Modification of Pressure Natriuresis by Long-term Losartan in Spontaneously Hypertensive Rats

Robert L. Kline, Fan Liu

Abstract  The goal of this study was to determine how long-term treatment of spontaneously hypertensive rats with losartan affects the pressure-natriuresis curve. Rats were treated with losartan (12 to 15 mg · kg⁻¹ · d⁻¹ in drinking water) starting at 4 to 5 weeks of age. At 8 to 9 weeks of age, pressure natriuresis was studied in treated and untreated anesthetized rats using a preparation involving volume expansion and fixed neural and hormonal influences on the kidney. In some untreated rats, losartan (10 or 30 mg · kg⁻¹ IV) was given acutely. Average initial mean arterial pressure (±SEM) for untreated rats was 164±2 mm Hg (n=13) and 131±3 mm Hg (n=13) for rats treated chronically with losartan (P<.01). Short-term losartan did not alter arterial pressure significantly. Glomerular filtration rate was not altered significantly by losartan, and renal blood flow was increased modestly by long- and short-term (10 mg · kg⁻¹) losartan at several levels of renal artery pressure. At renal artery pressures of 130 to 175 mm Hg, there were no significant differences between untreated and short-term losartan rats for urine flow, total and fractional sodium excretions, and renal interstitial hydrostatic pressure. The relation between renal artery pressure and urine flow, sodium excretion, or fractional sodium excretion was shifted to the left by long-term losartan treatment. At identical renal artery pressures, renal interstitial hydrostatic pressure was not significantly different among losartan-treated (short or long term) and respective control groups. The data indicate that long-term treatment of spontaneously hypertensive rats with losartan shifts the pressure-natriuresis curve to the left. The mechanism involves a net decrease in tubular reabsorption of sodium.

Key Words  • blood flow  • glomerular filtration rate  • blood pressure  • sodium  • angiotensin II

The role of the renin-angiotensin system in the development and maintenance of hypertension in spontaneously hypertensive rats (SHR) is not well understood; however, antagonism of the renin-angiotensin system is clearly an effective antihypertensive strategy in both young and adult SHR. Evidence in recent years has pointed toward the kidney as an important site of action of angiotensin II (Ang II) in the control of arterial pressure. For example, Ang II is known to be a powerful modulator of pressure natriuresis during changes in salt intake. As pressure natriuresis is thought to be a major determinant of the long-term level of arterial pressure, the presence or absence of Ang II will determine to some extent the long-term level of arterial pressure, especially at low to normal levels of salt intake. Therefore, it is not surprising that long-term administration of Ang I–converting enzyme (ACE) inhibitors has been shown to reduce arterial pressure in both normotensive and hypertensive animals.

Previous studies have shown that both short-term and long-term ACE inhibition shifts the pressure-natriuresis curve to the left in SHR. The mechanism for the effect of short-term ACE inhibition could involve decreased formation of Ang II and/or increased levels of kinins, although a kinin inhibitor did not alter the effect of short-term enalapril on the pressure-natriuresis curve in SHR. In addition to decreasing Ang II and increasing kinins, long-term ACE inhibition is known to alter vascular structure, which could also contribute to a shift in the pressure-natriuresis curve.

In a recent study, renal hemodynamic and excretory responses to Ang II were shown to be enhanced in SHR compared with those in Wistar-Kyoto rats, further supporting a role for Ang II at the level of the kidney in the development of hypertension in SHR. These intrarenal effects of Ang II were blocked by the selective Ang II type 1 (AT₁) receptor antagonist losartan. Similarly, Wood et al showed that intrarenal but not intravenous infusion of a low dose of valsartan, an AT₁ receptor antagonist, for up to 2 days decreased arterial pressure in adult SHR. Previous studies have shown losartan to be an effective antihypertensive agent when given chronically to SHR, so we hypothesized that losartan like ACE inhibitors would shift the pressure-natriuresis curve in SHR. We were also interested in comparing the effect of short- versus long-term blockade of the AT₁ receptor on pressure-natriuresis curves, as studies with short-term losartan in volume-expanded SHR have shown little effect on sodium excretion, and there are no studies reported in which renal function was measured in SHR after long-term administration of losartan. Our results show that under the conditions of our experiment only long-term losartan produced a shift of the pressure-natriuresis curve to the left.

Methods

Series 1: Long- and Short-term Losartan

Male SHR were ordered from Harlan Sprague Dawley Laboratories (colony #217) to arrive at 4 to 5 weeks of age.
They were housed individually in suspended wire-mesh cages under light- and temperature-controlled conditions. Protocols were approved by the University of Western Ontario Animal Care Committee. Rats were assigned randomly to a group (n=13) that received losartan potassium (DuPont Merck) in their drinking water (calculated to give a dose of 12 to 15 mg·kg⁻¹·d⁻¹) or to an untreated group (n=27) drinking tap water. Food was available ad libitum. Water intake was monitored twice weekly, at which time the animals were weighed and the appropriate amount of losartan was added to fresh water. For determination of the effect of short-term losartan on pressure natriuresis, 14 untreated SHR were given losartan potassium (10 mg · kg⁻¹ · IV) 1 hour before the pressure-natriuresis protocol was started (see below). We have found that this dose of losartan blocks the pressor response to a bolus of Ang II (250 ng · kg⁻¹ · IV) by 80% to 90% for the duration of these experiments and completely reverses the effect of long-term Ang II (30 ng·min·IV for 7 to 10 days) on the pressure-natriuresis curve in Sprague-Dawley rats.¹⁴

Series 2: Short-term High-Dose Losartan

Results from series 1 indicated that short-term losartan (10 mg · kg⁻¹) did not alter the pressure-natriuresis relation. For determination of whether a higher dose of losartan was necessary to shift the pressure-natriuresis curve in SHR, a second rat group was studied after a dose of 30 mg · kg⁻¹ · losartan potassium. Male SHR (colony #208) were purchased at 6 to 7 weeks of age and randomly assigned to control (n=8) or losartan (n=8) groups. As before, losartan was given 1 hour before the pressure-natriuresis protocol was started.

Experimental Preparation

The experimental preparation and protocol were essentially as described originally by Roman and Cowley¹⁵ and used by us previously in SHR.¹² At 7 to 8 weeks of age, the right adrenal gland and kidney were excised under Equithesin¹⁶ anesthesia (0.3 mL · 100 g⁻¹ body wt IP) through a lateral flank incision. The rats were allowed 7 to 10 days to recover, after which pressure-natriuresis experiments were done in rats at 8 to 9 weeks of age.

On the day of the experiment, the rats were anesthetized with thiobutabarbital (Inactin, 100 mg/kg body wt IP, BYK-Gulden) and placed on a heated board, and a tracheostomy was performed (PE-240 tubing) to facilitate breathing. Abdominal temperature was monitored with a thermistor (model 402, Yellow Springs Instrument Co) and maintained at 37±0.5 °C using a controller (model 73A, Yellow Springs Instrument Co). The left jugular vein was cannulated with PE-50 tubing for fluid and drug administration. A polyvinyl cocktail was composed of aldosterone (13.2 ng · kg⁻¹ · min⁻¹, Sigma Chemical Co), hydrocortisone (8.25 µg · kg⁻¹ · min⁻¹, Sigma), norepinephrine (333 ng · kg⁻¹ · min⁻¹, Sigma), and arginine vasopressin (0.17 ng · kg⁻¹ · min⁻¹, Sigma) dissolved in saline containing 1% albumin (fraction V bovine, Sigma). Also included in the cocktail were 1% inulin (Eastman Chemical Co) and 0.05% p-aminohippurate (Sigma) for the measurement of glomerular filtration rate (GFR) and effective renal blood flow (RBF), respectively. At these concentrations and this infusion rate, plasma levels of these hormones were reported to be elevated 8- to 10-fold compared with normal values obtained in conscious rats.¹³ The cocktail and infusion rate were designed to volume expand the rats and minimize reflex hormonal adjustments to the kidney, which may result from increasing or decreasing renal artery pressure (RAP) as described below.

The remaining kidney was exposed through an abdominal incision and denerve to eliminate reflex neural control of the kidney by stripping the adventitia from both the renal artery and vein and by applying 95% ethanol containing 10% phenol to each vessel to destroy any remaining nerve fibers. The remaining adrenal gland was isolated and removed. A silicone elastomer balloon cuff was placed around the aorta proximal to the renal artery and inflated at appropriate times during the experiment to set RAP below normal resting values. Snare clamps were placed around the lower abdominal aorta and superior mesenteric and celiac arteries to elevate RAP when necessary. Measurement of renal interstitial hydrostatic pressure (RIHP) was done using the method of Garcia-Estañ and Roman.¹⁷ An electrocautery needle was used to burn a 3-mm-deep hole in the lateral side of the kidney. A polyvinyl catheter (0.02-inch internal diameter x 0.02-inch wall, Norton Performance Plastics) with a polyethylene matrix (35-µm pore, Bel-Art Products) tip was inserted into the hole and sealed in place with cyanoacrylate glue. The catheter was connected to a pressure transducer (model CDX3, Cobe), and continual recordings were made on the polygraph, which was calibrated for 0 to 20 mm Hg. The catheter tip was located at the junction of the cortex and outer medulla. The sensitivity of the RHP catheter was tested by gently pressing on the renal vein with a cotton swab, and only those preparations in which RHP rose rapidly to 20 mm Hg and returned to control levels after the swab was removed were used.¹⁷ Finally, the left ureter was cannulated with a length of tapered PE-50 tubing, and the catheter tip was placed below body level so that urine drained freely into collection vials.

On average, surgery was completed within 90 minutes, at which time the abdomen was bathed in 0.9% NaCl and covered with gauze and plastic wrap to reduce water loss by evaporation. Arterial blood was then sampled for measurement of hematocrit. Based on the hematocrit reading, 1 to 3 mL of 6% albumin in 0.9% NaCl was given intravenously to restore hematocrit to normal levels of 0.40 to 0.45. The short-term dose of losartan was given at this time.

Experimental Protocol

Two hours after the hormone cocktail infusion was started and approximately 1 hour after surgery was completed, MAP level was determined and data for the pressure-natriuresis curve were collected as described below. In the control and short-term losartan groups, RAP was lowered to 130 mm Hg by inflating the occluder cuff proximal to the renal artery. After a 20-minute stabilization period, a 20-minute clearance period was taken. The cuff was then partially released to allow RAP to increase to 150 mm Hg. After a 20-minute stabilization period, a 20-minute clearance period was taken. RAP was then elevated to 175 mm Hg by fully releasing the cuff and occluding previously isolated abdominal vessels. After 15 minutes of stabilization, a 10-minute clearance period was taken.

In long-term losartan rats, the same time scale for clearance periods was followed. Ideally, similar RAP values should have been used. However, preliminary studies revealed that the range of RAP values attainable in animals treated chronically with losartan was different from that which could be attained in the short-term losartan and control groups. For clearance 1, RAP was decreased to approximately 115 mm Hg. RAP was then increased to 130 mm Hg for clearance 2 and further increased in clearance 3 to 130 mm Hg.
Analytical Techniques

Urinary volume was calculated gravimetrically after urine was collected under oil in preweighed vials. Hematocrit was calculated by the microcapillary tube method from arterial blood samples (300 μl) taken at the midpoint of each clearance. The concentrations of p-aminohippurate and inulin in both plasma and urine were measured by the method of Smith and the antherone method, respectively. RBF was calculated as the clearance of p-aminohippurate divided by (1–hematocrit), and GFR was calculated as the clearance of inulin. Urine and plasma were analyzed for sodium concentration with a flame photometer (FLM 3, Radiometer) for determination of both the total excretion of sodium (product of urine flow and urinary sodium concentration) and the fractional excretion of sodium (sodium excretion divided by the filtered load of sodium). At the end of each experiment the animal was killed by injection of a euthanasia solution (saturated KCl and MgSO4), and the kidney was removed, decapsulated, cut in half, blotted dry, and weighed. All renal function measurements are expressed per gram kidney weight. In series 1, the left ventricle and septum were also isolated, blotted dry, and weighed.

Statistical Analyses

All data are reported as mean±SEM. Renal function measurements obtained at different RAP values within a group were subjected to ANOVA with repeated measures, and when appropriate individual means were subjected to the Newman-Keuls test for statistical differences. The statistical significance of differences in measured values between control and treated groups at overlapping RAP values was determined using ANOVA followed by Bonferroni's test for multiple comparisons where appropriate. Calculated F and t values were considered significant at a value of P<.05.

Results

Series 1: Effect of Long- and Short-term Losartan

SHR treated chronically with losartan received 12±0.3 mg·kg\(^{-1}\)·d\(^{-1}\) (n=13) during the last week of the 3 to 4 weeks of treatment. Water intake did not differ significantly between rats receiving losartan and those not receiving losartan. Body weights were similar among treated and untreated rats on the day of the pressure-natriuresis experiment, although rats receiving long-term losartan were slightly but significantly (P<.05) heavier than rats in the short-term losartan group (Table 1). MAP under thiobutabarbitral anesthesia was significantly lower (P<.01) in rats receiving long-term losartan compared with MAP in either of the other two groups (Table 1). One hour after surgery and 2 hours after the hormone cocktail was started, MAP was still significantly (P<.01) lower in the long-term losartan group compared with that of the other groups. Note that the short-term losartan group had received losartan (10 mg·kg\(^{-1}\)·IV) 60 minutes before this measurement was taken. MAP was not significantly different between control and short-term losartan groups. Organ weights determined at the end of the experiment revealed no significant differences in kidney weight among the three groups, whereas left ventricular weight was significantly (P<.01) lower in rats receiving long-term losartan compared with values in the other two groups (Table 1).

Renal Hemodynamics in Control and Losartan-Treated SHR

Target RAP values were obtained reliably in all groups, as was seen by SEM values of less than 1 mm Hg around each target pressure average for each group (control, n=13; short-term losartan, n=14; long-term losartan, n=13). Hematocrit values during the first clearance period averaged 0.44±0.01, 0.44±0.01, and 0.42±0.01 for the control, short-term losartan, and long-term losartan groups, respectively. In control SHR, RBF was autoregulated over the range of RAP values studied (Fig 1). RBF in short-term losartan rats when compared with that in controls was similar at a RAP of 175 mm Hg, increased slightly but not significantly (P>.05) at 150 mm Hg, and increased significantly (P<.05) at 130 mm Hg. Rats receiving long-term losartan had significantly (P<.05) elevated RBF at 130 mm Hg compared with control rats, but RBF was similar to that in controls at 150 mm Hg. Short-term losartan rats had significantly (P<.05) higher RBF at 150 mm Hg compared with long-term losartan rats.

GFR values over the range of 130 to 175 mm Hg were not significantly different between control and short-term losartan rats (Fig 1). At 150 mm Hg, GFR was slightly but significantly (P<.05) lower in the long-term losartan group compared with that of the other two groups, but at 130 mm Hg there were no significant differences among the three groups. Filtration fraction (data not shown) tended to be lower in the two losartan groups compared with controls, but this was only significant (P<.05) at a pressure of 130 mm Hg. There were no significant differences in filtration fraction at any pressure between short- and long-term losartan groups.

Pressure Natriuresis in Control and Losartan-Treated SHR

All three groups showed a significant effect of RAP on urine flow and sodium excretion (Fig 2). Pressure-diuresis and pressure-natriuresis curves for control and short-term losartan rats were virtually identical over the range of 130 to 175 mm Hg. However, rats treated chronically with losartan had a leftward shift of the pressure-diuresis and pressure-natriuresis curves. For example, at a pressure of 150 mm Hg, sodium excretion

### Table 1. Effect of Long-term Administration of Losartan on Body Weight, Mean Arterial Pressure, Kidney Weight, and Left Ventricular Weight in Spontaneously Hypertensive Rats

<table>
<thead>
<tr>
<th>Measured Variable</th>
<th>Control (n=13)</th>
<th>Short-term Losartan* (n=14)</th>
<th>Long-term Losartan (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BW, g</td>
<td>244±3</td>
<td>239±3</td>
<td>250±3*</td>
</tr>
<tr>
<td>Initial MAP, mm Hg</td>
<td>173±2</td>
<td>166±2</td>
<td>135±2*</td>
</tr>
<tr>
<td>Cocktail MAP, mm Hg</td>
<td>164±2</td>
<td>154±4</td>
<td>131±3*</td>
</tr>
<tr>
<td>LKW/BW, mg/g</td>
<td>4.58±0.08</td>
<td>4.59±0.07</td>
<td>4.62±0.07</td>
</tr>
<tr>
<td>LVW/BW, mg/g</td>
<td>2.30±0.02</td>
<td>2.21±0.03</td>
<td>1.96±0.03*</td>
</tr>
</tbody>
</table>

*BW indicates body weight; initial MAP, mean arterial pressure under anesthesia before laparotomy; cocktail MAP, MAP just before the first clearance period, 2 hours after the hormone cocktail was started; LKW/BW, left kidney weight divided by body weight; and LVW/BW, left ventricular (plus septum) weight divided by body weight. Values are mean±SEM.

†P<.01 compared with short-term losartan.

‡P<.01 compared with other two groups.
FIG 1. Line graphs show relation between renal artery pressure and renal blood flow (top) and glomerular filtration rate (bottom) in control and losartan-treated spontaneously hypertensive rats. Values are mean±SEM. *P<.05 compared with control group value at that level of renal artery pressure; †P<.05 compared with chronic losartan group value at that level of renal artery pressure.

FIG 2. Line graphs show relation between renal artery pressure and urine flow (top) and sodium excretion (bottom) in control and losartan-treated spontaneously hypertensive rats. Values are mean±SEM. *P<.01 between chronic losartan group and other two groups at that renal artery pressure.

was 3.2±0.4, 3.8±0.4, and 9.0±1.4 μmol · min⁻¹ · g⁻¹ in control, short-term losartan, and long-term losartan rats, respectively. When RAP was set at 175 mm Hg in control and short-term losartan rats, sodium excretion increased to 9.0±1.3 and 9.3±1.0 μmol · min⁻¹ · g⁻¹, respectively. Therefore, under the conditions of these experiments, control and short-term losartan rats required a RAP approximately 25 mm Hg higher than long-term losartan rats to excrete a similar amount of sodium.

Fractional excretion of sodium and RHP increased significantly with increasing RAP in all three rat groups (Fig 3). As was seen for both urine flow and total sodium excretion, fractional sodium excretion was not significantly different in control and short-term losartan rats at RAP values from 130 to 175 mm Hg, whereas long-term losartan shifted the RAP–fractional sodium excretion curve to the left. There were no significant differences in RHP between control and short-term losartan rats over the pressure range studied, and at pressures of 130 and 150 mm Hg there were no significant differences in RHP among the three groups.

Series 2: Effect of Short-term High-Dose Losartan

Initial MAP was 176±3 mm Hg (n=8) and 172±7 mm Hg (n=8) in the two groups of untreated SHR used in this study. One hour after losartan (30 mg · kg⁻¹) and in the presence of the hormone cocktail, there was no significant difference in MAP between control (176±7 mm Hg) and treated (177±7 mm Hg) SHR. Hematocrit before the first clearance was started averaged 0.42±0.01 in both rat groups.

Table 2 summarizes renal hemodynamics and data obtained during the pressure-natriuresis protocol. GFR and RBF were autoregulated in both groups, and there were no significant differences between groups at any RAP studied. Both groups showed pressure-natriuresis responses, but there were no significant differences between control and losartan-treated rats for any of the measured variables at RAP values of 130, 150, or 175 mm Hg.

Discussion

The results of this study are consistent with the general concept that drugs which are effective antihypertensive agents produce a leftward shift of the short-term pressure-natriuresis curve.\(^{20}\) Similar to our previous studies with the ACE inhibitor enalapril,\(^1\) long-term administration of the Ang II AT\(_1\) receptor antagonist losartan resulted in decreased MAP in young SHR, and this decrease in MAP was associated with a significant leftward shift of the pressure-natriuresis curve. The mechanism for pressure natriuresis is reported to involve changes in medullary hemodynamics that in turn influence RHP to alter sodium reabsorption,\(^5\) so we compared RHP in control and long-
term losartan rats at several RAP levels. The data show no significant difference in RIHP between control and treated rats, suggesting that the change in fractional sodium excretion is caused by a direct tubular effect of losartan. This result is compatible with reports that losartan is an inhibitor of the Ang II-stimulated sodium chloride transport in the early proximal tubule.21

This explanation for the effect of long-term losartan on the pressure-natriuresis curve in SHR is perhaps too simple, considering the observation that there was a significant difference between the effects of short- and long-term losartan on the pressure-natriuresis curves. Although long-term losartan administration shifted the curve to the left, short-term losartan administration (10 mg • kg\(^{-1}\)) had no such effect. On the one hand, this was surprising to us, as short-term losartan is known to decrease proximal tubular sodium reabsorption,21 and short-term administration of enalapril has been shown to shift the pressure-natriuresis curve in SHR.8 On the other hand, our data are in agreement with those of Fenoy et al,13 who showed that short-term losartan (10 mg • kg\(^{-1}\)) had little effect on urine flow and sodium excretion in volume-expanded SHR. As our studies were done in volume-expanded rats using the hormone cocktail protocol of Roman and Cowley,15 it is possible that endogenous Ang II levels were low, thereby precluding an effect of short-term losartan. However, Fenoy et al13 provided evidence for decreased proximal tubular reabsorption of sodium (ie, increased fractional excretion of lithium) after short-term losartan. Apparently, at least in volume loading conditions, compensation by the distal nephron is able to offset changes in proximal tubular reabsorption of sodium produced by short-term losartan. Why this would not happen with long-term losartan or whether long-term losartan is acting at additional sites is not clear.

In series 1, both short- and long-term losartan produced significant increases in RBF. This response to short-term losartan agrees with previous studies in volume-expanded SHR,13 and the relation between the effects of these agents on RBF and RAP is similar to that seen in humans.22 With the use of blockers of the renin-angiotensin system in dogs, it was found that RBF actually increased in response to decreasing RAP. This may reflect tubular glomerular feedback control of afferent arteriolar resistance in the absence of Ang II22 effects on the efferent arteriole during autoregulation of GFR. However, this effect on RBF could not explain the shift of the scatter of RBF against pressure in the pressure-natriuresis curve after long-term losartan administration, as the greatest difference in RBF actually increased in response to decreasing RAP. This may reflect tubular glomerular feedback control of afferent arteriolar resistance in the absence of Ang II22 effects on the efferent arteriole during autoregulation of GFR. However, this effect on RBF could not explain the shift of the scatter of RBF against pressure in the pressure-natriuresis curve after long-term losartan administration, as the greatest difference in sodium excretion between short- and long-term losartan groups actually occurred at a RAP value at which RBF in short-term losartan rats was significantly elevated compared with that in long-term losartan rats. Similarly, there were no significant differences in filtration fraction between short- and long-term losartan rats at pressures that produced significantly different levels.
of fractional sodium excretion in the two groups. Therefore, other mechanisms must account for the differential effect of short- versus long-term losartan on the pressure-natriuresis curve in volume-expanded SHR.

It could be argued that short-term losartan does not provide the same degree of Ang II receptor blockade as long-term losartan at a similar dose. To determine whether that is the case, rats in series 2 were treated acutely with 30 mg·kg⁻¹ losartan. As seen with the low dose, losartan at the higher dose did not have a significant effect on the pressure-natriuresis curve compared with the curve obtained in control rats. The failure of losartan at this dose to produce an effect on RBF cannot be easily explained. (We note that SHR for series 2 came from a different SHR colony than those in series 1 and that they required larger amounts of albumin solution to lower the hematocrit to the proper level.) These data with the high dose, however, suggest that failure to produce adequate blockade of Ang II receptors is not the reason for the difference between short- and long-term effects of losartan on the pressure-natriuresis curve in volume-expanded SHR.

The role of RIHP and renal medullary blood flow in the pressure-natriuresis response has been of great interest recently. Changes in RAP have been shown to produce parallel changes in the medullary circulation and RIHP, giving rise to parallel changes in fractional sodium excretion that are independent of changes in GFR or total RBF. In SHR, both medullary blood flow and RIHP responses to changes in RAP are blunted compared with responses in Wistar-Kyoto rats. Although renal cortical blood flow is quite sensitive to Ang II and is increased by Ang II antagonists, the effect of Ang II on the medullary circulation is less clear. Recent studies using laser Doppler measurements of papillary blood flow in rats show little if any effect of short-term Ang II or losartan, although Ang II decreases papillary blood flow in the presence of indomethacin. Short-term administration of ACE inhibitors increases papillary blood flow, probably by a kinin-related mechanism, but this is not accompanied by an increase in RIHP. The latter variable may also be influenced by a decrease in renal venous resistance. In our study neither short- nor long-term losartan altered the relation between RAP and RIHP, suggesting that the medullary blood flow response to changes in RAP was not altered or that a decrease in renal venous resistance offset any changes in blood flow that would tend to elevate RIHP. Since fractional sodium excretion was three times greater at 150 mm Hg in long-term losartan rats compared with that in short-term losartan rats, and RIHP values in the two groups were not significantly different, the data suggest that tubular effects of losartan to increase sodium excretion are significantly more effective after long-term administration than after short-term administration. Conceivably, the active metabolite of losartan in the rat, EXP3174, could contribute differently to the effect of losartan given chronically compared with the effect of losartan given acutely; however, to our knowledge there is no evidence for this at present.

Other explanations for the differential effect of short- versus long-term losartan on the pressure-natriuresis curve are not obvious. Although long-term losartan decreases aldosterone levels significantly in SHR, the preparation itself involves infusion of aldosterone. With a 2-hour equilibration, there should be no significant differences in aldosterone influence between short- and long-term losartan groups. Another possible explanation for the difference between the effects of short- and long-term losartan on pressure-natriuresis curves in volume-expanded SHR is the well-described effect of inhibitors of the renin-angiotensin system on vascular structure. SHR are known to have altered vascular structure in the kidney, and long-term treatment with ACE inhibitors or losartan is known to attenuate the characteristic changes in vascular and cardiac structure in SHR. In our study, rats receiving losartan for 3 to 4 weeks had significantly lower heart weights and presumably less vascular hypertrophy in the kidney and elsewhere. Therefore, one could expect that changes in RAP would be transmitted more easily to the medullary circulation, which in turn would elevate RIHP and enhance sodium excretion. In fact, the relative importance of these structural changes in determining medullary blood flow, RIHP, and hence the position of the pressure-natriuresis curve is not known. Gebremedhin et al. have provided evidence that a functional-not a structural-based resistance is responsible for the elevated postglomerular vascular resistance in juxtapapillary nephrons in SHR, which presumably contributes to the blunted medullary blood flow and RIHP response to increasing RAP in this rat strain. Our own data showed that long-term losartan did not alter the RIHP response to increasing RAP, suggesting that changes in vascular structure had little effect on this parameter. On the other hand, studies by Morton et al. showed that treatment of SHR for 4 weeks (from 3 to 7 weeks of age) with losartan (15 mg·kg⁻¹·d⁻¹) did not produce significant regression of elevated wall-to-lumen ratios in mesenteric vessels, whereas treatment for 10 weeks did. Additional studies with longer treatment and off-treatment controls may be necessary to address the question of the relative importance of structural changes to the position of the pressure-natriuresis curve in SHR treated chronically with losartan.

In summary, we have confirmed that long-term losartan administration attenuates the development of hypertension in SHR and have demonstrated that this effect is associated with a shift of the pressure-natriuresis curve to the left. This effect of losartan is probably due to a direct effect on renal tubules to enhance sodium excretion. Based on previous studies emphasizing the important role of pressure natriuresis in the long-term control of MAP, we propose that this renal action of losartan is responsible for its antihypertensive effect in SHR. Short-term losartan administration did not alter the pressure-natriuresis curve in volume-expanded SHR. The mechanism responsible for the differential effects of short- versus long-term losartan in this pressure-natriuresis preparation remains to be explained.

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