Sodium Intake, Angiotensin II Receptor Blockade, and Baroreflex Function in Conscious Rats

Ling Xu, Virginia L. Brooks

Abstract The hypothesis that endogenous angiotensin II (Ang II) chronically supports baroreflex control of lumbar sympathetic nerve activity (LSNA) and heart rate (HR) via AT1 but not AT2 receptors was tested in conscious, normotensive rats fed either a sodium deficient diet (LS) to increase circulating Ang II or a high-sodium diet (HS) for 2 to 3 weeks. One to two days after surgery to implant catheters and nerve electrodes, baroreflex curves were produced before and 40 minutes after intravenous administration of the AT1 antagonist losartan (10 mg/kg) or the AT2 antagonist PD123319 (500 µg/kg+50 µg kg⁻¹ min⁻¹). Mean arterial pressure (MAP) after losartan was maintained at basal levels with methoxamine. Forty minutes after losartan in LS rats, LSNA (46±2 to 22±1% max) and HR (414±7 to 387±8 bpm) were decreased (P<05). Losartan decreased reflex control of LSNA more in LS than in HS rats (P<05), as indicated by reductions in maximum LSNA (98±2 to 78±3% max) and minimum LSNA (42±5 to 21±5% max). Losartan also shifted reflex control of LSNA to a lower pressure in both groups, but the effect was larger in LS rats (-21±3 [LS] versus -9±2 [HS] mm Hg at basal LSNA, P<05). Maximum gain was unaltered in either group. Similarly, losartan reduced maximum HR (534±2 to 495±9 bpm) and shifted the HR curve leftward (114±5 to 105±4 mm Hg) in LS but not in HS rats. In general, no changes were observed in MAP or baroreflex control of LSNA and HR after PD123319 in LS rats. These results suggest that in conscious, normotensive LS rats, endogenous Ang II supports LSNA and HR over a wide MAP range via AT1 but not AT2 receptors (Hypertension. 1997;29[part 2]:450-457.)

Key Words • losartan • PD123319 • baroreflex • sodium-deprived rats • lumbar sympathetic nerve activity • heart rate • AT1 • AT2

Artinal baroreceptor reflex function is impaired in established human hypertension and in experimental hypertension, as exemplified by a resetting of the baroreceptor to a higher pressure level and a decrease in baroreflex gain. In some types of hypertension, elevated plasma Ang II coexists with elevated plasma norepinephrine levels. Blockade of the renin-angiotensin system lowers blood pressure and shifts the baroreflex control of HR and sympathetic activity toward the normotensive range. Moreover, there are reports that Ang II blockade enhances baroreflex function in hypertensive subjects by increasing reflex gain. These results are consistent with a role for Ang II in the alteration of the baroreflex during hypertension, but whether Ang II contributes to baroreflex function in the normotensive state is not clear.

It is well established that chronic and acute blockade of Ang II lowers blood pressure in normotensive animals with elevated Ang II levels due to low sodium intake. Moreover, renal and lumbar sympathetic activity are reduced in sodium-deprived rats following acute blockade of AT1 receptors, when the hypotensive effect of Ang II blockade is reversed by infusion of α-adrenergic agonists. These findings indirectly suggest that the profound hypotension following Ang II blockade is due in part to an attenuation of reflex increases in sympathetic activity. However, whether Ang II blockade alters reflex control of sympathetic activity during sodium depletion has not been investigated. Blockade of the renin-angiotensin system shifts reflex control of HR and plasma vasopressin or adrenocorticotropic hormone levels to a lower pressure level. Therefore, the present experiments tested the hypothesis that acute blockade of Ang II receptors shifts baroreflex control of LSNA to a lower blood pressure level in LS-intake rats.

It has become increasingly apparent that Ang II and other Ang-related peptides can bind to at least two types of binding sites. The AT1 receptor mediates most of the cardiovascular actions of Ang II. Blockade of AT1 receptors with losartan decreases sympathetic activity relative to arterial pressure, suggesting that losartan would shift baroreflex control of sympathetic activity to a lower pressure level in sodium-deprived animals. This hypothesis was tested in the present study by comparing the effects of losartan in conscious rats on either an HS or LS diet. On the other hand, there is little evidence that circulating Ang II significantly alters cardiovascular function via AT2 receptors. Indeed, Ang II receptors in circumventricular organs, presumed major sites of action of chronic increases in Ang II, do not exhibit AT2 binding. Nevertheless, a recent study suggests that prolonged elevation of plasma Ang II may increase effects of Ang II mediated by the AT2 receptor. Because sodium deprivation is a state of chronically elevated plasma Ang II levels, it was also determined whether blockade of AT2 receptors alters blood pressure and baroreflex curves in LS-intake rats.
**Methods**

Eighteen male, Sprague-Dawley rats (Simonsen Lab, Gilroy, Calif) were used in this study. At 8 weeks of age (weight, 240 to 292 g), rats were placed on one of two diets (Harlan Teklad). Sodium-deficient (LS, NaCl=0.02%) or HS (NaCl=8%) rat chow. On the first 2 days on diet, rats in the LS group received a furosemide injection (1 mg kg\(^{-1}\) d\(^{-1}\) IP, Abbott Labs), while rats in the HS group received the 5% dextrose (D5W) vehicle (1 mL/kg IP). Rats were maintained on diet for 2 to 3 weeks before surgery for catheterization and nerve electrode implantation. All rats were housed in a room maintained on a 12 hour/12 hour light/dark cycle and were allowed to have food and distilled water ad libitum.

**Surgical Procedures**

Rats (weight, 272 to 352 g) were anesthetized initially with Brevetrol sodium (100 mg/kg in D5W IP in two injections over 5 minutes, Eli Lilly). After a venous catheter was inserted, anesthesia was maintained by Brevetrol infusion as needed (2.7 to 4 µL/min, 10 mL/mL D5W, IV). Two Tygon catheters (Norton Performance Plastics) were inserted into the right jugular vein and two into the left femoral vein for drug delivery. Finally, a catheter was advanced into the abdominal aorta via a femoral artery for the measurement of MAP and HR.

For the lumbar nerve electrode implantation, a midline abdominal incision was made. After retracting the intestines, the abdominal aorta and vena cava were gently pulled aside to expose the lumbar nerve. The nerve was then dissected free and placed on a bipolar electrode hook. The electrode was constructed with polytetrafluoroethylene-coated, three-stranded stainless steel wire (A&M Systems, No 7934) and was encased within silicone tubing (0.02×0.037", Specialty Manufacturing). When optimal nerve traffic was confirmed on an oscilloscope (model 2212, Tektronix), the nerve and electrode were placed in an abdominal aorta via a femoral artery for the measurement of MAP and HR.

Catheters and the electrode lead were tunneled subcutaneously to the back of the neck and exteriorized, and all incisions were closed with silk suture. The rats were returned to their home cage and allowed 20 to 40 hours recovery. Experiments were performed while rats remained in their home cage.

**Hemodynamic and Nerve Activity Recordings**

MAP was monitored via the femoral arterial catheter connected to a Statham pressure transducer and a Grass preamplifier (7P1). HR was measured using a Grass tachograph (7P4) triggered by the amplified arterial blood pressure pulse. The raw lumbar nerve activity was amplified using a Grass differential preamplifier (P511) with a band-pass filter of 30 Hz to 10 kHz. The gain (25000 to 70000×) of the preamplifier was adjusted so that the output of maximal nerve activity amplitude did not exceed the linear input range (±1.5 Vpeak-peak) of the Grass integrator (7P10), which was used for integrating raw nerve activity. The amplified nerve traffic was observed on the storage oscilloscope and was whole-wave rectified and integrated with a reset time of 1 second. Together with MAP and HR, integrated LSNA was recorded on chart paper using a Grass polygraph (7D) (Fig 1). Nerve activity was first quantified by averaging the integrated activity just before reset over 12 seconds (12 peaks) during stable and quasi-stable periods (slow or no change in measured parameters), or 3 to 4 sec (3 to 4 peaks) during transient periods (e.g., baroreflex curve). In addition, the noise level was quantified at the end of the experiment by averaging the integrated output over 12 seconds after efferent nerve activity was eliminated by combined use of a bolus injection of hexamethonium chloride (30 mg/kg in D5W, Sigma), a ganglionic blocker, and infusion of MET (Sigma). The noise output was then subtracted from average integrated nerve activity to yield a measure of net LSNA. In these experiments, the signal-to-noise ratio of basal nerve activity averaged 3.1 (range, 2.1 to 4.1). For each animal, LSNA was normalized to basal nerve activity in the control period and was expressed as %con. Basal nerve activity was defined as the average of resting activity at two time points 10 minutes before the first baroreflex curve was generated. Second, LSNA was normalized to the maximum nerve activity during the control period and was expressed as % max. Maximum LSNA was the peak LSNA in the baroreflex curves induced by NP infusion during the control period.

**Baroreceptor Reflex Curves**

Arterial pressure was varied by a slow infusion of either PE or NP (both from Elkins-Sinn) Increasing doses of PE were infused (0.68 to 27 µL/min, 1 mg/mL D5W, IV) to increase MAP up to 175 to 180 mm Hg, while increasing doses of NP were infused (1.35 to 68 µL/min, 1 mg/mL D5W, IV) to decrease MAP to <50 mm Hg (Fig 1). The ramp increase or decrease of MAP was completed in ≈2 minutes. Infusions of PE or NP were performed randomly MAP, LSNA, and HR were allowed to return to baseline (≈30 minutes) before a subsequent ramp of MAP was made.

**Protocols**

**Protocol 1**

This study tested the hypothesis that acute systemic blockade of the AT1 receptor with losartan shifts baroreflex control of LSNA and HR to a lower arterial pressure level and that the shift is greater in LS rats than in HS rats. After basal parameters were obtained and baroreflex control of HR and LSNA was studied during the control period, losartan was injected (10 mg/kg in 200 µL D5W, IV) generously provided by Dr Ronald D Smith, BPJ.
DuPont Merck Pharmaceutical, Wilmington, Del) in both LS (n=7) and HS (n=5) rats. Immediately afterward, IV infusion of MET (5 to 33 μg/min in DSW) was begun to prevent MAP from dropping. MAP, HR, and LSNA were monitored for at least 40 minutes following losartan administration, because previous studies \(^1\) indicated that it takes at least 40 minutes for the depressor effect of losartan to stabilize. After this, the postlosartan pressor response to Ang II bolus (100 μg/kg IV) was tested after losartan was maintained at levels not different from basal levels. In one HS rat, the HR tracing was not adequate because of a small blood pressure pulse that failed to trigger the tachograph. Thus, the HR results are presented for only four of five HS rats.

### Protocol 2

This experiment determined if acute systemic blockade of the AT\(_2\) receptor alters MAP or baroreflex control of LSNA and HR. Experiments were conducted only in LS rats with chronically elevated plasma Ang II levels (n=6). Procedures were the same as in Protocol 1, except that the AT\(_2\) receptor antagonist PD123319 (gift of Dr Joan A Keiser, Parke-Davis, Ann Arbor, Mich), was given instead of losartan. A dose (500 μg/kg prime + 50 μg kg\(^{-1}\) min\(^{-1}\), 10 μL/min, IV) was chosen that is within a range which has proved effective in previous studies.\(^2\)\(^-\)\(^2^3\) No manipulation was applied to maintain MAP, since PD123319 did not affect MAP. The pressor responses to Ang II before (20±5 mm Hg) and after (31±6 mm Hg) PD123319 administration were not different. LSNA was lost before the experiment in two of the six LS rats. The HR tracing of three rats was not acceptable during baroreflex curve generation at high MAP.

### Data Analysis and Statistics

A logistic relation, slightly modified from Kent et al,\(^2\) was used to analyze baroreflex curves: \(Y = d + (a-d)(1+ \exp(b(X-c)))\), where \(X\) is MAP, \(Y\) is LSNA or HR, \(a\) is the maximum of LSNA or HR, \(b\) is the slope coefficient, \(c\) is MAP at the midpoint of the range of LSNA or HR, and \(d\) is the minimum of LSNA or HR. In each animal, raw data of MAP and LSNA (or HR) were fit to the logistic function to generate parameters \(a\), \(b\), \(c\), and \(d\), using graphing software (Sigmaplot, Jandel Scientific). Constraints of maximum and minimum LSNA (or HR) were set for the fitting process and were determined in each experiment when the high (or low) plateau of LSNA and HR was reached while MAP was still decreasing by NP infusion (or increasing by PE infusion). The range of the baroreflex curve, \(c\), was defined as \(a-d\), and the maximum gain of the baroreflex curve as \(-b/\)\(b\)\(^2\)\(^-\)\(^1\)\(^.\)\(^1\) Mean ± SEM values of individual curve-fit parameters were calculated, and statistical analysis was performed to determine within and between group differences in parameters (Tables 1, 2, and 3). The averaged \(a\), \(b\), \(c\), and \(d\) were then used to generate averaged baroreflex curves (Figs 4 and 6).

In addition, the MAP, LSNA (% max), and HR data of all rats in each diet group were pooled by calculating the mean and SEM of all data points collected within 5−10 mm Hg increments of MAP. Multiple points within the same MAP range in each animal were averaged before pooling. The means of pooled data were plotted with SEM of LSNA (or HR) and then fit to the logistic function (Figs 3, 5, and 8).

All data are presented as mean±SEM. Data were analyzed using two-way or one-way ANOVA repeated one way (time or drug administration) and the post hoc Newman-Keuls test.\(^2\)\(^4\) All analyses were performed using GR-STAT software (Dynamic Microsystems, Inc). A significance level of \(P<0.05\) was accepted.

### Results

#### AT1 Receptor Blockade

**Time Course of Changes in LSNA and HR**

As shown in Fig 2, basal HR and LSNA were not different between LS and HS groups, although basal MAP was lower in LS rats than in HS rats (\(P<0.05\)). MAP during the first 10 minutes after losartan decreased slightly due to the time needed to adjust the infusion speed of MET, but was maintained at levels not different from basal levels thereafter in each group. Losartan reduced both LSNA and HR in LS rats (\(P<0.05\)), but this effect took time to be developed. LSNA decreased beginning 20 minutes after losartan (\(P<0.01\)), reaching 22±1% max at 40 minutes. The reduction in HR was significant (\(P<0.05\)) only at 40 minutes after losartan. In contrast, no significant changes in LSNA or HR were observed in HS rats after losartan.

#### Baroreflex Control of LSNA

Losartan reduced LSNA at a given MAP more in LS than in HS rats (Figs 3 and 4; Table 1), as indicated by significant differences in several logistic parameters. First, losartan decreased the maximum LSNA in LS rats (\(P<0.01\)) but not in HS rats. This difference was observed.

### Table 1. Effects of Losartan on Baroreflex Control of LSNA in LS and HS Rats

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control LS (n=7)</th>
<th>Losartan LS</th>
<th>Control HS (n=5)</th>
<th>Losartan HS</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSNA (% max)</td>
<td>224±21</td>
<td>179±20</td>
<td>268±36</td>
<td>265±39</td>
</tr>
<tr>
<td>Slope coefficient</td>
<td>0.11±0.008</td>
<td>0.15±0.045</td>
<td>0.09±0.010</td>
<td>0.093±0.010</td>
</tr>
<tr>
<td>MAP (μg/min)</td>
<td>102±3</td>
<td>90±3</td>
<td>101±3</td>
<td>94±3</td>
</tr>
<tr>
<td>Minimum LSNA (%)</td>
<td>42±5</td>
<td>21±5</td>
<td>43±7</td>
<td>34±7</td>
</tr>
<tr>
<td>Range</td>
<td>18±2±3</td>
<td>15±17±4</td>
<td>225±34</td>
<td>232±45</td>
</tr>
<tr>
<td>Maximum gain</td>
<td>-5.05±0.78</td>
<td>-5.55±1.29</td>
<td>-5.62±1.20</td>
<td>-5.55±1.23</td>
</tr>
<tr>
<td>MAP (μm Hg)</td>
<td>98±2</td>
<td>73±3</td>
<td>100±0</td>
<td>98±3</td>
</tr>
<tr>
<td>Slope coefficient</td>
<td>0.11±0.008</td>
<td>0.15±0.045</td>
<td>0.098±0.010</td>
<td>0.093±0.010</td>
</tr>
<tr>
<td>MAP (μg/min)</td>
<td>102±3</td>
<td>90±3</td>
<td>101±3</td>
<td>94±3</td>
</tr>
<tr>
<td>Minimum LSNA (%)</td>
<td>19±3</td>
<td>9±2</td>
<td>17±3</td>
<td>15±4</td>
</tr>
<tr>
<td>Range</td>
<td>79±3</td>
<td>74±14</td>
<td>99±4</td>
<td>8±7</td>
</tr>
<tr>
<td>Maximum gain</td>
<td>-2.18±0.22</td>
<td>-2.50±0.67</td>
<td>-2.04±0.26</td>
<td>-1.98±0.31</td>
</tr>
</tbody>
</table>

Values are mean±SEM.

*\(P<0.05\) vs control in the same diet group.

+ \(P<0.05\) LS vs HS during control period.

+ \(P<0.05\) LS vs HS during losartan period.
FIG 2. Time course of changes in LSNA and HR after losartan administration, while MAP was maintained at levels of basal MAP with MET infusion in LS- (n=7) and HS-intake rats (n=5). *Significant difference compared with basal values in either diet group (P<0.05) #Significant difference at the same time points between LS and HS rats (P<0.05)

whether LSNA was normalized to the maximum (Fig 3, Table 1) or basal LSNA (Fig 4; Table 1). Second, losartan reduced minimum LSNA in LS rats (P<0.05) but not in HS rats (Fig 4, Table 1). Finally, losartan decreased the extrapolated LSNA at basal MAP (LS, 109±2 mm Hg; HS, 111±1 mm Hg) in LS (46±5 to 18±3% max, P<0.01) but not in HS rats (40±3 to 30±5% max).

Baroreflex control of LSNA was shifted leftward by losartan in both groups, and the shift was greater in LS rats (Figs 3 and 4, Table 1). The MAP at midrange of the curve (MAP_md) was reduced (P<0.01) in both groups (Table 1), but the difference in the MAP_md shift between LS (−12±2 mm Hg) and HS rats (−7±1 mm Hg) was not significant (P=0.06). However, because the logistic parameter MAP_md may be altered by the decreased maximum of LSNA in LS rats after losartan (Table 1), comparing MAP_md shift between the LS and HS groups may not reflect a true difference in the shift of baroreflex curve caused by losartan. Therefore, values of MAP at 100% con LSNA (MAP_100), extrapolated from the fitted baroreflex curves (Fig 4), were compared. In the control period, MAP_100 was not different (LS, 109±3 mm Hg versus HS, 112±2 mm Hg; Fig 4). After losartan, MAP_100 was reduced (P<0.05) in both groups, but the reduction was greater in LS rats (−21±3 mm Hg) than in HS rats (−9±2 mm Hg) (P=0.01), indicating baroreflex control of LSNA was shifted leftward more in LS rats than in HS rats.

FIG 3. Effect of losartan on baroreflex control of LSNA (% baroreflex maximum) in LS- (n=7) and HS-intake rats (n=5).

Baroreflex Control of HR

Losartan altered baroreflex control of HR in LS rats but not in HS rats (Figs 5 and 6). After losartan administration in LS rats (n=7), the maximum, range, and MAP_md as well as the maximum gain were all reduced (P<0.05), although the slope coefficient and minimum of the baroreflex curve did not change (Table 2). In contrast, losartan did not significantly alter any of the parameters in HS rats (Table 2).

FIG 4. Effects of sodium intake and losartan on baroreflex control of LSNA (% control) in LS- (n=7) and HS-intake rats (n=5).

100% con LSNA

MAP (mm Hg)

Control (LS)

Losartan (LS)

Control (HS)

Losartan (HS)
The maximum HR during the control period was higher in LS rats than in HS rats (Table 2, Fig 6; \( P<.01 \)). After losartan, maximum HR in LS rats was reduced to a level that was not significantly different from the maximum HR in HS rats before or after losartan (Table 2, Fig 6).

**Discussion**

Salt intake can change on almost a daily basis in animals. Subsequent salt imbalance could lead to potentially serious consequences, including threats to the constancy of the extracellular fluid volume and therefore blood pressure. However, powerful homeostatic mechanisms exist that act to maintain day-to-day levels of arterial pressure in the face of a constantly changing sodium balance. One such mechanism involves the sympathetic nervous system. It has been proposed\(^2\) that chronic decreases in sodium balance and/or extracellular fluid volume increase circulating levels of Ang II, which in turn support elevated levels of sympathetic activity. The increases in sympathetic activity, in concert with other homeostatic mechanisms, act to maintain arterial pressure despite decreases in volume.

Consistent with this idea, a previous study showed that losartan decreases renal and lumbar sympathetic activity in sodium-deprived rats, but only if the hypotensive effect of Ang II blockade is reversed.\(^12\) Importantly, losartan had no effect in rats on a high-salt diet and produced only a small decrease in nerve activity in rats on a normal salt diet, suggesting a role for a sympathetic nervous system-angiotensin interaction in sodium balance homeostasis.\(^12\)

The present study sought to extend these results by deter-
The important new findings are (1) losartan suppresses LSNA and HR in LS rats when blood pressure is not allowed to decrease significantly, and the suppression takes a slow time course; (2) losartan shifts reflex control of LSNA to the left more in LS rats than in HS rats without affecting maximum gain, effectively decreasing LSNA at any given blood pressure; (3) losartan shifts baroreflex control of HR to a lower blood pressure and decreases maximum HR in LS rats only; and (4) PD123319 is generally without effect on resting parameters or baroreflex control of LSNA and HR in LS rats. These findings support the conclusion that endogenous Ang II increases LSNA and HR over a wide range of MAP in LS rats through AT1 but not AT2 receptors.

It is likely that the suppression of LSNA and HR after losartan in LS rats is due to blockade of AT1 receptors rather than other nonspecific effects. One potential problem is that Ang II blockade often decreases arterial pressure, which could produce acute pressure-dependent baroreflex resetting. However, a key feature of the present study is that MAP was clamped at basal levels after losartan with MET infusion. Second, a direct effect of MET to decrease LSNA and HR independent of effects on pressure is unlikely, since in our previous study nerve activity and HR were suppressed after losartan regardless of whether MAP was maintained at basal levels with either MET or PE. Moreover, adrenergic agonists decrease sympathetic activity by increasing pressure to activate baroreceptor afferents. In the present study, MET was used to maintain pressure, not increase it. Third, the sympathomimetic was not due to activation of cardiopulmonary baroreceptors, since neither losartan or losartan plus MET significantly affects central venous pressure.

In LS rats, losartan decreased sympathetic activity over the entire pressure range of the baroreflex, suggesting that Ang II is critical for maintenance of sympathetic activity and its baroreflex regulation during decreases in salt intake. Blockade of the renin-angiotensin system also shifts baroreflex control of sympathetic activity in other pathophysiological states such as hypertension, congestive heart failure, and birth. Thus, it is becoming increasingly apparent that Ang II is a major participant in long-term control of the sympathetic nervous system in both hypertensive and normotensive states.

While the present study clearly demonstrates that losartan decreases sympathetic activity in LS rats, it is not clear if it is blocking an effect of Ang II to maintain normal nerve activity or to increase nerve activity above normal. The uncertainty lies in the difficulty in quantifying long-term changes in sympathetic activity. Nevertheless, present and previous results suggest that Ang II may increase sympathetic activity above normal during sodium deprivation. In the present study, maximum reflex-induced LSNA before losartan was lower in LS than in HS rats when nerve activity was expressed as % of control, in agreement with a previous report. This result could be explained by an effect of sodium deprivation to decrease maximal reflex activity or to increase basal activity. The

### Table 3: Effects of PD123319 on Baroreflex Control of LSNA and HR in LS Rats

<table>
<thead>
<tr>
<th></th>
<th>LSNA (%con) (n=4)</th>
<th>LSNA (% max) (n=4)</th>
<th>HR (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>PD123319</td>
<td>Control</td>
</tr>
<tr>
<td>Maximum</td>
<td>177±16</td>
<td>162±15</td>
<td>100±1</td>
</tr>
<tr>
<td>Slope coefficient</td>
<td>0.078±0.005</td>
<td>0.075±0.008</td>
<td>0.078±0.005</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>116±4</td>
<td>106±2</td>
<td>116±4</td>
</tr>
<tr>
<td>Minimum</td>
<td>23±9</td>
<td>30±9</td>
<td>15±6</td>
</tr>
<tr>
<td>Range</td>
<td>154±24</td>
<td>100±24</td>
<td>96±6</td>
</tr>
<tr>
<td>Maximum gain</td>
<td>-2.97±0.46</td>
<td>-2.41±0.30</td>
<td>-1.65±0.13</td>
</tr>
</tbody>
</table>

Values are mean±SEM of baroreflex logistic parameters
*P< 0.05, PD123319 vs control
latter possibility is supported by several lines of evidence. First, in the present study maximum reflex-induced increases in HR, for which absolute values can be obtained, were higher in LS rats. Second, a number of studies indirectly assessing the degree of activation of the sympathetic nervous system through measurements of circulating catecholamines, norepinephrine turnover, absolute nerve activity, or levels of the rate-limiting enzyme involved in catecholamine production, tyrosine hydroxylase, conclude that sympathetic activity is increased during sodium deprivation. Finally, other pathophysiological states associated with decreases in effective arterial blood volume, such as congestive heart failure, also appear to exhibit increased sympathetic activity.

Collectively, these data suggest that sodium deprivation, presumably by decreasing extracellular fluid volume, increases renin and Ang II levels. The increased Ang II then chronically supports elevated sympathetic outflow and the position of the baroreflex curve, which will tend to help maintain arterial pressure at normal levels by increasing peripheral resistance and promoting fluid retention despite volume depletion.

Ang II could also participate in the regulation of baroreflex function during decreases in salt intake by decreasing reflex gain. However, neither changes in salt intake or losartan administration altered LSNA baroreflex gain. The lack of effect of salt intake on gain has been observed by others, but the lack of effect of losartan on gain is in conflict with reports that Ang II blockade increases baroreflex sensitivity in animals with hypertension and congestive heart failure. While the explanation for this difference is not known, it is not surprising from a physiological point of view that baroreflex sensitivity is regulated differently in hypertensive versus normotensive rats.

Baroreflex control of HR was also decreased by losartan in LS rats. This result is in agreement with previous work and suggests that Ang II increases activity of a number of baroreceptor reflex effectors.

The site of action of losartan was not investigated, but the brain is the most plausible candidate given the wide range of baroreceptor effectors affected by Ang II blockade in sodium-deprived animals. Since losartan can penetrate the BBB, it is possible that losartan suppresses sympathetic nerve activity by blockade of AT1 receptors beyond the BBB in the brain or by blockade of receptors in circumventricular organs lacking this barrier, such as the area postrema or subfornical organ. Because losartan takes a slow time course in decreasing MAP, renin, and HR, it is tempting to speculate that Ang II acts in part at a site behind the BBB. However, losartan also slowly reverses the hypertension produced by intravenous Ang II infusion. This finding suggests that at least a component of the effect of losartan is via blockade of circulating Ang II binding in circumventricular organs.

Baroreflex control of LSNA in HS rats was also shifted slightly after losartan to a lower blood pressure level, although this effect was smaller than that in LS rats. However, experiments were performed 1 to 2 days after surgery, which attenuates eating and drinking behavior. The subsequent volume depletion may offset the effect of chronic HS diet on the suppression of the renin-angiotensin system. In previous experiments in HS rats, which were performed 2 to 5 hours after surgery, losartan did not affect MAP, LSNA, or HR.

While abundant research has documented that neither acute or chronic AT2 receptor blockade significantly alters blood pressure, a few reports suggest that under some circumstances AT2 receptor effects may be revealed. For example, chronic increase in exogenous Ang II in combination with AT2 receptor blockade increases arterial pressure and vessel density more than Ang II alone. AT2 effects on the cerebral vasculature have also been reported. However, the specific AT2 antagonist PD 123319 failed to alter arterial pressure or baroreflex function during sodium depletion in sharp contrast to the effects of AT1 blockade. This finding reaffirms the dominance of AT1 over AT2 cardiovascular effects. The results are also consistent with a previous study that AT2 blockade does not alter arterial pressure or baroreflex control of sympathetic activity in spontaneously hypertensive rats.

In conclusion, endogenous Ang II chronically supports LSNA and HR over a wide range of MAP through AT1 but not AT2 receptors in conscious normotensive LS rats. During sodium deprivation, the position or the set point of baroreflex control of LSNA and HR, but not the gain, depends in part on the chronically elevated endogenous Ang II levels.

Acknowledgments

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