Angiotensin receptor antagonist improves cardiac reflex control of renal sodium handling in heart failure

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DiBona, Gerald F., Susan Y. Jones, and Linda L. Sawin. Angiotensin receptor antagonist improves cardiac reflex control of renal sodium handling in heart failure. Am. J. Physiol. 274 (Heart Circ. Physiol. 43): H636–H641, 1998.—In rats with congestive heart failure, type 1 angiotensin II receptor antagonist treatment (losartan) decreases basal renal sympathetic nerve activity and improves arterial baroreflex regulation of renal sympathetic nerve activity. This investigation examined the effect of losartan on cardiac baroreflex regulation of renal sympathetic nerve activity and renal sodium handling in rats with congestive heart failure. Losartan treatment decreased arterial pressure from 120 ± 3 to 93 ± 5 mmHg and increased the afferent (from 0.95 ± 0.21 to 2.22 ± 0.42%) and efferent vagal nerve activity (mean ± SD) by 2.22 ± 0.42% and 3% of the load, respectively. Inosartan treatment improved cardiac baroreflex regulation of renal sympathetic nerve activity, which was associated with improved ability to excrete acute and chronic sodium loads.

The renin-angiotensin system is increased in this model of CHF, as reflected by our previous multiple demonstrations of a two- to threefold increase in plasma renin activity compared with control rats (4). In CHF rats, intravenous and intracerebroventricular losartan each decreased the heightened basal level of RSNA by ~20% and improved the reduced gain of arterial baroreflex control of RSNA by ~60% (4).

Cardiac baroreflex suppression of RSNA contributes substantially to the ability of the kidney to appropriately excrete sodium in response to acute and chronic sodium loads (6). A treatment that improves cardiac baroreflex regulation of RSNA in CHF would be expected to improve the natriuretic response to acute and chronic sodium loads. This study examined the effect of losartan on cardiac baroreflex regulation of RSNA in CHF and on the natriuretic response to acute and chronic sodium loads.

METHODS

Adult male Sprague-Dawley rats (275–325 g) allowed free access to normal sodium rat pellet diet (Teklad; Na+ = 172 meq/kg, K+ = 180 meq/kg) and tap water drinking fluid were used for all studies.

CHF. A previously described technique (3, 4, 7, 8) involving ligation of the left coronary artery was used to produce chronic CHF. Rats were anesthetized with methohexital sodium (50 mg/kg ip); an oral endotracheal tube was inserted, and mechanical ventilation with room air was instituted. Via a left thoracotomy, the heart was exteriorized, and the left coronary artery was ligated between the pulmonary outflow tract and the left atrium. The heart was returned to its normal position, and the thorax was closed with removal of air. After recovery from anesthesia and removal of the ventilator, rats were returned to individual metabolism cages with free access to normal-sodium rat pellet diet and tap water drinking fluid. All subsequent studies were performed 3–4 wk after left coronary artery ligation. Sham rats (Sham) were subjected to similar anesthesia and surgical procedures, except the left coronary artery was not ligated.

Losartan treatment. CHF and Sham rats were each divided into two groups and were placed on a normal-sodium rat
pellet diet and tap water drinking fluid. The losartan group (CHF-Los, Sham-Los) received daily injections of losartan (5 mg/kg ip, 0.2 ml in isotonic saline); the vehicle group (CHF-Veh, Sham-Veh) received daily injections of vehicle (0.2 ml isotonic saline) throughout the study.

Cardiac baroreflex function. After 7 days of losartan or vehicle treatment, rats were anesthetized with methohexital (50 mg/kg ip) and placed on a heating pad to maintain body temperature between 37° and 38°C. After incision of a tracheal cannula via a midline neck incision, mechanical ventilation was instituted. Anesthesia was maintained with alphadoline-alphaxalone acetate (Saffan; 6–9 mg·kg⁻¹·h⁻¹ total steroids) and pancuronium bromide (1 mg·kg⁻¹·h⁻¹) diluted in isotonic saline and infused at 0.05 ml/min. PE-50 catheters were inserted into the inferior vena cava via the left femoral vein for administration of drugs and intravenous volume loading and into the left femoral artery for measurement of arterial pressure. The left femoral arterial catheter was connected to a Statham P23Db pressure transducer for the measurement of mean arterial pressure (MAP) and to a Grass 7P44 Tachometer for the measurement of HR. The peak MAP responses to ANG II (10 ng iv; 0.1 ml isotonic saline) were recorded. A Tygon catheter was inserted into the right atrium via the right jugular vein and connected to a Statham P23Db pressure transducer positioned at the level of the rat’s thorax for measurement of mean right atrial pressure (MRAP). Arterial baroreceptors were denervated according to the method of Krieger (11).

The left kidney was exposed via a left flank incision, and a renal nerve bundle was dissected in the angle between the abdominal aorta and the renal artery. The nerve bundle was placed on a bipolar platinum electrode (Cooner Wire, Chatsworth, CA) for recording of RSNA. When an optimal RSNA signal with clear pulse synchronous rhythmicity was obtained, the electrode was fixed to the nerve bundle with silicone cement (Sil-Gel 601, Wacker Chemie, Munich, Germany).

The sheath from the left cervical vagus nerve was removed, and a strand containing ~25% of the total fibers was placed on a bipolar platinum electrode, fixed with silicone cement, and cut centrally. A screening procedure previously employed to identify filaments containing afferent fibers (including single units) linked to cardiac receptors was used (8). This involved identifying filaments in which the recorded activity increased during a phenylephrine-induced rise in intracardiac pressure. The remaining fibers from the left and right vagus nerves remained intact. The afferent vagal nerve activity (AVNA) signal was evaluated by its respiratory synchronous discharge and its marked increase in response to 2-methylserotonin (50 µg/kg iv) (14).

The nerve signals were amplified ×20,000 and filtered (30 Hz low and 3,000 Hz high) with Grass P511 band-pass amplifiers. The amplified and filtered signals were displayed on a oscilloscope (Tektronix 5113), an audio monitor (model AM 8, Grass), and a polygraph (model 7P3, Grass) at time constants of 20 ms.

After completion of surgery, arterial baroreceptor denervation was verified by complete absence of inhibition of RSNA in response to a 40-mmHg increase in MAP produced by phenylephrine (3 µg/kg iv). Inhibition of RSNA due to afferent vagal nerve stimulation was again tested with 2-methylserotonin (50 µg/kg iv). This produced a transient increase in AVNA of 70–150% and a decrease in RSNA of 70–100% accompanied by a decrease in MAP and HR.

The experimental protocol consisted of a 45-min postsurgical equilibration period, after which continuous measurements of MAP, HR, MRAP, AVNA, and RSNA were begun and a 10-min control period was initiated. After the control period, isotonic saline was infused rapidly (12.5 ml·kg⁻¹·min⁻¹ iv) to produce an increase in MRAP of 3 mmHg within 30–60 s. Measurements were continued for a further 5-min period beyond the end of acute volume loading. Then a catheter was inserted in the right carotid artery and advanced into the left ventricle for measurement of left ventricular end-diastolic pressure (LVEDP). The rats were then killed by an intravenous overdose of methohexital. AVNA and RSNA recorded 30 min after death were subtracted from the experimental values to correct for background noise. The pleural and abdominal cavities were examined for presence of hydrothorax and ascites. The hearts were excised, drained, and weighed.

Acute intravenous isotonic saline load. Rats were anesthetized with methohexital (50 mg/kg ip) and instrumented with right jugular vein and carotid arterial catheters as well as a urinary bladder catheter. The peak MAP responses to ANG II (10 ng iv; 0.1 ml isotonic saline) were recorded. The rats were allowed to recover from anesthesia and returned to their home cages. Two days later, they were placed in individual restraining devices and received isotonic saline (0.05 ml/min iv). Sixty minutes later, during a 30-min control period, MAP and HR were measured and urine was collected. Then, a 5% body weight isotonic saline load was administered intravenously over 30 min. The experimental urine collection period encompassed the 30 min during the administration of the load and the following 120 min. The rats were reanesthetized with methohexital (25 mg/kg iv), and the right carotid artery catheter was advanced into the left ventricle for measurement of LVEDP. The rats were killed by an intravenous overdose of methohexital. The pleural and abdominal cavities were examined for presence of hydrothorax and ascites. The hearts were excised, drained, and weighed.

Urinary sodium excretion rates (U_sodium) were calculated for the control and experimental periods. In addition, the total sodium excreted during the experimental period was expressed as a percentage of the total sodium load administered.

Chronic sodium load. Rats were placed on a low-sodium diet (sodium <2 meq/kg) and tap water drinking fluid. The rats were placed in individual metabolic balance cages, and body weight, volume of tap water drinking fluid consumed, urine volume, and urine sodium concentration were measured daily. After 2 days of control measurements and while the animals continued to consume a low-sodium diet, the tap water drinking fluid was switched to 0.9% NaCl drinking fluid and experimental measurements were continued for 5 days. On the following day, they were anesthetized with methohexital (50 mg/kg ip) and instrumented with right jugular vein and carotid artery catheters. MAP and HR were recorded for 30 min. Then the peak MAP responses to ANG II (10 ng iv; 0.1 ml isotonic saline) were recorded. The right carotid artery catheter was advanced into the left ventricle for measurement of LVEDP. The rats were killed by an intravenous overdose of methohexital. The pleural and abdominal cavities were examined for presence of hydrothorax and ascites. The hearts were excised, drained, and weighed.

The amount of sodium in the food was considered negligible, so daily sodium intake was equal to drinking fluid sodium concentration times daily drinking fluid volume. In the absence of diarrhea, stool sodium was considered negligible, so daily sodium excretion was equal to daily urine sodium concentration times daily urine volume. Daily sodium
balance was equal to daily sodium intake minus daily sodium excretion. Cumulative sodium balance was equal to daily sodium balance serially added.

Analysis. Analog data (MAP, HR, MRAP, AVNA, RSNA) were recorded on videotape with a Vetter 4000 PCM recording adapter. The tape-recorded data were sampled at 1 Hz with a Data Translation DT2801 analog-to-digital converter using Labtech Notebook 7.4 software and an IBM personal computer. For evaluation of cardiac baroreflex regulation of RSNA, changes in AVNA and RSNA were expressed as percentage of their control period values. As a measure of the gain of the total cardiac baroreflex (total gain), the slope of the regression of percent change in RSNA on MRAP (%ΔRSNA/ΔmmHg MRAP) was calculated for each rat. As a measure of the gain of the afferent limb (afferent gain), the slope of the regression of percent change in AVNA on MRAP (%ΔAVNA/ΔmmHg MRAP) was calculated for each rat. As a measure of the central and efferent limb (central/efferent gain), the slope of the regression of percent change in RSNA on percent change in AVNA (%ΔRSNA/Δ% AVNA) was calculated for each rat.

Urine volume was measured gravimetrically, and urinary sodium concentration was measured with a flame photometer.

Statistical analysis (16) was performed using analysis of variance with repeated measures and Scheffe's test for comparison among means in the acute and chronic sodium loading experiments. Single comparisons in the cardiac baroreflex function experiments were performed with the unpaired t-test. The significance level was set at P < 0.05. Values are means ± SE.

RESULTS

Effects of losartan treatment. The effects of losartan treatment on basal values for body weight, MAP, HR, heart weight-to-body weight ratio, and LVEDP are shown in Table 1. Body weight was significantly greater in CHF-Veh and CHF-Los than in Sham-Veh and Sham-Los, respectively. MAP was significantly lower in Sham-Los and CHF-Los than in Sham-Veh and CHF-Veh, respectively. In CHF-Veh and CHF-Los rats, heart weight-to-body weight ratio and LVEDP were significantly higher than in Sham-Veh and Sham-Los, respectively, as reported previously (3, 4, 7, 8).

Table 1. Effects of losartan treatment on basal values in Sham-Veh, Sham-Los, CHF-Veh, and CHF-Los rats

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Body wt, g</th>
<th>MAP, mmHg</th>
<th>HR, beats/min</th>
<th>Heart weight/body weight, %</th>
<th>LVEDP, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham-Veh</td>
<td>382 ± 7</td>
<td>125 ± 4</td>
<td>375 ± 9</td>
<td>0.42 ± 0.03</td>
<td>2.9 ± 0.3</td>
</tr>
<tr>
<td>Sham-Los</td>
<td>385 ± 7</td>
<td>105 ± 3*</td>
<td>382 ± 8</td>
<td>0.41 ± 0.03</td>
<td>3.0 ± 0.3</td>
</tr>
<tr>
<td>CHF-Veh</td>
<td>415 ± 5†</td>
<td>120 ± 3</td>
<td>394 ± 9</td>
<td>0.65 ± 0.02†</td>
<td>9.2 ± 0.8†</td>
</tr>
<tr>
<td>CHF-Los</td>
<td>417 ± 6‡</td>
<td>93 ± 5*</td>
<td>415 ± 10</td>
<td>0.68 ± 0.03†</td>
<td>11.9 ± 1.1†</td>
</tr>
</tbody>
</table>

Values are means ± SE. Sham-Veh and Sham-Los, sham-operated rats treated with vehicle and losartan, respectively; CHF-Veh and CHF-Los, rats with congestive heart failure treated with vehicle and losartan, respectively; MAP, mean arterial pressure; HR, heart rate; LVEDP, left ventricular end-diastolic pressure. * P < 0.05, Sham-Los vs. Sham-Veh and CHF-Los vs. CHF-Veh; † P < 0.05, CHF-Veh vs. Sham-Veh and CHF-Los vs. Sham-Los.

Bilateral hydrothorax and ascites were found in CHF-Veh and CHF-Los but not in Sham-Veh and Sham-Los rats.

Cardiac baroreflex function. The MAP pressor response to the test dose of ANG II was 29 ± 4 and 26 ± 3 mmHg in Sham-Veh and CHF-Veh rats, respectively, and 1 ± 2 and 2 ± 3 mmHg in Sham-Los and CHF-Los rats, respectively (P < 0.001 for both).

Figure 1 shows components of the cardiac baroreflex in one Sham-Veh rat. In Fig. 1, top, in response to the acute volume loading, MRAP increased from −0 to 4.0 mmHg while simultaneously measured AVNA increased and RSNA decreased. The gains were derived from the slopes of the linear regression of each nerve activity on MRAP. In Fig. 1, bottom, the relationship between AVNA and RSNA defines the central gain, i.e., the change in RSNA in response to change in AVNA.

Mean group data on the afferent, central/afferent, and total gains of cardiac baroreflex regulation of RSNA in all groups of rats are shown in Table 2. Mean curves using these average gains and the average
increase in MRAP during acute volume loading are shown in Fig. 2. During a 3- to 4-mmHg increase in MRAP, afferent, central/efferent, and total gain were significantly lower in CHF-Veh than in Sham-Veh rats. Treatment with losartan did not affect afferent, central/efferent, or total gain in Sham (Sham-Los vs. Sham-Veh). Treatment with losartan significantly increased afferent, central/efferent, and total gain in CHF (CHF-Los vs. CHF-Veh); the increase in afferent gain (234%) was greater than the increase in central/efferent gain (158%). Losartan treatment did not normalize total or afferent gain in CHF (CHF-Los vs. Sham-Veh or Sham-Los) but did normalize central/efferent gain in CHF.

The net effect of losartan treatment in CHF was that, for a similar degree of increase in MRAP, RSNA was decreased significantly more, i.e., 3.7-fold, in CHF-Los than in CHF-Veh rats.

Acute intravenous isotonic saline load. The MAP pressor response to the test dose of ANG II was 30 ± 3 and 28 ± 3 mmHg in Sham-Veh and CHF-Veh rats, respectively, and 2 ± 3 and 2 ± 2 mmHg in Sham-Los and CHF-Los rats, respectively (P < 0.001 for both). Table 3 shows that U NaV in the control period was slightly (but not significantly) lower in CHF-Veh than in Sham-Veh. Treatment with losartan did not affect control or experimental period U NaV in Sham (Sham-Los vs. Sham-Veh). Treatment with losartan significantly increased U NaV in the experimental period in CHF (CHF-Los vs. CHF-Veh). Losartan treatment did not normalize U NaV in the experimental period in CHF (CHF-Los vs. Sham-Veh or Sham-Los). As a percentage of sodium load excreted, CHF-Veh was significantly less than Sham-Veh. Losartan treatment did not affect Sham (Sham-Veh vs. Sham-Los) but significantly improved CHF (CHF-Los vs. CHF-Veh).

Chronic sodium load. The MAP pressor response to the test dose of ANG II was 30 ± 2 and 30 ± 4 mmHg in Sham-Veh and CHF-Veh rats, respectively, and 2 ± 2 and 1 ± 3 mmHg in Sham-Los and CHF-Los rats, respectively (P < 0.001 for both). Figure 3 shows that cumulative sodium balance was significantly greater in CHF-Veh than in Sham-Veh on each day after the change from low to high dietary sodium intake. Treatment with losartan did not affect cumulative sodium balance in Sham (Sham-Los vs. Sham-Veh). Treatment with losartan significantly decreased cumulative sodium balance in CHF (CHF-Los vs. Sham-Los). Losartan treatment did not normalize cumulative sodium balance in CHF (CHF-Los vs. Sham-Veh or Sham-Los).

Table 3. Urinary sodium excretion responses to acute intravenous isotonic saline loading in Sham-Veh, Sham-Los, CHF-Veh, and CHF-Los rats

<table>
<thead>
<tr>
<th></th>
<th>Sham-Veh (n = 8)</th>
<th>Sham-Los (n = 8)</th>
<th>CHF-Veh (n = 8)</th>
<th>CHF-Los (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>U NaV, µeq/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>4.2 ± 1.1</td>
<td>4.1 ± 1.2</td>
<td>2.4 ± 0.8</td>
<td>3.0 ± 1.0</td>
</tr>
<tr>
<td>Experimental</td>
<td>20.5 ± 2.4</td>
<td>21.1 ± 2.6</td>
<td>10.5 ± 1.3*</td>
<td>15.1 ± 1.8†</td>
</tr>
<tr>
<td>%Sodium load excreted</td>
<td>78 ± 5</td>
<td>82 ± 5</td>
<td>52 ± 3*</td>
<td>65 ± 4†</td>
</tr>
</tbody>
</table>

Values are means ± SE of 9 rats in each group. U NaV, urinary sodium excretion. *P < 0.05, CHF-Veh vs. Sham-Veh; †P < 0.05, CHF-Los vs. CHF-Veh.
On the 5th day of the high dietary sodium intake, cumulative sodium retention was significantly less in CHF-Los (4.2 ± 0.4 meq) than in CHF-Veh rats (7.8 ± 1.6 meq, P < 0.05). Both values are significantly greater than 1.80 ± 0.10 meq in Sham-Veh and 1.78 ± 0.09 meq in Sham-Los.

**DISCUSSION**

This study demonstrates that treatment of CHF rats with losartan significantly improves cardiac baroreflex regulation of RSNA and facilitates suppression of RSNA during volume expansion. This improvement in cardiac baroreflex suppression of RSNA was associated with an improved ability of the kidney to excrete acute and chronic sodium loads.

Losartan treatment improved afferent and central/efferent gain of the cardiac baroreflex regulation of RSNA in sinoaortic-denervated CHF rats. Previous studies identified a defect at the level of the peripheral cardiac baroreceptor in CHF wherein increases in cardiac filling pressure elicit increases in AVNA that are less than those observed in control animals without CHF (8, 17). This could be related to alterations in the mechanical properties of the cardiac chamber wall or their coupling to the nerve terminal or to the nerve terminal itself (12, 17). The increased levels of ANG II in CHF are thought to contribute to the structural cardiac remodeling that occurs in CHF (2). This cardiac structural remodeling may include alterations in distensibility and wall stress, with desensitization of the cardiac baroreceptor. AT1 receptor antagonist treatment, like angiotensin-converting enzyme inhibitor therapy, is capable of favorably affecting the cardiac structural remodeling in CHF (2), which may lead to improvement in cardiac baroreceptor sensitivity.

During chronic systemic administration, losartan is known to cross the blood-brain barrier (13). In addition, losartan has access to the circumventricular organs (e.g., area postrema), areas that are not completely shielded by the blood-brain barrier because of their fenestrated capillaries, which contain substantial concentrations of AT1 receptors (15) and have neural connections that participate in cardiac baroreflex regulation of RSNA (10). In previous studies of arterial baroreflex regulation of RSNA in CHF (4), the beneficial effect of losartan was observed with an intracerebroventricular dose of losartan that was 0.1% of the intravenous dose. Therefore, it is likely that chronic losartan treatment acts centrally to improve the central/efferent gain of the cardiac baroreflex regulation of RSNA.

The combined effects of improved afferent and central/efferent gain of cardiac baroreflex regulation of RSNA resulted in a nearly fourfold increase in the total gain. At every level of increase in MRAP, RSNA was nearly fourfold lower in CHF-Los than in CHF-Veh (Fig. 2). Losartan treatment increased the magnitude of renal sympathoinhibition during volume expansion. As previously demonstrated (6), the extent of renal sympathoinhibition that occurs during volume expansion is an important contributor to the associated natriuretic response, with a greater absolute decrease in RSNA during volume expansion being associated with a larger natriuretic response than a smaller absolute decrease in RSNA. Prior renal denervation, preventing the renal sympathoinhibition during the volume expansion, attenuated the natriuretic response to volume expansion in proportion to the magnitude of the renal sympathoinhibition. Thus it was postulated that losartan's effect to enhance the renal sympathoinhibitory response to volume expansion in CHF would be associated with an enhanced ability to excrete acute and chronic sodium loads. In CHF rats treated with losartan, the natriuretic response to an acute intravenous isotonic saline load was enhanced and the magnitude of the cumulative sodium retention during transition from a low to high dietary sodium intake was attenuated compared with CHF rats treated with vehicle.

We attempted to differentiate how much of the beneficial effect of losartan on renal sodium handling was due to its action to enhance cardiac baroreflex inhibition of RSNA with a decreased antinatriuretic effect of RSNA vs. its action to oppose the antinatriuretic actions of ANG II on the kidney. From our previous study (6), it can be calculated that a 10% decrease in RSNA was associated with a 15.8 μeq/min increase in UNaV. From the values for total gain obtained in this study, the decrease in RSNA that would occur with a 3-mmHg increase in MRAP, as produced by volume loading, may be calculated. Losartan treatment resulted in a 9.2% greater reduction in RSNA (CHF-Los vs. CHF-Veh). This could account for a 14.5 μeq/min increase in the UNaV response to volume loading. Losartan treatment resulted in a 4.0 μeq/min increase in the UNaV response to volume loading (CHF-Los vs. CHF-Veh). Thus the greater reduction in RSNA during volume loading is sufficient to account for the increased natriuretic response observed during losartan treatment (CHF-Los vs. CHF-Veh).
In Sham, losartan treatment (Sham-Los vs. Sham-Veh) decreased basal MAP but did not affect cardiac baroreflex regulation of RSNA or the ability of the kidney to excrete acute or chronic sodium loads. These results suggest that the level of activity of the renin-angiotensin system in normal rats consuming a normal sodium diet contributes to basal MAP (likely via circulating ANG II) but does not seem to influence cardiac baroreflex regulation of RSNA (likely via central nervous system ANG II). Comparison of the effects of systemic with central nervous system administration of losartan, as employed previously (4), may clarify this. Inasmuch as losartan treatment did not alter cardiac baroreflex regulation of RSNA, its contribution to the ability of the kidney to excrete acute or chronic sodium loads was not anticipated (and not found) to be affected.

The studies of acute intravenous isotonic saline loading and chronic sodium loading were performed in conscious rats. The studies examining cardiac baroreflex regulation of RSNA involved simultaneous recordings of afferent vagal and efferent RSNA portions of the reflex arc were performed in anesthetized rats, inasmuch as such measurements are not possible in conscious rats. Alphadoline-alphaxalone acetate was chosen, inasmuch as it has been reported that reflex neurohormonal control of the circulation is well maintained in rats with this anesthetic (9).

In summary, losartan treatment of rats with CHF improves cardiac baroreflex regulation of RSNA. This results in enhanced suppression of RSNA during volume loading, which is associated with improved ability of the kidney to excrete acute and chronic sodium loads.

Perspectives

In CHF, where ANG II concentrations are increased, blockade of the effects of ANG II on AT_{1} receptors on the renal vasculature with increased renal blood flow and glomerular filtration rate, on the renal tubule with decreased renal tubular sodium reabsorption, and on the renal sympathetic nerve terminal with diminished norepinephrine release can contribute to an increased ability of the kidney to excrete sodium. However, an additional factor contributing to the increased ability of the kidney to excrete sodium is blockade of the effects of ANG II on AT_{1} receptors possibly located in cardiac chamber walls as well as in discrete central nervous system areas, which improves cardiac baroreflex regulation of RSNA, facilitates renal sympathoinhibition during volume loading, and enhances the ability of the kidney to excrete acute and chronic sodium loads.

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