining suitable membrane preparations for the study of receptor regulation. For this reason, other sources of smooth muscle have been employed as a model for angiotensin II receptors of vascular tissue. Angiotensin II is a potent stimulus of uterine muscle contraction, and this response, like that of vascular smooth muscle, is modulated by sodium balance. In previous studies of the rat uterus, we observed a significant decrease in angiotensin II receptors after 7 days of sodium restriction, suggesting that vascular smooth muscle receptors could also be down-
regulated during decreased sodium intake (Aguilera et al., 1978). However, the use of the uterus as a model to study the regulation of vascular angiotensin II receptors is complicated by variations in basal receptor levels according to the changing secretion profile of sex steroids. In the rat uterus, the concentration of angiotensin II receptors changes markedly throughout the ovarian cycle and during early pregnancy (Schirar et al., 1980a, 1980b). However, the urinary bladder has been shown recently to provide a useful model for studies on the regulation of smooth muscle angiotensin II receptors, based on a comparison of the effects of altered sodium balance on angiotensin II binding in particulate fractions of bladder and mesenteric artery (Aguilera and Catt, 1980). The present studies have shown that the angiotensin II receptors in both vesicular and vascular smooth muscle are regulated by changes in sodium balance in a manner consistent with the altered pressor responsiveness to angiotensin II.

Methods

Synthetic [Asp¹, Ile⁶]angiotensin II and its analogues [Sar¹, Ala¹]- and [des-Asp¹-angiotensin II] were obtained from Beckman Bioproducts Inc. Monoiodinated ¹²⁵I-angiotensin II with specific activities ranging from 900 to 1500 cpm/μg was prepared by the chloramine T method and purified by anion exchange chromatography (Nielsen et al., 1971).

Male Sprague-Dawley rats, 50 days old (Charles River Inc.), were maintained on a normal diet (0.1% sodium and 0.7% potassium chloride) for at least 3 days prior to each experiment. The effect of dietary sodium intake on smooth muscle angiotensin II receptors was evaluated in rats placed on diets containing low (0-0.01%), normal (0.1%), or high (0.3%) sodium chloride (Ziegler Brothers Inc.) for 4 days. Angiotensin II infusion was performed by intraperitoneal implantation of osmotic minipumps (Alza) for 2 days. Angiotensin II was dissolved in 0.01 N acetic acid at concentrations of 0.6-9 μg/μl to obtain infusion rates from 10 to 150 ng/min per rat.

Rats were killed by decapitation and approximately 5 ml of blood were collected into 20 ml of aceticone for angiotensin II determination (Cain et al., 1972). Tissues were removed rapidly, placed in ice-cold phosphate buffer, cleaned of connective tissue, and homogenized in 20 mM sodium bicarbonate (approximately 1:20, wt/vol with 6-10 strokes of a mechanical homogenizer (Tekmar Co.). Homogenates were stirred at 4°C for 20 minutes, filtered through nylon gauze, and centrifuged at 900 g for 10 minutes. The supernatant was centrifuged at 30,000 g for 30 minutes and the pellet resuspended in 50 mM Tris-HCl buffer pH 7.4 for subsequent binding assay.

For receptor binding studies, 50–200 μg of protein were incubated with ¹²⁵I-angiotensin II (0.1-0.4 nM) in a final volume of 250 μl of Tris-HCl buffer containing 10 mM MgCl₂, 1 mM dithiothreitol (DTT), 1 mM EGTA, and 0.2% bovine serum albumin. Nonspecific binding was measured in the presence of 1 μM angiotensin II, and was 0.98 ± 0.03% (mean ± se) of the total added radioactivity. Specific binding was calculated as the difference between total and nonspecific binding. Receptor-bound ¹²⁵I-angiotensin II was separated from the free peptide by filtration through 0.45-μm Millipore nitrocellulose HAWP filters and analyzed in a γ spectrometer. Binding capacity and affinity were calculated by computer analysis of the experimental data (Ketelslegers et al., 1975).

α-Adrenergic and β-adrenergic receptors were measured by binding of [²H]dihydroergocriptine and [²H]dihydroalprenolol, respectively. Urinary bladders were homogenized in 50 mM Tris-HCl, pH 7.4, and the 30,000 g membrane fraction was prepared as described for angiotensin II binding. The pellet was resuspended in 50 mM Tris-HCl pH 7.4 containing 10 mM MgCl₂ and 0.01 mM pargyline, and incubated for 5 minutes at 37°C to inhibit monoaminoxidase activity. Aliquots of the membrane suspension were incubated for 10 minutes at room temperature in a final volume of 250 μl of Tris-HCl buffer containing 10 mM MgCl₂, 0.1% ascorbic acid, and approximately 4 nM [²H]dihydroergocriptine or [²H]dihydroalprenolol. Nonspecific binding was determined in the presence of 10 μM phentolamine (Ciba) or propranolol (Sigma) for α- and β-adrenergic receptors, respectively. Bound radioactivity was separated by filtration through Whatman GF/B glass fiber filters and assayed by liquid scintillation spectrometry.

The statistical significance of the differences between experimental groups was determined by analysis of variance.

Results

Angiotensin II Binding in Vascular and Nonvascular Smooth Muscle

A suitable model for the study of receptor regulation in smooth muscle was sought by analyzing the binding of angiotensin II to particulate preparations from several tissues. Binding studies were performed at equilibrium under conditions that were found to minimize angiotensin II degradation and to give maximum binding capacity. The distribution of angiotensin II binding in different vascular and nonvascular sources of smooth muscle is shown in Figure 1. In general, angiotensin II binding to vascular particles was relatively low. The highest binding capacity was found in mesenteric artery, in which specific binding was more than double the nonspecific value. Of the nonvascular tissues, the urinary bladder displayed the highest binding capacity, which was similar to that of the uterus and about 6-fold higher than the nonspecific binding.

The properties of angiotensin II receptors in ur-
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Binding of $^{125}$I-angiotensin II to vascular and nonvascular smooth muscle particles. Bars represent the mean ±SE of data from three to seven experiments.

The ability of several angiotensin II analogues to compete with $^{125}$I-angiotensin II for binding to angiotensin receptors was identical in vascular and urinary bladder smooth muscle particles (Fig. 2).

Angiotensin II Receptors during Altered Sodium Intake

The effects of altered sodium intake on angiotensin II binding in vascular and vesicular particles are shown in Figure 4. After 4 days of low sodium diet, the angiotensin II receptor concentration in mesenteric artery particles was significantly decreased ($P<0.05$). Conversely, after sodium loading the angiotensin II receptor concentration was increased by 30% above the control value ($P<0.05$). In urinary bladder particles, angiotensin II receptor concentration also showed significant changes during altered sodium intake, parallel to those in the mesenteric artery ($P<0.02$ and $<0.005$ after low and high sodium diet, respectively). Scatchard analysis of the binding data for the urinary bladder revealed that the changes in angiotensin II binding induced by dietary sodium were due to changes in receptor concentration, without variations in binding affinity. The results of one of three similar experiments are shown in Figure 5.

To examine the specificity of dietary sodium effects on the smooth muscle angiotensin receptors, we measured $\alpha$- and $\beta$-adrenergic receptors in urinary bladder particles from rats fed on low or high sodium diet. As shown in Table 1, angiotensin II...
Angiotensin II receptors again exhibited the expected changes, decreasing with the low sodium diet and increasing with sodium loading. In contrast, no changes were observed in α- and β-adrenergic receptors measured as binding of [3H]dihydroergocriptine and [3H]dihydroalprenolol, respectively.

The decreased pressor activity of angiotensin II during salt deprivation has been suggested to result from occupancy of receptor sites by the endogenous hormone (Thurston and Laragh, 1975). Evaluation of this possibility by two different approaches did not support the participation of occupancy in the receptor changes occurring in response to variations in dietary sodium. First, measurement of angiotensin II by radioimmunoassay in acetic acid/acetone extracts of the membranes revealed only negligible amounts of the peptide in rat urinary bladder particles, independent of the sodium intake. Also, no changes in angiotensin II binding were observed after treatment of the membrane preparations with 3 M MgCl₂, which completely dissociates bound angiotensin II from the receptors (Fig. 6). In the second approach, we sought to eliminate in vivo occupancy by administering converting enzyme inhibitors to lower the circulating levels of angiotensin II in sodium-restricted rats. As shown in Table 2, after 4 days of sodium restriction angiotensin II receptors in vesicular membranes were decreased by 50%, compared with the sodium-loaded controls (P < 0.001). In sodium-restricted rats, the angiotensin II receptor concentration in smooth muscle particles did not increase after injection of the converting enzyme inhibitors SQ 14,225 or SQ 20,881, despite the rapid decrease in blood angiotensin II to the levels observed in the sodium-loaded rats (P < 0.001). The changes in angiotensin II binding were not due to differential degradation of the free peptide during the binding assay. As shown in Figure 7, radioimmunoassay of angiotensin II in the media after 45 minutes of incubation revealed no differences in degradation in the presence of smooth muscle or adrenal membranes from control or sodium-restricted rats.

### Effects of Angiotensin II Infusion on Smooth Muscle Receptors

Infusion of angiotensin II at rates of 25-50 ng/min, from intraperitoneal osmotic minipumps, elevated circulating angiotensin II to the levels seen during sodium restriction. As shown in Figure 8, these rates of infusion reduced the angiotensin II receptor concentration in urinary bladder particles. More marked decreases in receptors were observed after higher infusion rates that elevated blood angiotensin II levels beyond the physiological levels associated with sodium deprivation.

<table>
<thead>
<tr>
<th>Diet</th>
<th>[3H]Dihydroergocriptine (fmol/mg)</th>
<th>[3H]Dihydroalprenolol (fmol/mg)</th>
<th>[3H]-Angiotensin II (fmol/mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>56 ± 5</td>
<td>287 ± 15</td>
<td>84 ± 9</td>
</tr>
<tr>
<td>Low sodium</td>
<td>51 ± 4</td>
<td>312 ± 12</td>
<td>90 ± 6*</td>
</tr>
<tr>
<td>High sodium</td>
<td>51 ± 9</td>
<td>254 ± 4</td>
<td>122 ± 9*</td>
</tr>
</tbody>
</table>

Values correspond to the mean and SE of three experiments

* Significantly different from normal control (P < 0.05)
Discussion

These studies have demonstrated that the well-known changes in pressor responsiveness to angiotensin II during altered sodium balance are accompanied by parallel changes in vascular receptors for the peptide. In particular, the use of the rat mesenteric artery as a source of smooth muscle has provided evidence that vascular angiotensin II receptors are reduced during sodium restriction, and increased during sodium loading (Aguilera and Catt, 1980). The use of the mesenteric artery as a source of vascular angiotensin II receptors has also been described by Gunther et al. (1980a), whose values for receptor affinity and capacity were almost identical with those observed in the present study. The similar changes we observed in urinary bladder particles indicate the value of this nonvascular smooth muscle as a model for the study of vascular angiotensin II receptors. The properties of angiotensin II binding to urinary bladder particles were identical to those of mesenteric artery smooth muscle in terms of receptor affinity, ionic dependence, and competition with angiotensin analogues. In male animals, the absence of cyclical effects of gonadal steroids on vesicular binding sites facilitates the analysis of physiological changes in angiotensin receptors, and makes the urinary bladder a useful model for the study of angiotensin II receptor regulation in smooth muscle.

Whereas sodium restriction led to decreased receptors in arterial and vesicular smooth muscle, sodium loading caused the converse changes, with increased concentration of angiotensin II receptors in both mesenteric artery and urinary bladder. It is likely that such changes in smooth muscle receptors contribute to the altered sensitivity of the pressor responses to angiotensin II during changes in sodium intake. The cellular location of the angiotensin II binding sites in smooth muscle particles has

Table 2: Effect of Acute Converting Enzyme Blockade on Smooth Muscle Angiotensin II Receptors

<table>
<thead>
<tr>
<th>Experiment no.</th>
<th>Experimental condition</th>
<th>Blood angiotensin II (pg/ml)</th>
<th>Angiotensin II receptors (fmol/mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Low sodium diet</td>
<td>35.7 ± 4.0</td>
<td>58 ± 7.0</td>
</tr>
<tr>
<td>2</td>
<td>Low sodium + SQ 14,225</td>
<td>5.3 ± 1.9*</td>
<td>58 ± 3.5</td>
</tr>
<tr>
<td>3</td>
<td>Low sodium + SQ 20,881</td>
<td>ND</td>
<td>58</td>
</tr>
<tr>
<td>4</td>
<td>High sodium diet</td>
<td>5.9 ± 1.0*</td>
<td>128 ± 9.8*</td>
</tr>
<tr>
<td>5</td>
<td>High sodium + SQ 14,225</td>
<td>ND</td>
<td>115</td>
</tr>
</tbody>
</table>

SQ 14,225, 1 mg/kg, iv at -15 minutes; SQ 20,881, mg/kg, iv at -30 minutes. ND, not determined. Experiments 3 and 5 are single observations included for comparison with the data shown for effects of SQ 14,225 (experiment 2) and high sodium diet (experiment 4) upon angiotensin II receptors. Other values are the mean and SE of three experiments.

* P < 0.001 by comparison with low sodium diet (experiment 1).
not been defined, but is presumed to be at the plasma membrane as previously observed for the adrenal (Glossmann et al., 1974) and uterine (Devyck et al., 1976) angiotensin receptors. The increased particulate binding observed in association with high sodium diet probably represents a change in the membrane receptor content, although an effect upon as yet unidentified intracellular sites cannot be excluded.

It is interesting to note that des-Asp'-angiotensin II was less potent than the octapeptide in displacing 125I-angiotensin II from vascular and nonvascular smooth muscle particles. This finding is consistent with the weaker pressor activity of the heptapeptide in humans and experimental animals (Kono et al., 1975; Campbell et al., 1977; Carey et al., 1978). In the adrenal, although the biological activities of the two peptides are less discrepant than in smooth muscle, des-Asp'-angiotensin II is again less potent than angiotensin II as a stimulus of aldosterone production, both in vivo and in vitro (Kono et al., 1975; Carey et al., 1978; Aguilera et al., 1979; Mendelson and Kachel, 1980). The lower potency of des-Asp'-angiotensin II in adrenal glomerulosa cells is due largely to the more rapid degradation of the heptapeptide by comparison with angiotensin II (Aguilera et al., 1979; Mendelson and Kachel, 1980). In smooth muscle particles, the relative rate of degradation of the heptapeptide is even more rapid than in the adrenal during incubation in vitro (Gregory and Aguilera, 1981). Such preferential degradation of des-Asp'-angiotensin II in smooth muscle would contribute for the apparently lower binding affinity of the heptapeptide, due to a rapid decrease in free peptide concentration during the binding assay. More rapid degradation of des-Asp'-angiotensin II could also occur in vivo, further contributing to the weaker pressor effect of the heptapeptide. It is clear that further studies are necessary to clarify the relative contributions of ligand degradation and decreased receptor affinity to the lower pressor activity of des-Asp'-angiotensin II.

Sodium depletion markedly stimulates the renin-angiotensin system, and the consequent rise in angiotensin II causes increased aldosterone secretion. However, there is no increase in blood pressure associated with the physiological increases of circulating angiotensin II during sodium restriction. In contrast to their decreased concentration in smooth muscle, angiotensin II receptors in the adrenal glomerulosa zone are increased during sodium deficiency, consistent with the enhanced aldosterone response to angiotensin II during low sodium intake. The reciprocal changes in angiotensin II receptors and responsiveness in adrenal glomerulosa cells and vascular smooth muscle could serve as a mechanism by which aldosterone secretion and sodium conservation are regulated by angiotensin II without affecting the blood pressure.

The receptor changes observed in smooth muscle during altered sodium intake appear to be specific for angiotensin II, since no alterations in α- and β-adrenergic receptors were found. This is consistent with the minor change in pressor responsiveness to norepinephrine observed during sodium restriction (Oliver and Cannon, 1978), and supports the proposal that regulation of smooth muscle receptor sites by sodium intake is a determinant of the altered pressor responses to angiotensin II (Aguilera et al., 1978; Aguilera and Catt, 1980). A similar conclusion has been reached by Gunther et al. (1980b) during studies of the effects of sodium restriction and Captopril administration upon mesenteric artery receptors in the rat.

The mechanism by which sodium intake alters smooth muscle angiotensin II receptors is probably dependent on the direct action of circulating angiotensin II on its receptors. It has been suggested that increased metabolism of angiotensin II during sodium restriction could explain the decrease in sensitivity to the peptide. Studies performed on the isolated perfused kidney have shown that tissue preparations from sodium-loaded rats removed significantly less angiotensin from the perfusate than kidneys from rats on a normal sodium diet (Leary and Ledingham, 1970). However, although increased degradation of the free peptide during the binding assay could result in falsely low binding values, such a decrease in binding would be reflected in the receptor affinity rather than in receptor number as in the present observations. In the present studies (Fig. 7), differential degradation of the peptide was excluded as a participating factor.
in the observed sodium-induced changes in angiotensin II receptors in smooth muscle.

The elevated levels of angiotensin II that accompany sodium restriction may account for the reduction of angiotensin II receptors in smooth muscle. The present observations support this possibility, since angiotensin II infusion clearly decreased angiotensin II receptors in urinary bladder particles. This down-regulating action of angiotensin II on its smooth muscle receptors was evident after infusion of doses that elevate the circulating peptide to the levels observed during sodium restriction. This effect is opposite to that exerted on the adrenal glomerulosa zone, where elevations of blood angiotensin II concentration within the sodium-restricted range clearly increase the angiotensin II receptor concentration (Aguilera et al., 1980).

It remains possible that factors other than angiotensin II receptor regulation could contribute to the decreased pressor responses to angiotensin during sodium restriction. A direct action of extracellular sodium on vascular reactivity is not likely, since no major variations in plasma sodium have been observed during dietary sodium restriction. In addition, it has been shown that short term alterations in sodium and water balance by hemodilution in nephrectomized dogs do not affect vascular sensitivity to angiotensin II (Cowley and Lohmeir, 1978). In contrast, decreased sensitivity to angiotensin II has been observed during acute sodium and volume depletion by furosemide, a condition in which angiotensin II levels are markedly increased (Oliver and Cannon, 1978).

The pressor response to angiotensin II in sodium-restricted rats (Thurston and Laragh, 1975) and dogs (Oliver and Cannon, 1978) is potentiated by inhibition of converting enzyme activity. These observations led to the proposal that the decreased pressor responses to angiotensin II during sodium restriction are due to prior occupancy of receptor sites by the endogenous hormone. In both reports, the pressor responsiveness to angiotensin II was increased a short time after injection of the converting enzyme inhibitor, SQ 20,881, suggesting that rapid dissociation of bound angiotensin II from the vascular receptor occurs when circulating levels of the hormone are decreased. However, in the present experiments, the decreased vesicular angiotensin II receptor concentration was still evident in sodium-restricted rats when the tissue was obtained 10 minutes after the injection of converting enzyme inhibitor. The use of more drastic methods to dissociate bound angiotensin II, such as treatment of the particles with MgCl2, also failed to increase the angiotensin II receptor concentration in smooth muscle from sodium-restricted rats.

The affinity of smooth muscle angiotensin II sites is such that any bound endogenous angiotensin II would be expected to be dissociated during preparation of the particulate fraction, and the observed decrease in angiotensin II receptor concentration would reflect a true loss of receptors. Direct evidence for such rapid dissociation of recently bound radioactive angiotensin II has been provided by analysis of mesenteric artery sites after perfusion with the tritiated peptide (Gunther et al., 1980b). However, it is possible that the decrease in responsiveness to the exogenous peptide in vivo is accentuated by occupancy of receptor sites secondary to the prevailing high levels of angiotensin II during sodium restriction. This could explain the increases in the pressor response to exogenous angiotensin shown in sodium-restricted rats and dogs after converting enzyme inhibition (Thurston and Laragh, 1975; Oliver and Cannon, 1978). The relative importance of putative receptor occupancy and actual receptor loss in the decreased sensitivity to angiotensin II during sodium deficiency has yet to be defined. Under other experimental conditions, receptor occupancy cannot explain the changes in vascular sensitivity to angiotensin II during altered sodium intake. Dietary sodium-induced changes in responsiveness to angiotensin II in rabbit aorta are still apparent in vitro after equilibration of the tissue in angiotensin-free medium, in which any bound angiotensin II would presumably dissociate (Stewler et al., 1972; Sybert and Peach, 1980). Under such conditions, the maintenance of altered vascular reactivity could reflect the effects of changes in angiotensin II receptor concentration, such as those demonstrated in the present study.

It is likely that modulation of angiotensin II receptors in smooth muscle by the circulating levels of the peptide contributes to the altered vascular responsiveness to angiotensin II observed in a variety of pathological conditions (Kaplan and Silah, 1964). In several clinical situations, such as malignant hypertension, cirrhosis of the liver, and Bartter's syndrome, increased plasma angiotensin II levels are accompanied by decreased pressor responsiveness to the octapeptide. Conversely, increased responsiveness to angiotensin II is observed in conditions in which circulating angiotensin II concentrations are low, such as primary hyperaldosteronism and low renin essential hypertension. The changes we have observed in vascular and vesicular angiotensin II receptors during altered sodium intake and infusion of angiotensin II suggest that variations in circulating angiotensin II concentrations are low, such as primary hyperaldosteronism and low renin essential hypertension. The extent to which these changes in smooth muscle receptors are responsible for the modulation of pressor responsiveness has yet to be defined, but such alterations in the effector sites for angiotensin II probably participate in the control of vascular reactivity. The reciprocal regulation of adrenal and vascular angiotensin II receptors is a functionally appropriate mechanism to accommodate the dual actions of angiotensin II on aldosterone secretion and vasoconstriction. In particular, the simultaneous and opposite changes in angiotensin II receptors in the
two target tissues would minimize the vascular effects of altered angiotensin II concentration during the variations in renin secretion that are associated with the control of sodium balance.

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