Abstract To investigate the effects of antihypertensive treatment with four currently used agents (trichlormethiazide, atenolol, nicardipine, and enalapril) on the arterial baroreceptor function at the early phase of hypertension, we administered the agents to spontaneously hypertensive rats and Wistar-Kyoto rats from 8 to 10 weeks of age and examined the aortic nerve activity function. In untreated spontaneously hypertensive rats, the relation between the arterial pressure and aortic nerve activity was shifted to the right, that is, to a higher pressure level (threshold pressure, 90±3 versus 76±1 mm Hg, P<.05), and the maximum gain which was obtained by logistic function analysis was depressed (1.55±0.08% versus 2.13±0.09% maximum/mm Hg, P<.05). The antihypertensive agents affected neither the blood pressure nor the aortic nerve activity in Wistar-Kyoto rats. These findings suggest that antihypertensive treatment with the four classes of agents equally enhances the arterial baroreceptor function through blood pressure reduction but not through specific depressor mechanisms at the early stage of hypertension. (Hypertension. 1994;24:808-815.)

Key Words • baroreceptors • trichlormethiazide • rats, inbred SHR • atenolol • nicardipine • enalapril

Baroreceptor activity transmitted to the central nervous system (CNS) is a primary signal concerning moment-to-moment alterations in arterial pressure and represents a fundamental mechanism in the neural control of the circulation because it triggers reflex inhibition of sympathetic nerve activity and excitation of parasympathetic nerve activity that buffers the rise in pressure. It is known that the baroreceptor function is depressed in several forms of hypertension.1-3 Impaired baroreceptor input to the CNS elicits instability of the circulation,4 which tends in turn to lead to increases in cardiovascular morbidity and mortality. Agents that effectively potentiate the baroreceptor function are considered preferable in the treatment of hypertension. Early studies have shown that conventional antihypertensive therapy with combinations of drugs (diuretics, vasodilators, and adrenergic antagonists) increased the baroreceptor sensitivity in spontaneously hypertensive rats (SHRs).5-7 On the other hand, recent investigations have demonstrated that various antihypertensive drugs including calcium antagonists and angiotensin-converting enzyme (ACE) inhibitors, which have become widely used in clinical practice, differently modulate acute resetting of the baroreceptors to hypotension.8,9 We inferred, therefore, that various classes of antihypertensive agents might exert distinct effects on the baroreceptor function through specific pharmacological actions when administered chronically to hypertensive subjects. To test this hypothesis, we treated SHRs with one of four currently used agents (a diuretic, a β-adrenergic blocker, a calcium channel blocker, and an ACE inhibitor) for 2 weeks and examined the effects on the aortic baroreceptor function. Moreover, we used relatively young SHRs (10 weeks of age) in which the characteristics of the aorta are less damaged by hypertension3,10 in order to focus on the actions on the baroreceptors themselves. The results obtained thus provided information on what kinds of agents exert more beneficial influences on the arterial baroreceptors during the developmental phase of hypertension.

Methods

General Procedures

Eight-week-old male SHRs and Wistar-Kyoto (WKY) rats were purchased from Charles River Japan Co. The rats were divided into untreated and treated groups. Untreated SHRs (n=9) and WKY rats (n=9) were fed a normal diet (20 g/d, 0.38% NaCl; Nippon Clea). Treated SHRs (n=36) and WKY rats (n=24) were assigned to four groups and given trichlormethiazide (10 mg/kg per day; Schering Corp), atenolol (90 mg/kg per day; ICI PLC), nicardipine (150 mg/kg per day; Yamanouchi Pharmaceutical Co), or enalapril maleate (10 mg/kg per day; Merck Sharp & Dohme) mixed in the diet. The antihypertensive treatment was continued from 8 to 10 weeks of age. All surgical and experimental procedures were approved by the Institutional Animal Care Guidelines.

At 10 weeks of age, polyethylene catheters prepared from PE-10 (Clay Adams) fused with PE-50 were placed into the

© 1994 American Heart Association, Inc.
Fig 1. Tracings from an enalapril-treated spontaneously hypertensive rat showing arterial pressure, mean arterial pressure, heart rate, original neurogram of aortic nerve activity, mean aortic nerve activity, and root-mean-square of aortic nerve activity during ramp increases in arterial pressure induced by phenylephrine infusion (A) and during ramp decreases in arterial pressure induced by nitroglycerine infusion (B).

abdominal aorta and inferior vena cava through the femoral artery and vein, respectively, under ether anesthesia. One day after implantation of the catheters, the arterial pressure was recorded in the conscious state (AP-611G, Nihon Kohden Co).

Recording and Quantification of Aortic Nerve Activity

The rats were anesthetized with pentobarbital sodium (30 mg/kg IV, Abbott Laboratories), which was supplemented as needed (5 mg/kg IV) to maintain the absence of eyelid and paw-pinch reflexes. A previously described technique for recording renal sympathetic nerve activity (RSNA)" was modified to record aortic nerve activity. After making a midline cervical incision, the left aortic nerve was identified, dissected out, and placed on Teflon-coated multistrand stainless wire electrodes (A-M System, Inc) under a dissecting microscope (SMZ, Nikon). The nerve and the electrodes were fixed with Wacker Sil-Gel 604 (Wacker-Chemie). Aortic nerve activity was amplified using a differential amplifier (AVB-10, Nihon Kohden) with a band pass filter of 50 to 3000 Hz. The amplified activity was rectified and integrated by a root-mean-square integrator (EI-601G, Nihon Kohden) with a time constant of 28 milliseconds and further filtered at 0.08 Hz. We designated this signal as the mean aortic nerve activity and used it as a measure of this parameter. Aortic nerve activity was recorded during changes in mean arterial pressure (MAP). To lower the MAP by 50 to 60 mm Hg in about 20 seconds, nitroglycerine (2.2 mmol/L) was infused at rates of 0.1 to 0.39 mL/min. To raise the MAP by 60 to 70 mmHg in about 20 seconds, phenylephrine (4.9 mmol/L) was infused at rates of 5.86 to 11.5 μL/min.

Data Analysis

The threshold pressure was designated as the MAP at which aortic nerve activity firing disappeared, and the saturation pressure was designated as the MAP at which aortic nerve activity no longer increased, even though the arterial pressure continued to increase.14 The absolute levels of aortic nerve activity measured are dependent on the recording conditions and vary from animal to animal. The data for aortic nerve activity were analyzed using one-way analysis of variance (ANOVA) with Bonferroni post hoc tests. Differences were considered statistically significant at P<.05.

Fig 2. Bar graphs show absolute values of the maximum (top) and baseline (bottom) aortic nerve activity. The maximum aortic nerve activity was similar among all groups. The baseline aortic nerve activity was greater in spontaneously hypertensive rats (SHR) than in Wistar-Kyoto (WKY) rats. U indicates untreated group; TCM, trichlormethiazide-treated group; ATE, atenolol-treated group; NIC, nicardipine-treated group; and EN, enalapril-treated group. Values are mean±SEM. *P<.01, †P<.05 vs Wistar-Kyoto rats.

Downloaded from http://hyper.ahajournals.org/ by guest on April 19, 2017
activity were thus normalized in two ways. In one method, we defined the value of the maximum aortic nerve activity as 100% \cite{1,2}. In the other method, we defined the value of the aortic nerve activity at the baseline MAP as 100% \cite{3,4}. A recent study has demonstrated the existence of two types of firing patterns with static pressure increase in single baroreceptor discharge: (1) a sigmoidal pattern and (2) a hyperbolic pattern \cite{3,4}. In the present study, we recorded the whole nerve activity during natural pulsatile pressure and observed a sigmoidal-shaped curve for the MAP-aortic nerve activity relation. We therefore plotted aortic nerve activity at 5-mm Hg intervals of MAP and fitted the data to a logistic function curve \cite{5,6} by using a nonlinear regression program (PROC NLIN, SAS Institute Inc) on a computer (PS/2 model 50Z, IBM Co). Four parameters were derived from the equation \cite{5,6}:

\[
\text{aortic nerve activity} = P_1 + P_2/(1 + \exp[P_3(P_4 - \text{MAP})])
\]

where \(P_1\) is the aortic nerve activity range, \(P_2\) is the slope coefficient (independent of the range), \(P_3\) is the MAP at the midpoint of the aortic nerve activity range (BP), and \(P_4\) is the lower plateau of aortic nerve activity. The goodness of fit, which was determined by the percentage of the total sums of squares that were accounted for by the model, was greater than 95% in the present study. The sensitivity index of aortic nerve activity was defined as the maximum gain of the logistic function curve: maximum gain = \(P_1 \cdot P_2/P_3\) \cite{7,8,9,10,11}


### Statistical Analysis

Body weight, MAP, absolute values of the maximum and baseline aortic nerve activity, threshold pressure, saturation pressure, and parameters obtained from the logistic function curves were compared by one-way ANOVA with nonrepeated measures in which the effects of strain and treatment were considered independently. This was followed by Scheffe's F test for multiple comparisons. Values are expressed as mean±SEM, and statistical significance was set at \(P<.05\) for untreated.

### Results

Body weight was smaller in SHRs than in WKY rats (198±9 versus 216±10 g, \(P<.05\)); however, within one strain, it was not significantly different between the groups with and without antihypertensive treatment.

### Mean Arterial Pressure

As shown in Table 1, MAP did not significantly differ between the conscious state and the anesthetized state in all groups of rats. The MAP of untreated SHRs was greater than that of untreated WKY rats (\(P<.01\)). The MAPs of the four groups of treated SHRs were lower than that of untreated SHRs (\(P<.01\)) but were still higher than that of WKY rats (\(P<.05\)). MAP did not differ among the four groups of treated SHRs. Antihypertensive treatment did not reduce MAP in WKY rats. These MAP findings were compatible with our previous data \cite{7}.

### Maximum and Baseline Values of Aortic Nerve Activity

Absolute values of the maximum and baseline aortic nerve activity as measured are presented in Fig 2. The maximum aortic nerve activity was comparable between untreated SHRs and untreated WKY rats and was not altered by antihypertensive treatment. On the other hand, the baseline aortic nerve activity was greater in untreated SHRs than in untreated WKY rats (\(P<.01\)). The baseline nerve activity levels in the treated SHR groups were also higher than those in untreated WKY rats (\(P<.05\)) but slightly less than that in untreated SHRs, although the difference did not reach statistical significance. The baseline nerve activity was similar among the four treated SHR groups. The baseline nerve activity did not differ between untreated and treated WKY rats.

### Threshold Pressure and Saturation Pressure of Aortic Nerve Activity

The threshold pressure and saturation pressure as measured are listed in Table 2. Compared with untreated SHRs, although the difference did not reach statistical significance. The baseline nerve activity was similar among the four treated SHR groups. The baseline nerve activity did not differ between untreated and treated WKY rats.

### Table 2. Threshold Pressure and Saturation Pressure of Aortic Nerve Activity in Untreated and Treated Rats

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Untreated (n=9)</th>
<th>TCM (n=6)</th>
<th>ATE (n=6)</th>
<th>NIC (n=6)</th>
<th>EN (n=6)</th>
<th>Untreated (n=9)</th>
<th>TCM (n=6)</th>
<th>ATE (n=6)</th>
<th>NIC (n=6)</th>
<th>EN (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threshold pressure, mm Hg</td>
<td>76±1</td>
<td>76±2</td>
<td>75±3</td>
<td>76±2</td>
<td>78±2</td>
<td>90±3†</td>
<td>78±2</td>
<td>76±3§</td>
<td>76±2</td>
<td>78±2§</td>
</tr>
<tr>
<td>Saturation pressure, mm Hg</td>
<td>146±4</td>
<td>152±5</td>
<td>150±4</td>
<td>145±3</td>
<td>146±3</td>
<td>181±3†</td>
<td>152±7‡</td>
<td>154±4§</td>
<td>157±6§</td>
<td>156±4§</td>
</tr>
</tbody>
</table>

TCM indicates trichlormethiazide-treated group; ATE, atenolol-treated group; NIC, nicardipine-treated group; and EN, enalapril-treated group. Values are mean±SEM.  
\(†P<.01, ‡P<.05\) vs Wistar-Kyoto rats.  
§\(P<.01, §P<.05\) vs untreated.
treated WKY rats, untreated SHRs had an increased threshold pressure ($P<.05$) and an increased saturation pressure ($P<.01$). In all the treated SHR groups, the threshold pressure ($P<.05$) and saturation pressure ($P<.05$ to .01) were decreased compared with those in untreated SHRs. In WKY rats, antihypertensive agents
Hypertension Vol 24, No 6 December 1994

TABLE 3. Logistic Analysis Parameters and Maximum Gain in the Mean Arterial Pressure–Aortic Nerve Activity Relation Expressed as Percentages of the Maximum Nerve Activity

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Untreated (n=9)</th>
<th>TCM (n=6)</th>
<th>ATE (n=6)</th>
<th>NIC (n=6)</th>
<th>EN (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic nerve activity range (P1, % of maximum)</td>
<td>101.2±0.3</td>
<td>101.4±0.2</td>
<td>101.3±0.2</td>
<td>100.7±0.1</td>
<td>101.4±0.2</td>
</tr>
<tr>
<td>Slope coefficient (P2/mm Hg)</td>
<td>0.086±0.005</td>
<td>0.080±0.005</td>
<td>0.082±0.004</td>
<td>0.095±0.005</td>
<td>0.088±0.004</td>
</tr>
<tr>
<td>BP50 (P3, mm Hg)</td>
<td>112±2</td>
<td>115±2</td>
<td>111±3</td>
<td>108±2</td>
<td>110±2</td>
</tr>
<tr>
<td>Lower plateau (P4, % of maximum)</td>
<td>-0.4±0.2</td>
<td>-0.7±0.1</td>
<td>-0.6±0.1</td>
<td>-0.5±0.1</td>
<td>-0.8±0.2</td>
</tr>
<tr>
<td>Maximum gain (P5, % of maximum/mm Hg)</td>
<td>2.18±0.13</td>
<td>2.02±0.15</td>
<td>2.08±0.10</td>
<td>2.40±0.16</td>
<td>2.23±0.10</td>
</tr>
</tbody>
</table>

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

*P<.01 vs Wistar-Kyoto rats.

did not alter either the threshold pressure or the saturation pressure.

Logistic Function Analysis of the Mean Arterial Pressure–Aortic Nerve Activity Relation

Normalization to Maximum Aortic Nerve Activity

The changes in aortic nerve activity in response to changes in arterial pressure and the parameters of logistic function analysis, expressed as percentages of the maximum nerve activity, are shown in Fig 3 and Table 3, respectively. BP50 was higher in untreated SHRs than in untreated WKY rats (P<.01). In the four treated SHR groups, BP50 was decreased as compared with that in untreated SHRs (P<.05). The range of aortic nerve activity was approximately 100% in all groups. Compared with untreated WKY rats, untreated SHRs exhibited a decreased slope coefficient (P<.01). The slope coefficients in the four groups of treated SHRs were increased compared with that in untreated SHRs (P<.05 to .01) to a level similar to that in untreated WKY rats. Accordingly, the maximum gain was decreased in untreated SHRs (P<.01) compared with that in untreated WKY rats, and the maximum gains in the four treated SHR groups were increased compared with that in untreated SHRs (P<.05). Antihypertensive treatment influenced none of the parameters of the aortic nerve activity in WKY rats.

Normalization to Baseline Aortic Nerve Activity

The changes in aortic nerve activity in response to changes in arterial pressure and the parameters of logistic function analysis, expressed as percentages of the baseline nerve activity, are shown in Fig 4 and Table 4, respectively. The slope coefficient and BP50 were the same as those obtained in the analysis with normalization to the maximum nerve activity, since these parameters are independent of normalization. The range of aortic nerve activity was smaller (P<.01) in untreated SHRs than in untreated WKY rats. The aortic nerve activity ranges in all of the treated SHR groups were greater than that in untreated SHRs (P<.01) but were still less than that in WKY rats (P<.01). As a result, also with this normalization method, the maximum gain was smaller in untreated SHRs (P<.01) than in untreated WKY rats, and the maximum gains in all treated SHR groups were increased compared with that in untreated SHRs (P<.05 to .01). In WKY rats, antihypertensive treatment had no effect on the aortic nerve activity function.

TABLE 4. Logistic Analysis Parameters and Maximum Gain in the Mean Arterial Pressure–Aortic Nerve Activity Relation Expressed as Percentages of Baseline Nerve Activity

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Untreated (n=9)</th>
<th>TCM (n=6)</th>
<th>ATE (n=6)</th>
<th>NIC (n=6)</th>
<th>EN (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic nerve activity range (P1, % of baseline)</td>
<td>355±12</td>
<td>369±15</td>
<td>347±14</td>
<td>352±3</td>
<td>338±15</td>
</tr>
<tr>
<td>Slope coefficient (P2/mm Hg)</td>
<td>0.086±0.005</td>
<td>0.080±0.005</td>
<td>0.082±0.004</td>
<td>0.095±0.005</td>
<td>0.088±0.004</td>
</tr>
<tr>
<td>BP50 (P3, mm Hg)</td>
<td>112±2</td>
<td>115±2</td>
<td>111±3</td>
<td>108±2</td>
<td>110±2</td>
</tr>
<tr>
<td>Lower plateau (P4, % of baseline)</td>
<td>-1.5±0.9</td>
<td>-2.6±0.5</td>
<td>-2.1±0.4</td>
<td>-1.1±0.5</td>
<td>-2.5±0.6</td>
</tr>
<tr>
<td>Maximum gain (P5, % of baseline/mm Hg)</td>
<td>7.62±0.56</td>
<td>7.24±0.41</td>
<td>7.06±0.25</td>
<td>8.39±0.70</td>
<td>7.36±0.28</td>
</tr>
</tbody>
</table>

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

*P<.01 vs Wistar-Kyoto rats.

TABLE 3. Logistic Analysis Parameters and Maximum Gain in the Mean Arterial Pressure–Aortic Nerve Activity Relation Expressed as Percentages of the Maximum Nerve Activity

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Untreated (n=9)</th>
<th>TCM (n=6)</th>
<th>ATE (n=6)</th>
<th>NIC (n=6)</th>
<th>EN (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic nerve activity range (P1, % of maximum)</td>
<td>101.2±0.3</td>
<td>101.4±0.2</td>
<td>101.3±0.2</td>
<td>100.7±0.1</td>
<td>101.4±0.2</td>
</tr>
<tr>
<td>Slope coefficient (P2/mm Hg)</td>
<td>0.086±0.005</td>
<td>0.080±0.005</td>
<td>0.082±0.004</td>
<td>0.095±0.005</td>
<td>0.088±0.004</td>
</tr>
<tr>
<td>BP50 (P3, mm Hg)</td>
<td>112±2</td>
<td>115±2</td>
<td>111±3</td>
<td>108±2</td>
<td>110±2</td>
</tr>
<tr>
<td>Lower plateau (P4, % of maximum)</td>
<td>-0.4±0.2</td>
<td>-0.7±0.1</td>
<td>-0.6±0.1</td>
<td>-0.5±0.1</td>
<td>-0.8±0.2</td>
</tr>
<tr>
<td>Maximum gain (P5, % of maximum/mm Hg)</td>
<td>2.18±0.13</td>
<td>2.02±0.15</td>
<td>2.08±0.10</td>
<td>2.40±0.16</td>
<td>2.23±0.10</td>
</tr>
</tbody>
</table>

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

*P<.01 vs Wistar-Kyoto rats.

TABLE 4. Logistic Analysis Parameters and Maximum Gain in the Mean Arterial Pressure–Aortic Nerve Activity Relation Expressed as Percentages of Baseline Nerve Activity

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Untreated (n=9)</th>
<th>TCM (n=6)</th>
<th>ATE (n=6)</th>
<th>NIC (n=6)</th>
<th>EN (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic nerve activity range (P1, % of baseline)</td>
<td>355±12</td>
<td>369±15</td>
<td>347±14</td>
<td>352±3</td>
<td>338±15</td>
</tr>
<tr>
<td>Slope coefficient (P2/mm Hg)</td>
<td>0.086±0.005</td>
<td>0.080±0.005</td>
<td>0.082±0.004</td>
<td>0.095±0.005</td>
<td>0.088±0.004</td>
</tr>
<tr>
<td>BP50 (P3, mm Hg)</td>
<td>112±2</td>
<td>115±2</td>
<td>111±3</td>
<td>108±2</td>
<td>110±2</td>
</tr>
<tr>
<td>Lower plateau (P4, % of baseline)</td>
<td>-1.5±0.9</td>
<td>-2.6±0.5</td>
<td>-2.1±0.4</td>
<td>-1.1±0.5</td>
<td>-2.5±0.6</td>
</tr>
<tr>
<td>Maximum gain (P5, % of baseline/mm Hg)</td>
<td>7.62±0.56</td>
<td>7.24±0.41</td>
<td>7.06±0.25</td>
<td>8.39±0.70</td>
<td>7.36±0.28</td>
</tr>
</tbody>
</table>

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

*P<.01 vs Wistar-Kyoto rats.
TABLE 3. (Continued)

<table>
<thead>
<tr>
<th>Parameter</th>
<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>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic nerve activity range</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(P, % of maximum)</td>
<td>102.0±0.3</td>
<td>101.6±0.2</td>
<td>101.6±0.2</td>
<td>101.4±0.3</td>
<td>100.9±0.3</td>
</tr>
<tr>
<td>Slope coefficient (P, /mm Hg)</td>
<td>0.061±0.003*</td>
<td>0.086±0.005§</td>
<td>0.076±0.004§</td>
<td>0.085±0.007§</td>
<td>0.089±0.006§</td>
</tr>
<tr>
<td>BP, (P, mm Hg)</td>
<td>128±2*</td>
<td>119±3§</td>
<td>116±2§</td>
<td>115±2§</td>
<td>116±2§</td>
</tr>
<tr>
<td>Lower plateau (P, % of maximum)</td>
<td>-0.9±0.2</td>
<td>-0.8±0.1</td>
<td>-0.6±0.1</td>
<td>-0.8±0.2</td>
<td>-0.6±0.2</td>
</tr>
<tr>
<td>Maximum gain (% of maximum/mm Hg)</td>
<td>1.55±0.08*</td>
<td>2.19±0.16§</td>
<td>1.93±0.09§</td>
<td>2.15±0.20§</td>
<td>2.25±0.16§</td>
</tr>
</tbody>
</table>

**Discussion**

The present experiments demonstrate that antihypertensive treatment with four kinds of agents (trichlormethiazide, atenolol, nicardipine, and enalapril) equally augments the aortic baroreceptor function at the early phase of hypertension independent of depressor mechanisms. The decrease in blood pressure per se thus appears to be responsible for the potentiation of the baroreceptor function.

Consistent with earlier studies, the relation between arterial pressure and aortic baroreceptor activity was shifted to a higher pressure level in SHRs. In the present study, we demonstrated a shift not only by the threshold pressure but also by BP, (the arterial pressure at the midpoint of the curve) and saturation pressure. This result indicates that the pressure–baroreceptor activity relation was entirely displaced to a higher pressure level in SHRs.

Interpretation of the data concerning the maximum gain depends in part on the method used to normalize the data. We therefore examined the maximum gain with two methods of normalization, that is, normalization to the maximum and baseline levels. We observed that the maximum gain of the baroreceptor activity in SHRs was depressed compared with that in WKY rats in the analysis with both normalization methods. The decreased maximum gain in SHRs was primarily attributable to the decreased slope coefficient, which is independent of normalization. In normalization to the baseline level, the maximum gain in SHRs was further reduced as compared with that in WKY rats by the decreased range, which resulted from an increased baseline activity. A sustained increase in the baseline baroreceptor activity might be led by a progressive rise in pressure at this developmental phase of hypertension, since at more chronic stage of hypertension the baseline baroreceptor activity in SHRs was similar to that in WKY rats (Ichikawa et al, unpublished observations). The finding that the baseline baroreceptor activity was elevated in early hypertensive SHRs is compatible with previous studies that revealed that the increases in RSNA and blood pressure after ablation of the baroreceptors were greater in SHRs than in WKY rats at this relatively young age. Moreover, this observation indirectly supports the hypothesis that elevated sympathetic nerve activity in SHRs is derived not from the baroreceptors but from central mechanisms such as an enhanced brain renin-angiotensin system (RAS).

Early investigations showed that antihypertensive therapy with combinations of vasodilators, diuretics, and adrenergic antagonists improved the baroreceptor function in SHRs. Recently, Salgado and Krieger have demonstrated that decreases in pressure induced by the calcium antagonist verapamil and hemorrhage similarly

TABLE 4. (Continued)

<table>
<thead>
<tr>
<th>Parameter</th>
<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>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic nerve activity range</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(P, % of baseline)</td>
<td>186±5*</td>
<td>255±12‡</td>
<td>260±9‡</td>
<td>250±10‡</td>
<td>244±8‡</td>
</tr>
<tr>
<td>Slope coefficient (P, /mm Hg)</td>
<td>0.061±0.003*</td>
<td>0.086±0.005§</td>
<td>0.076±0.004§</td>
<td>0.085±0.007§</td>
<td>0.089±0.006§</td>
</tr>
<tr>
<td>BP, (P, mm Hg)</td>
<td>128±2*</td>
<td>119±3§</td>
<td>116±2§</td>
<td>115±2§</td>
<td>116±2§</td>
</tr>
<tr>
<td>Lower plateau (P, % of baseline)</td>
<td>-1.7±0.4</td>
<td>-1.6±0.3</td>
<td>-2.1±0.3</td>
<td>-1.6±0.5</td>
<td>-1.5±0.6</td>
</tr>
<tr>
<td>Maximum gain (% of baseline/mm Hg)</td>
<td>2.84±0.22*</td>
<td>5.37±0.32‡</td>
<td>4.94±0.35§</td>
<td>5.28±0.57‡</td>
<td>5.41±0.48‡</td>
</tr>
</tbody>
</table>
elicited acute baroreceptor resetting. On the other hand, de Abreu and Salgado\textsuperscript{7} reported that acute baroreceptor resetting induced by another calcium antagonist, nifedipine, was greater than that induced by hemorrhage. In vitro studies have also revealed conflicting results, suggesting that baroreceptor activity was affected\textsuperscript{24} or not affected\textsuperscript{25} by calcium antagonists. Regarding ACE inhibitors, it has been reported that captopril facilitated acute baroreceptor resetting to hypotension.\textsuperscript{9} Based on these studies, the hypothesis was put forward that chronic antihypertensive treatment with various types of agents could exert different effects on the baroreceptor function. To examine this hypothesis, we administered one of four agents (a diuretic, a $\beta$-adrenergic blocker, a calcium channel blocker, and an ACE inhibitor) to relatively young SHRs (10 weeks of age) for 2 weeks. Since the aorta in which the baroreceptors are situated is not hypertrophic\textsuperscript{10} and its distensibility is not reduced at this age,\textsuperscript{3} the more direct effects of drug treatment on the baroreceptors could be determined. The treatment period was sufficiently long to evaluate fully the effects of the treatment, since it takes less than 6 days for changes in pressure to alter the baroreceptor function.\textsuperscript{1,2} In this way, we obtained data indicating that antihypertensive treatment with the four classes of agents produced a leftward resetting and potentiated the maximum gain to a similar extent, although different pharmacological actions may mediate the blood pressure reduction. The similarly increased maximum gain in the four treated SHR groups was demonstrated in the analysis with normalization to both the maximum and baseline levels. In addition, the same treatment did not affect the baroreceptor function of WKY rats, in which the blood pressure was unchanged. The decrease in pressure thus appears to be the determinant factor for the augmentation of the baroreceptor function, in agreement with work of Moreira et al.\textsuperscript{1,2} The mechanism whereby the decrease in pressure potentiated the baroreceptor function was not clear from the present study. Humoral factors, which can alter baroreceptor activity through actions on vascular smooth muscle tone, endothelium, and the baroreceptors themselves,\textsuperscript{16,26-28} might be involved in the mechanism. However, specific changes in humoral factors directly related to the actions of the drugs might not have played a role, since the four agents differently influence those factors. Nevertheless, the possibility remains that a decrease in pressure may lead to changes in humoral and/or paracrine factors, which could potentiate the baroreceptor function.

The present results are compatible with data reported by us showing that the four agents similarly potentiated the baroreflex control of heart rate and RSNA.\textsuperscript{12} The similarly enhanced baroreceptor function induced by each of the four agents may well play a crucial role in the potentiation of whole baroreflex responses. It could be argued why in the analysis with normalization to the baseline activity, the maximum gain of the baroreceptor activity in treated SHRs was not comparable with that in WKY rats while the maximum gain of the baroreflex control of RSNA in treated SHRs was comparable with that in WKY rats. Since in the analysis with normalization to the baseline value, the maximum gain is influenced by the difference in the baseline nerve activity, we could not draw, solely from the data normalized to the baseline level, a conclusion as to whether the "true" baroreceptor sensitivity was similar or different between treated SHRs and WKY rats. Alternatively, the discrepancy might be explained by differences in the experimental conditions. Although the baroreflex control of RSNA was examined in conscious rats, the baroreceptor function was examined in anesthetized rats. First, anesthesia may activate the RAS. Brooks et al\textsuperscript{19} demonstrated that angiotensin II (Ang II) reset the baroreflex by pressure-dependent and -independent mechanisms. The site where Ang II affects the baroreflex could include the baroreceptors\textsuperscript{26,27} and the CNS.\textsuperscript{11,22} However, we found in the present study that enalapril, which suppresses the RAS, exerted no effect on the baroreceptor activity in WKY rats while tri-chlormethiazide, which may stimulate or at least does not inhibit the RAS, and enalapril had similar effects on the baroreceptor activity in SHRs. It seems unlikely therefore that the anesthesia affected the baroreceptors through actions on the RAS. Second, arginine vasopres-sin (AVP) secretion also may be stimulated by anesthesia. Several studies have shown that AVP mainly acts centrally to modulate the baroreflex.\textsuperscript{11,13,29,30} In addition, Guo et al\textsuperscript{30} reported that AVP increased baroreceptor activity in rabbits. On the other hand, Yang and Andressen\textsuperscript{27} demonstrated in an in vitro rat aortic arch preparation that AVP exerted inconsistent effects on the baroreceptors, although it tended to decrease baroreceptor activity. No clear conclusion can be drawn, therefore, as to whether or not AVP mediated the possible effects of anesthesia on the baroreceptors. Finally, anesthesia may alter the basal tone of sympathetic nerve activity and its reflex changes.\textsuperscript{31} Since cervical sympathetic nerves have been shown to influence baroreceptor activity,\textsuperscript{32} alterations in sympathetic nerve activity under anesthesia might make some contribution to the discrepancy. As discussed above, it remains unclear whether or how anesthetics may affect the baroreceptor function.

Study Limitations

One limitation of the present study is that the results apply only at the early stage of hypertension and with relatively short-term treatment. During more chronic phases of hypertension and longer treatment, the four agents might affect the baroreceptor function in different ways (Ichikawa et al, unpublished observations).

Summary

The present experiments demonstrated that antihypertensive treatment with the four classes of agents equally induced a leftward resetting and equally increased the maximum gain of the aortic baroreceptor activity in early hypertensive SHRs.

Acknowledgments

This work was supported by a research grant (No. 04770552) from the Ministry of Education, Japan. The findings described in this study were presented in part at the 47th Annual Fall Conference and Scientific Sessions of the Council for High Blood Pressure Research, San Francisco, Calif, September 28 through October 1, 1993.

References


Effects of antihypertensive agents on baroreceptor function in early hypertensive rats.
M Ichikawa, H Suzuki, K Kumagai, M Ryuzaki, H Kumagai, M Jimbo, M Nishizawa and T Saruta

Hypertension. 1994;24:808-815
doi: 10.1161/01.HYP.24.6.808
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1994 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on
the World Wide Web at:
http://hyper.ahajournals.org/content/24/6/808

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally
published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center,
not the Editorial Office. Once the online version of the published article for which permission is being
requested is located, click Request Permissions in the middle column of the Web page under Services.
Further information about this process is available in the Permissions and Rights Question and Answer
document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/