Effects of Antihypertensive Agents on Arterial Baroreceptor Reflexes in Conscious Rats

Kazuhiro Kumagai, Hiromichi Suzuki, Munekazu Ryuzaki, Hiroo Kumagai, Masashi Ichikawa, Masahito Jimbo, Yasuo Matsumura, and Takao Saruta

The effects of antihypertensive treatment with four currently used agents (trichlormethiazide, atenolol, nicardipine, and enalapril) on the arterial baroreceptor reflex control of renal sympathetic nerve activity and heart rate were investigated in 45 conscious spontaneously hypertensive rats and 37 age-matched Wistar-Kyoto rats. Antihypertensive agents were administered for 2 weeks beginning at 8 weeks of age to treat and prevent the development of hypertension. Blood pressure was reduced to a similar level (−13±3 mm Hg, p < 0.05) by each antihypertensive agent. Blood pressure, heart rate, and renal sympathetic nerve activity were recorded in the conscious state during phenylephrine and nitroglycerin ramp infusion. The gain in the baroreceptor reflex was determined from the maximum slope of logistic function curves.

Untreated spontaneously hypertensive rats exhibited decreased sensitivity of reflex control of renal sympathetic nerve activity and heart rate (−1.78±0.07% of control/mm Hg and −2.16±0.05 beats per minute/mm Hg, respectively) compared with untreated Wistar-Kyoto rats (−3.62±0.18% of control/mm Hg, p < 0.01, and −3.46±0.11 beats per minute/mm Hg, p < 0.05, respectively). The gains in baroreceptor reflex control of renal sympathetic nerve activity and heart rate were greater in trichlormethiazide- (−2.99±0.15%/mm Hg and −3.05±0.13 beats per minute/mm Hg, respectively), atenolol- (−3.22±0.22%/mm Hg and −3.31±0.08 beats per minute/mm Hg, respectively), nicardipine- (−3.48±0.23%/mm Hg and −3.17±0.06 beats per minute/mm Hg, respectively), and enalapril- (−3.11±0.08%/mm Hg and −3.54±0.17 beats per minute/mm Hg, respectively) treated spontaneously hypertensive rats (all p < 0.05) than in untreated spontaneously hypertensive rats. The antihypertensive agents affected neither blood pressure nor the baroreceptor reflex function curves in Wistar-Kyoto rats. These results indicate that attenuation of the development of hypertension by the antihypertensive agents is responsible for the restoration of impaired baroreceptor reflex control of renal sympathetic nerve activity and heart rate in conscious early hypertensive spontaneously hypertensive rats, although different antihypertensive mechanisms may mediate the blood pressure reduction. (Hypertension 1992;20:701-709)

KEY WORDS: • sympathetic nervous system • baroreceptors • rats, inbred SHR • atenolol • trichlormethiazide • nicardipine • enalapril

Reduction of high blood pressure and prevention of end-organ damage are the major goals of antihypertensive therapy. Recent advances in clinical pharmacology have provided us with a huge armamentarium of antihypertensive agents. Excessive reduction of blood pressure may decrease the regional organ blood flow, leading to serious complications such as myocardial ischemia, renal dysfunction, cerebral ischemia, and at times even death. Evidence has been provided that an arterial baroreceptor reflex mechanism modifies regional blood flow1,2 and that the effectiveness of the baroreceptor reflex mechanism would be very limited if the resetting process was not reversible.3 Restoration of baroreceptor reflex function (i.e., normalization of reflex sensitivity and reversibility of baroreceptor resetting) is important in preserving end-organ function since it may alleviate the risk of decreasing regional blood flow.

It is insufficient to rely solely on the reflex response of heart rate (HR) as evidence of generalized abnormalities in the arterial baroreceptor reflex since dissociated efferent responses between HR and sympathetic nerve activity have been shown.4,5 Control of sympathetic outflow to the kidney is particularly important in hypertension because of the influence of renal nerves on renal vascular resistance, sodium excretion, and renin release. Therefore, we examined the baroreceptor reflex control of renal sympathetic nerve activity (RSNA) as well as of HR using logistic function curves.

Previously, numerous investigations with respect to arterial baroreceptor reflex sensitivity, resetting, and antihypertensive treatment were carried out under a variety of conditions (i.e., different ages, species, levels of blood pressure reduction, and uses of anesthesia). Results have been inconsistent; baroreceptor reflex sensitivity was increased, decreased, or not affected by the various antihypertensive agents. To eliminate these factors, the present study was conducted on conscious rats of similar ages with similar levels of blood pressure...
reduction. Four currently used antihypertensive agents (a diuretic, a \( \beta \)-adrenergic receptor blocker, a calcium channel blocker, and an angiotensin converting enzyme inhibitor), each having a different primary mechanism of action, were administered. The results clarify more direct effects of the antihypertensive agents on arterial baroreceptor reflexes.

### Methods

**General Procedures**

Eight-week-old male Okamoto spontaneously hypertensive rats (SHR) and corresponding Wistar-Kyoto (WKY) normotensive rats were purchased from Charles River Japan Co., Atsugi, Japan. The rats were housed in group cages, fed rat chow and water ad libitum, and maintained in a room with a constant temperature and on a 12-hour light/dark cycle. Untreated SHR (n = 9) and WKY (n = 9) rats were fed a normal diet (20 g/day, 0.38% NaCl; Nippon Clea, Tokyo) for 2 weeks. Treated SHR (n = 36) and WKY (n = 28) rats were randomly assigned to one of four groups and given trichlormethiazide (10 mg/kg per day; Schering Corp., Kenilworth, N.J.), atenolol (90 mg/kg per day; ICI PLC, London), nicardipine (150 mg/kg per day; Yamanouchi Pharmaceuticals Co., Tokyo), or enalapril maleate (10 mg/kg per day; Merck Sharp & Dohme, West Point, Pa.) mixed in the diet. The dose of each agent that lowered the blood pressure to a similar level was determined in preliminary experiments. To prevent excessive reduction of blood pressure, a specific reduction that is defined as clinically effective (i.e., 10–15 mm Hg as mean arterial pressure [MAP]) was targeted. Antihypertensive treatment was continued for 2 weeks, from 8 to 10 weeks of age, to treat and prevent the development of hypertension.

One day before the experiments, venous and arterial catheters and electrodes to record RSNA were implanted into each rat under anesthesia with pentobarbital sodium (40 mg/kg i.p., supplemented with 10 mg/kg as needed; Abbott Laboratories, North Chicago, Ill.). The left femoral vein was catheterized with two modified polyethylene tubes made from PE-10 tubing (Clay Adams, Parsippany, N.J.) fused with PE-50 tubing (Clay Adams, Parsippany, N.J.) mixed in the diet. The left femoral artery was catheterized with two modified polyethylene tubes made from PE-10 tubing (Clay Adams, Parsippany, N.J.) fused with PE-50 tubing to infuse either phenylephrine (PE) or nitroglycerin (NTG). The use of two venous catheters eliminated the need to flush the catheters between drug infusions. The venous catheters were inserted into the bifurcation through the femoral vein. The arterial catheter was inserted into the lower abdominal aorta via the femoral artery for measurement of the arterial pressure and HR. The catheters were passed subcutaneously to the back of the neck, fixed, and occluded. Each catheter was filled with heparin (100 units/ml; Novo Nordisk A/S, Gentofte, Denmark) in 0.9% sterile saline. After arterial and venous catheterization, procaine penicillin (50,000 units/kg i.m.) diluted with 0.9% sterile saline was given.

**Recording of Renal Sympathetic Nerve Activity**

Following recent protocols\(^8\)–\(^10\) with our modifications, the left kidney was exposed via the retroperitoneal approach through a left flank incision using a sterile technique. Under a dissecting microscope (SMZ, Nikon, Tokyo, Japan) a renal nerve was identified, isolated, and carefully dissected. This renal nerve was then placed on Teflon-coated multistrand stainless steel wire electrodes (A-M System, Inc., Everett, Wash.).

The quality of the RSNA signal was evaluated by examining the magnitude of the change in recorded RSNA during intravenous administration of PE and NTG. After observing an optimal signal, the recording electrodes were secured to the nerve with Wacker Sil-Gel 604A and 604B (Wacker-Chemie Gimble, Munich, FRG) to prevent the nerve tissue from drying. Finally, the flank incision was closed in layers, the electrodes were exteriorized at the back of the neck, and the rats were allowed to recover.

**Test for Baroreceptor Reflex Sensitivity**

After surgical preparation, the rats were housed in individual cages. A minimum of 24 hours later, each conscious rat was placed in a nonrestraining holder that permitted forward and backward movement. The arterial catheter was connected to a transducer (TP-200T, Nihon Kohden Co., Tokyo) for measurement of arterial blood pressure (AP-611G, Nihon Kohden) and HR (AT-601G, Nihon Kohden). The RSNA recording electrodes were connected to a high-impedance probe (JB101J, Nihon Kohden) that was connected to a differential amplifier (AVB-10, Nihon Kohden) with a band-pass filter (low, 50 Hz; high, 3 kHz). The RSNA was amplified using the differential amplifier with the band-pass filter. Amplified and filtered RSNA was monitored on an oscilloscope (VC-10, Nihon Kohden). In accordance with previous reports,\(^11\),\(^12\) the root mean square (RMS) of RSNA was defined as the whole-nerve activity obtained by rectifying and integrating the activity with an RMS integrator (EI-601G, Nihon Kohden) that had a time constant of 28 msec, and mean RSNA was defined as the RMS of RSNA further filtered at 0.08 Hz for quantification. The RSNA remaining after maximum inhibition after PE administration was similar to the background noise observed at approximately 30 minutes postmortem; this value was subtracted from all experimental values of RSNA. The arterial pressure, MAP, HR, original renal neurogram, mean RSNA, and the RMS of RSNA were recorded on a thermal array recorder (RTA-1300, Nihon Kohden) for visualization. The data were stored in a multichannel data recorder (A-89, Sony Inc., Tokyo). The arterial pressure, HR, and RSNA were recorded continuously as arterial pressure was changed with PE and NTG alternately. After allowing 60 minutes for blood pressure to stabilize, MAP, HR, and RSNA were recorded. To raise blood pressure by approximately 40 mm Hg for 1–2 minutes, PE (0.5–1.0 mg/ml) was infused at rates of 2.34–6.43 \( \mu \)l/min. To lower blood pressure by approximately 40 mm Hg in 10–15 seconds, NTG (0.5 mg/ml) was infused at rates of 0.1–0.39 ml/min. The infusions of PE were delivered with a 1-ml syringe mounted on a syringe pump (955E microliter syringe pump, Harvard Apparatus, Millis, Mass.). The infusions of NTG were delivered with a 5-ml syringe mounted on a syringe pump (975 compact infusion pump, Harvard Apparatus). At least 30 minutes were allowed to pass between drug infusions.
TABLE 1. Mean Arterial Pressure, Heart Rate, and Body Weight in Untreated and Treated Rats

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Wistar-Kyoto rats</th>
<th>Spontaneously hypertensive rats</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Untreated</td>
<td>Treated</td>
</tr>
<tr>
<td></td>
<td>(n=9)</td>
<td>(n=7)</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>99±2</td>
<td>99±4</td>
</tr>
<tr>
<td></td>
<td>96±3</td>
<td>97±2</td>
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<tr>
<td></td>
<td>95±2</td>
<td>126±5*</td>
</tr>
<tr>
<td></td>
<td>115±2t</td>
<td>115±2t</td>
</tr>
<tr>
<td></td>
<td>113±4t</td>
<td>110±2t</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>370±8</td>
<td>369±14</td>
</tr>
<tr>
<td></td>
<td>366±7</td>
<td>374±8</td>
</tr>
<tr>
<td></td>
<td>374±8</td>
<td>408±9t</td>
</tr>
<tr>
<td></td>
<td>399±4</td>
<td>381±10</td>
</tr>
<tr>
<td></td>
<td>410±6t</td>
<td>403±11</td>
</tr>
<tr>
<td>Body weight (g)</td>
<td>206±7</td>
<td>208±5</td>
</tr>
<tr>
<td></td>
<td>213±5</td>
<td>212±6</td>
</tr>
<tr>
<td></td>
<td>212±6</td>
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<tr>
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<td>187±8</td>
<td>193±7t</td>
</tr>
<tr>
<td></td>
<td>195±7t</td>
<td>190±6t</td>
</tr>
</tbody>
</table>

Values are mean±SEM. TCM, trichlormethiazide-treated group; ATE, atenolol-treated group; NIC, nicardipine-treated group; EN, enalapril-treated group; bpm, beats per minute.

* p<0.01, †p<0.05 different from Wistar-Kyoto rats.

†p<0.05 different from untreated.

§p<0.05 different from atenolol-treated.

Data Analysis

The basal values of MAP, RSNA, and HR were taken as their 5-minute averages before the infusion of each drug. For data analysis, RSNA and HR were plotted at 5-mm Hg intervals of MAP. Data for the MAP-RSNA or MAP-HR relations after infusion of PE and NTG were fitted to a logistic function curve by employing a nonlinear regression program (PROC NUN, SAS Institute Inc., Cary, N.C.) on a computer (PS/2 model 50Z, IBM Co., Armonk, N.Y.). The best fit of the curve was obtained with the above computer program. Four parameters were derived from the equation RSNA or HR=P4+P1/[1+e-P2(MAp-p3)], where P1 is the RSNA range or HR range, P2 is the slope coefficient (independent of the range), P3 is the MAP at half the RSNA or HR range, and P4 is the lower plateau of RSNA or HR.\(^\text{13}\) The curve was forced through the average basal values of MAP, RSNA, and HR. In the present study, the goodness of fit was between 95% and 99%. The baroreceptor reflex sensitivity index is defined as the maximum gain of the logistic function curve, \(G_{\text{max}}=\frac{P1 \cdot P2/4}{P3}\).\(^\text{14,15}\)

We defined several appropriate terms according to previous studies.\(^\text{16,17}\) The operating point is defined as the average basal values of MAP, RSNA, and HR. The basal value of mean RSNA is defined as 100% before

![FIGURE 1](http://hyper.ahajournals.org/)

FIGURE 1. Tracings from conscious spontaneously hypertensive rat showing arterial pressure, mean arterial pressure, heart rate, original neurogram of renal sympathetic nerve activity (RSNA), mean RSNA, and RSNA integrated by root mean square integrator (RMS of RSNA) during ramp increases in arterial pressure induced by phenylephrine infusion (panel A) and during ramp decreases in arterial pressure induced by nitroglycerin infusion (panel B).
Table 2. Parameters of Mean Arterial Pressure-RSNA Function Curves in Untreated and Treated Rats

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Untreated (n=9)</th>
<th>TCM (n=7)</th>
<th>ATE (n=7)</th>
<th>NIC (n=7)</th>
<th>EN (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum gain (% control/mm Hg)</td>
<td>-3.62±0.18</td>
<td>-3.49±0.10</td>
<td>-3.35±0.09</td>
<td>-3.77±0.08</td>
<td>-3.68±0.12</td>
</tr>
<tr>
<td>RSNA range (% control)</td>
<td>216±14</td>
<td>215±10</td>
<td>233±14</td>
<td>225±12</td>
<td>220±13</td>
</tr>
<tr>
<td>Upper plateau (% control)</td>
<td>220±8</td>
<td>221±12</td>
<td>237±9</td>
<td>229±10</td>
<td>224±10</td>
</tr>
<tr>
<td>Lower plateau (% control)</td>
<td>6±2</td>
<td>6±2</td>
<td>3±1</td>
<td>5±1</td>
<td>4±2</td>
</tr>
<tr>
<td>Range of reflex sympathetic excitation (% control)</td>
<td>120±10</td>
<td>126±10</td>
<td>137±11</td>
<td>130±14</td>
<td>126±12</td>
</tr>
<tr>
<td>Range of reflex sympathetic inhibition (% control)</td>
<td>96±4</td>
<td>89±4</td>
<td>96±6</td>
<td>94±5</td>
<td>94±6</td>
</tr>
<tr>
<td>BP50 (mm Hg)</td>
<td>96±2</td>
<td>95±2</td>
<td>92±2</td>
<td>93±3</td>
<td>92±2</td>
</tr>
</tbody>
</table>

Values are mean±SEM. TCM, trichlormethiazide-treated group; ATE, atenolol-treated group; NIC, nicardipine-treated group; EN, enalapril-treated group; RSNA, renal sympathetic nerve activity; BP50, mean arterial pressure at midpoint of RSNA range.

\*p<0.01, \$p<0.05 different from Wistar-Kyoto rats.

\*p<0.05, \$p<0.01 different from untreated.

drug infusion. The upper plateau of RSNA and HR is defined as P1 plus P4. The range of reflex sympathetic excitation or range of reflex tachycardia is defined as P1 plus P4 minus basal RSNA or HR. The range of reflex sympathetic inhibition or range of reflex bradycardia is defined as basal RSNA or HR minus P4. The BP50 is consistent with P3 but is not the same as the operating point. Mean values of the above parameters taken from individual curves for each rat were used to construct average curves for the different groups of animals studied.

Statistical Analysis

The data were analyzed with the StatView II program for Macintosh computers. Basal values of MAP, HR, and the parameters obtained from logistic function curves were compared by one-way analysis of variance with repeated measures in which the effects of strain and treatment were considered independently. This was followed by Scheffe's F test as a multiple comparison procedure. Values were expressed as mean±SEM, and p<0.05 was considered as the criterion of statistical significance.

Measurement of Plasma Drug Concentrations

At the end of antihypertensive treatment, the rats were decapitated to collect blood for the measurement of plasma concentrations of each agent in preliminary experiments. The plasma concentrations of trichlormethiazide, atenolol, and nicardipine were determined by high-performance liquid chromatography,18-20 and that of enalapril was determined by radioimmunoassay.21

Results

Body weight was less in SHR than in WKY rats (p<0.05) but within a strain was not significantly different between groups with and without treatment (Table 1).
Figure 1 illustrates typical recordings showing arterial pressure, MAP, HR, original renal neurogram, mean RSNA, and the RMS of RSNA in response to an increase in blood pressure induced by PE infusion (Figure 1A) and a decrease in blood pressure induced by NTG infusion (Figure 1B) in a conscious SHR.

### Hemodynamic Parameters

Table 1 shows MAP and HR in all groups. Untreated SHR had a greater MAP than untreated and treated WKY rats (p<0.01). The four groups of treated SHR had lower MAPs than untreated SHR (p<0.05) but greater MAPs than untreated and treated WKY rats (p<0.05). Untreated and nicardipine-treated SHR had greater HRs than the corresponding WKY groups (p<0.05). None of the treated SHR groups revealed any differences in HR compared with untreated SHR. Nicardipine-treated SHR had a greater HR than atenolol-treated SHR (p<0.05). In preliminary experiments, MAP in 8-week-old untreated SHR (n=6) was already higher than in age-matched untreated WKY rats (108±5 versus 97±4 mm Hg, p<0.05) but lower than in 10-week-old untreated SHR (108±5 versus 126±3 mm Hg, p<0.05). This is compatible with data in our laboratory.

### Mean Arterial Pressure–Renal Sympathetic Nerve Activity Relation

Figure 2 depicts the MAP–RSNA function curves for untreated WKY rats, untreated SHR, and the four groups of treated SHR. The operating point of the curve was shifted to the left (i.e., downward resetting) in each group of treated SHR compared with untreated SHR. Table 2 shows the parameters of the MAP–RSNA function curves in WKY rats and SHR with and without treatment. Untreated SHR had a lower G^ than untreated and treated WKY rats (p<0.01), and the four groups of treated SHR each had a greater G^ than untreated SHR (p<0.05). Untreated SHR had a decreased RSNA range compared with untreated and treated WKY rats (p<0.01). Untreated SHR had a decreased RSNA range compared with untreated and treated WKY rats (p<0.01). The RSNA range was greater in trichlormethiazide-, atenolol-, and nicardipine-treated SHR (p<0.01) and in enalapril-treated SHR (p<0.05) than in untreated SHR. The RSNA range of enalapril-treated SHR did not exceed that of untreated and treated WKY rats.

**TABLE 2. Continued**

<table>
<thead>
<tr>
<th>Untreated (n=9)</th>
<th>TCM (n=9)</th>
<th>ATE (n=9)</th>
<th>NIC (n=9)</th>
<th>EN (n=9)</th>
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<tbody>
<tr>
<td>-1.78±0.07*</td>
<td>-2.99±0.15†</td>
<td>-3.22±0.22†</td>
<td>-3.48±0.23†</td>
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<tr>
<td>151±10*</td>
<td>226±12‡</td>
<td>237±16‡</td>
<td>236±14‡</td>
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<tr>
<td>165±10*</td>
<td>234±2‡</td>
<td>240±15‡</td>
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<td>14±3§</td>
<td>8±2†</td>
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<tr>
<td>66±10*</td>
<td>134±5‡</td>
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<tr>
<td>132±3*</td>
<td>108±2†§</td>
<td>108±2†§</td>
<td>106±3†§</td>
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</tr>
</tbody>
</table>

**FIGURE 3.** Plots show logistic function curves for mean arterial pressure–heart rate relation for untreated Wistar-Kyoto (WKY) rats (○), untreated spontaneously hypertensive rats (SHR) (•), and treated SHR (×); n=9 in all groups. Untreated SHR had decreased sensitivity compared with untreated WKY rats (p<0.05), and each group of treated SHR had increased sensitivity compared with untreated SHR (p<0.05).
Untreated SHR had decreased upper plateau and range of reflex sympathetic excitation (\(p<0.01\)) and increased lower plateau (\(p<0.05\)) and \(BP_{50}\) (\(p<0.01\)) compared with untreated and treated WKY rats. The upper plateau and range of reflex sympathetic excitation were increased in trichlormethiazide-, atenolol-, and nicardipine-treated SHR (\(p<0.01\)) and in enalapril-treated SHR (\(p<0.05\)) compared with untreated SHR. The upper plateau and range of reflex sympathetic excitation of enalapril-treated SHR did not exceed those of untreated and treated WKY rats. The four groups of treated SHR each had a decreased lower plateau compared with untreated SHR (\(p<0.05\)). The range of reflex sympathetic inhibition was similar in all groups. The four groups of treated SHR each had a \(BP_{50}\) lower than that of untreated SHR (\(p<0.05\)) but greater than that of untreated and treated WKY rats (\(p<0.05\)).

**Mean Arterial Pressure–Heart Rate Relation**

Figure 3 depicts the MAP–HR function curves for untreated WKY rats, untreated SHR, and the four groups of treated SHR. Atenolol-treated SHR had a decrease in the operating point of HR along with a leftward shift compared with untreated SHR. Nicardipine-treated SHR had a slight increase in the operating point along with a leftward shift compared with untreated SHR. Table 3 shows the parameters of the MAP–HR function curves in WKY rats and SHR with and without treatment. Untreated SHR had a lower \(G_{\text{max}}\) than untreated and treated WKY rats (\(p<0.05\)), and the four groups of treated SHR each had a greater \(G_{\text{max}}\) than untreated SHR (\(p<0.05\)). Untreated SHR had decreased HR range (\(p<0.01\)) and range of reflex tachycardia (\(p<0.05\)) and increased lower plateau and \(BP_{50}\) (\(p<0.01\)) than untreated and treated WKY rats. The HR range was greater in trichlormethiazide- and atenolol-treated SHR (\(p<0.05\)) and in nicardipine- and enalapril-treated SHR (\(p<0.01\)) than in untreated SHR. Trichlormethiazide- and atenolol-treated SHR had a lower HR range than untreated and treated WKY rats (\(p<0.05\)). None of the groups of treated SHR had any differences in upper plateau compared with untreated SHR. Nicardipine-treated SHR had greater upper plateau and lower plateau than untreated and treated WKY rats and atenolol-treated SHR (\(p<0.05\)). Nicardipine-treated SHR had a greater range of reflex tachycardia than atenolol-treated SHR (\(p<0.05\)). Atenolol-treated SHR had a decreased lower plateau compared with untreated SHR (\(p<0.05\)) but not compared with the other three groups of treated SHR. Trichlormethiazide-, nicardipine-, and enalapril-treated SHR had a greater range of reflex tachycardia than untreated SHR (\(p<0.05\)), but atenolol-treated SHR did not. Untreated SHR had a decreased range of reflex bradycardia compared with untreated and treated WKY rats (\(p<0.01\)). Atenolol- and enalapril-treated SHR had a greater range of reflex bradycardia than untreated SHR (\(p<0.05\)), but the other two groups of treated SHR did not. The four groups of treated SHR each had a \(BP_{50}\) lower than that of untreated SHR (\(p<0.05\)) but greater than that of untreated and treated WKY rats (\(p<0.05\)).

Table 4 shows the percentage restoration of \(G_{\text{max}}\) in the MAP–RSNA and MAP–HR function curves by antihypertensive agent. Mean±SEM restoration in the MAP–RSNA and MAP–HR relations was 88±8% and 94±5%, respectively.

**Drug Concentrations**

The plasma concentration of trichlormethiazide was 46±7 ng/ml, that of atenolol was 165±17 ng/ml, that of nicardipine was 28±9 ng/ml, and that of enalapril was 67±18 ng/ml. All concentrations were compatible with the therapeutic ranges in patients treated with each agent.18,22–25

**Discussion**

We investigated the effects of four different antihypertensive agents on the arterial baroreceptor reflex control of RSNA and HR in conscious early hypertensive SHR and age-matched WKY rats using logistic function curves. Blood pressure was reduced to similar levels in all groups. Five major findings were obtained: 1) untreated SHR had an impaired sensitivity and a decreased range of baroreceptor reflex control of RSNA and HR compared with untreated WKY rats, 2) attenuation of the development of hypertension by each antihypertensive agent prevented not only the impaired sensitivity of baroreceptor reflex control of RSNA and HR but also the decreased reflex range of RSNA and HR in SHR, 3) leftward shifts in the operating points of the MAP–RSNA and MAP–HR function curves (i.e., downward resetting) were induced by the four antihy-
pertensive agents in SHR, 4) restoration of baroreceptor reflex sensitivity induced by antihypertensive treatment was almost complete whereas blood pressure was not reduced to the level in untreated WKY rats, and 5) neither blood pressure nor baroreceptor reflex control of RSNA and HR were altered by the four antihypertensive agents in WKY rats.

Our present observation that untreated SHR had an impaired baroreceptor reflex control of HR and a decreased HR range compared with WKY rats is consistent with a previous study by Widdop et al.15 The present study further demonstrates that untreated SHR have an impaired sensitivity of baroreceptor reflex control of RSNA and a decreased RSNA range compared with untreated WKY rats. It has been shown that the sensitivity of baroreceptor reflex control of HR in conscious hypertensive rats is attenuated.4,7,32 However, the baroreceptor reflex control of sympathetic nerve activity in conscious hypertensive rats has been seldom investigated. Conflicting results,5,7 such as normal and increased sensitivity of baroreceptor reflex control of splanchnic nerve activity (SpNA), have been reported. Previous data, in which dissociated responses between HR and SpNA were observed, indicate that the central neural integration of autonomic function is impaired in hypertensive rats. Reasons for the differences between previous results and ours may be ascribed to the different species, ages, nerves, and analyses used. According to the previous method, analyzing only the pressor side,4 our findings of range of reflex sympathetic inhibition calculated from analysis of the pressor side were similar to their data. Another previous study6 using bolus injection could not give an estimate of the β-sympathetic component.7,27 Another important point that should be discussed focuses on the quantification of RSNA. Since the present study was intended to compare the long-term effects of four different antihypertensive agents, it is difficult to compare the absolute values of RSNA before and after treatment in the same rats. Therefore, we used relative changes in the integrated values of voltage and frequency of RSNA.

We observed that SHR had decreased ranges of reflex sympathetic excitation and reflex bradycardia compared with WKY rats. The decreased range of reflex sympathetic excitation in SHR indirectly supports the view that SHR may have increased basal values of sympathetic nerve activity29-31 since the operating point of the MAP-RSNA function curve was increased. The decreased range of reflex bradycardia in SHR may be due to impairment of both vagal activation and β-sympathetic withdrawal since we used the ramp infusion procedure, which gives an estimate of both vagal and β-sympathetic components.27 Thus, our findings support the previous view of impaired central neural integration in hypertensive rats. Moreover, we observed that SHR had no dissociated responses between HR and RSNA. It is, therefore, likely that the impairment of the baroreceptor reflex in SHR may reside in the afferent portion of the reflex arc as well as in the central nervous system.

In SHR, it has been demonstrated that angiotensin II (Ang II), through a central mechanism of action,32 has an inhibitory effect on the baroreceptor reflex.33 Recently, the brain Ang II activity has been shown to impair the baroreceptor reflex in SHR.34 However, in humans and in several forms of experimental hypertension in animals, other factors have been considered as the cause of the impaired baroreceptor reflex. For example, baroreceptor reflex dysfunction appears to be a consequence, rather than a cause, of hypertension,35,36 such as due to decreased carotid and aortic distensibility.37,38 Our findings obtained from SHR treated with each agent show that other factors besides brain Ang II activity might relate to the restoration of baroreceptor reflex sensitivity, at least in early hypertensive SHR.

Hemodynamically, all four agents reduced the blood pressure to a similar level: Downward resetting was induced by antihypertensive treatment with each agent in SHR. In previous studies, direct evidence that the resetting of baroreceptors in hypertension is a reversible process was demonstrated.39 Complete reversal of the baroreceptor resetting was observed within the first 6 hours after pressure normalization, and reversal of the resetting associated with an increase in the sensitivity was also demonstrated.40 Our observations support the previous studies. Since we administered the antihypertensive agents for 2 weeks, the duration is adequate for the downward resetting to occur. The blood pressure reduction per se, which is the common denominator in the resetting associated with an increase in the sensitivity, was almost complete whereas blood pressure was not reduced to the level in untreated WKY rats. Blood pressure reduction per se may restore the baroreceptor reflex sensitivity by three
mechanisms. First, it may reverse functional changes of the baroreceptors. Second, it may reverse changes in the distensibility or structure of the carotid sinus and aortic arch. Third, it may restore the responsiveness of vascular smooth muscle in the carotid sinus and aortic arch to vasodilating substances.

In terms of structural changes, it has been shown that hypertension is associated with decreases in distensibility of the carotid sinus and aortic arch.\(^{41-43}\) It has also been proposed that blood pressure per se is an important determinant of arterial distensibility.\(^{44}\) However, it has been recently demonstrated that without increasing the arterial compliance, a brief period of normalization of blood pressure results in restoration of baroreceptor function.\(^{45}\) Furthermore, as noted previously,\(^{46}\) at 10 weeks of age the aortic wall characteristics of SHR and WKY rats are equivalent. This notion is supported by other investigators,\(^{47}\) who observed that baroreceptor reflex sensitivity increased with age in WKY rats and that the low baroreceptor reflex sensitivity was retained throughout 4–20 weeks of age in SHR. Therefore, we speculate that the reduction in blood pressure restores the impaired baroreceptor sensitivity in early hypertensive SHR, in which vessel distensibility is little damaged.

Other mechanisms besides blood pressure reduction should also be taken into consideration. It has been shown that in SHR, lifelong captopril treatment restores baroreceptor reflex sensitivity via inhibition of brain Ang II activity.\(^{34,48}\) Since enalapril has hydrophilic properties, it seems less likely that this agent restores the baroreceptor reflex sensitivity directly via suppression of brain Ang II activity. However, we cannot completely rule out the possibility of suppression of brain Ang II activity by enalapril since by long-term administration enalapril can penetrate the circumventricular organs of the brain such as the area postrema, which has a fenestrated blood–brain barrier.\(^{49}\) Furthermore, our observations, in which the RSNA range and the range of reflex sympathetic excitation of enalapril-treated SHR did not exceed those of untreated WKY rats and the range of reflex bradycardia was increased by enalapril, may have resulted from the agent's exerting a sympathoinhibitory or a vagomimetic action, or both.\(^{50,51}\) Therefore, enalapril may exert its effect on baroreceptor reflex sensitivity partially via suppression of brain Ang II activity in addition to blood pressure reduction. Additionally, we observed that the restoration of baroreceptor reflex sensitivity is also induced by the other three agents as well as by enalapril. From the mechanisms of action of the other three agents, atenolol may have mainly suppressed the peripheral renin-angiotensin system; conversely, trichlormethiazide and nico-
dipine may have activated it. It seems less likely that the three other agents restore the baroreceptor reflex sensitivity via modulating brain Ang II activity. Thus, we consider that suppression of brain Ang II activity and other mechanisms including blood pressure reduction contribute to the restoration of baroreceptor reflex sensitivity.

Finally, it has been shown that norepinephrine\(^{52}\) or prostaglandin\(^{53}\) sensitizes the baroreceptors and that volume expansion blunts the arterial baroreceptor reflex sensitivity via the cardiopulmonary baroreceptor reflex.\(^{54}\) Each agent used in the present study has been postulated or shown to affect the baroreceptor reflex by the following possible mechanisms. Diuretics may induce volume reduction, increase the norepinephrine concentration, or both. \(\beta\)-Adrenergic receptor blockers may increase baroreceptor afferent discharges.\(^{55}\) Dihydropyridine calcium channel blockers may increase the norepinephrine levels or modulate the central nervous system.\(^{56,57}\) Angiotensin converting enzyme inhibitors may increase the baroreceptor firing rate or stimulate the synthesis of vasodilating prostaglandins.\(^{58}\) However, it is less likely that different agents restore the baroreceptor reflex sensitivity by different mechanisms since we found no differences in the sensitivity of baroreceptor reflex control of RSNA and HR in treated WKY rats.

In summary, the present study demonstrates that attenuation of the development of hypertension by antihypertensive treatment is responsible for restoration of the impaired sensitivity and decreased range of baroreceptor reflex control of RSNA and HR in conscious early hypertensive SHR, although different antihypertensive mechanisms may mediate the blood pressure reduction. These observations have the following implication: at the early hypertensive stage, blood pressure reduction associated with restoration of baroreceptor reflex sensitivity may lead to a lessened risk of end-organ damage due to reduction in regional blood flow regulated by arterial baroreceptor reflexes.

**References**

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**Table 4. Percentage Restoration of Maximum Gain by Antihypertensive Agents in Rats**

<table>
<thead>
<tr>
<th>Function</th>
<th>Untreated</th>
<th>TCM</th>
<th>ATE</th>
<th>NIC</th>
<th>EN</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal sympathetic nerve activity</td>
<td>49±7</td>
<td>83±7</td>
<td>89±9</td>
<td>96±9</td>
<td>86±5</td>
<td>88±8</td>
</tr>
<tr>
<td>Heart rate</td>
<td>62±4</td>
<td>88±6</td>
<td>96±4</td>
<td>92±4</td>
<td>102±7</td>
<td>94±5</td>
</tr>
</tbody>
</table>

Values are fraction of response in spontaneously hypertensive rats over that in untreated Wistar-Kyoto rats. TCM, trichlormethiazide; ATE, atenolol; NIC, nico
dipine; EN, enalapril.
Baroreflex Reactors and Antihypertensive Agents


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