Unique Resistance to Guanethidine-Induced Chemical Sympathectomy of Spontaneously Hypertensive Rats
A Resistance Overcome by Treatment with Antibody to Nerve Growth Factor

EUGENE M. JOHNSON, JR., AND RICHARD A. MACIA

SUMMARY The chronic administration of high doses of guanethidine to rats produces complete destruction of the peripheral sympathetic nervous system. In a study of the effect of guanethidine-induced sympathectomy on the development of hypertension in spontaneously hypertensive rats (SHR, Okomoto strain), only a partial sympathectomy could be produced as assessed by biochemical parameters (tyrosine hydroxylase activity in ganglia and tissue norepinephrine concentrations) and by evaluation of response to stimulation of vasomotor outflow in pithed rat preparations. Other strains of rats (Sprague-Dawley, American Wistar, Kyoto Wistar) were uniformly sensitive to guanethidine sympathectomy. The resistance to guanethidine was not due to a lower accumulation of guanethidine in the neurons of SHR. Addition to the guanethidine treatment of low doses of antibody to nerve growth factor (NGF), which itself produced only a modest sympathectomy, resulted in an almost complete sympathectomy. SHR did not become hypertensive when sympathectomized by combined guanethidine-anti NGF. These results show that the sympathetic neurons of SHR differ from those of other strains with respect to sensitivity to guanethidine cytotoxicity and suggest the possibility of a role for NGF in that altered responsiveness. Circ Res 45: 243-249, 1979

THE ROLE of the sympathetic nervous system in human essential hypertension and in animal models of essential hypertension remains controversial despite intensive study for many years. A major ap-
to nerve growth factor (immunosympathectomy; Levi-Montalcini and Angeletti, 1966) or 6-hydroxydopamine (Angeletti and Levi-Montalcini, 1970). The chemical sympathectomy produced by the neonatal administration of 6-hydroxydopamine also has the disadvantage of producing marked effects on central noradrenergic neurons (Clark et al., 1972; Jacks et al., 1972), and hence, it does not produce a strictly peripheral sympathectomy. Both methods produce permanent sympathectomy only when administered to neonates.

Over the last few years, we have systematically characterized (Johnson et al., 1976; Johnson and O'Brien, 1976) the permanent chemical sympathectomy produced in rats by the chronic administration of guanethidine to neonatal or adult rats (Jensen-Holm and Juul, 1971; Burnstock et al., 1971; Eranko and Eranko, 1971). We have shown that the sympathectomy is superior to that caused by previously used methods in that: (1) functional innervation of the vasculature is destroyed in the neonate and reduced by about 90% in rats treated as adults (as determined in pithed rat preparations); (2) there are no discernible transient or permanent effects on central noradrenergic neurons; and (3) this sympathectomy is achieved with little or no mortality or growth deficit in the Sprague-Dawley (S-D) rat.

Having characterized (in S-D rats) this model of sympathectomy, we proceeded to apply the method to spontaneously hypertensive rats (SHR, Okomoto strain). Our objectives were to determine the effect of sympathectomy in neonates (prior to development of hypertension) and adults (after hypertension is developed) on the hypertension in these rats. Unexpectedly, we found that SHR are resistant to guanethidine-induced chemical sympathectomy, a resistance not shared by normal Wistar and Kyoto Wistar rats. An essentially complete sympathectomy was achieved by adding a small amount of nerve growth factor (NGF) antiserum to the treatment regimen in neonatal rats.

Methods

Treatment of Animals

Pregnant S-D or American Wistar rats were obtained from commerical suppliers (Zivic-Miller and Charles River, respectively). SHR and Kyoto Wistar rats were obtained from the National Institutes of Health and bred in this laboratory. SHR were brother/sister mated. Neonates were treated as previously described (Johnson et al., 1976) by subcutaneous injection of guanethidine sulfate, 50 mg/kg per day (kindly supplied by Ciba), 5 days per week for 3 weeks starting at 7 days of age. Adult SHR (9-14 weeks) were treated with 40 mg/kg per day, 5 days/week for 5 weeks (Johnson and O'Brien, 1976).

The biochemical studies were carried out on rats killed by decapitation. Tissues were removed, rinsed in iced saline, blotted dry, and frozen on dry ice. Norepinephrine (NE) was assayed in tissues homogenized in 3-5 ml of cold 0.4 N HClO₄. After centrifugation, catecholamines were adsorbed onto alumina at pH 8.2-8.4 and eluted into 2 ml of 0.1 N acetic acid. NE was determined by the trihydroxyindole method as described by Chang (1964).

Tyrosine hydroxylase (TOH) activity was determined as described by Mueller et al. (1969) (Tables 2 and 4) or by a minor modification of the method described by Phillipson and Sandler (1975) (Table 7). Final concentrations of 40 μM tyrosine and 825 μM DMHP, were used. Assays were carried out under conditions linear with time and enzyme concentration. Protein was measured by the method of Lowry et al. (1951).

Experiments to evaluate functional innervation of the vasculature were done by measuring the response to stimulation of the sympathetic vaso-motor outflow in the pithed rat preparation (Gillespie and Muir, 1967). Rats were anesthetized with sodium pentobarbital (35 mg/kg, ip) and the trachea, jugular vein, and carotid artery were cannulated. Blood pressure and heart rate were recorded via the carotid artery by means of a Statham pressure transducer and recorded on a Grass polygraph or Beckman dynagraph.

Bilateral adrenalectomy was performed via an abdominal incision and the abdomen closed with wound clips. The rats were allowed to stabilize, and blood pressure and heart rate were recorded. The rats were then artificially respired (Harvard rodent respirator) with room air and were pithed through an orbit of the eye with a steel rod. After pithing, the rats were administered d-tubocurarine (1.2 mg/kg, iv) and atropine sulfate (1.5 mg/kg, iv) to block somatic and parasympathetic outflows, respectively. The blood pressure rise elicited by stimulation of the vasomotor outflow was determined by stimulating the steel rod with a Grass stimulator with supramaximal rectangular pulses (60 V, 1 msec in duration) of increasing frequency for 20 seconds. Three to 5 minutes were allowed between each stimulation.

Guanethidine accumulation in ganglia was determined in neonatal animals treated with 50 mg/kg per day as described above. Ganglia were removed and assayed for guanethidine content by a fluorometric method based on the formation of a phenanthrenequinone derivative (Johnson and Hunter, in press).

Antibody to NGF was prepared by injecting NGF prepared by the method of Bocchini and Angeletti (1969) (kindly supplied by Dr. Ralph Bradshaw) into foot pads of New Zealand rabbits (1 mg protein in 50% saline-50% complete Freunds adjuvant) with periodic boosting. Rabbits were bled and sera obtained. Sera were bioassayed in the classical dorsal root ganglion assay (Levi-Montalcini et al., 1954). All sera used obliterated the response of 1 BU of
NGF at a dilution of 1/1000 or greater. Anti-NGF was administered (0.2–0.3 ml sc) to rats on the 4th day of each treatment week (i.e., days 11, 18, and 25 of age).

Analysis of the statistical significance of differences between treated and control groups were by Student’s t-test (two-tailed). In Tables 6 and 7, comparisons among the four groups were made by the analysis of variance followed by multiple comparisons using the Scheffe test for variables showing homogeneity of variance with Bartlett’s test (Blood pressure, Table 6).

For the other variables (heart rate, Table 6; Table 7), a logarithmic transformation failed to produce homogeneity of variances. Therefore, the Kruskal-Wallis rank test, which is not dependent on this assumption or the normality assumption, was used with multiple comparisons made by the appropriate formula (Gibbons, 1976).

Results

Neonatal SHR were treated with guanethidine using a protocol which previously (Johnson et al., 1976) had been shown to produce an essentially complete sympathectomy of S-D rats. Unexpectedly, guanethidine-treated SHR showed no evidence of functional denervation of vasculature as assessed in the pithed rat preparation (Fig. 1). Similar increases in pressure in response to nerve stimulation were seen in treated and control rats. Raising the dose of guanethidine and extending the treatment did not result in functional denervation (Fig. 1).

Because of the striking difference in the response of S-D rats and SHR to the guanethidine treatment, other strains of rats were examined. Treatment of neonatal Kyoto Wistar rats, the parent strain of the SHR, resulted in a complete abolition of the response to stimulation of vasomotor outflow (Fig. 2). Similarly, guanethidine treatment produced functional denervation of the vasculature in Wistar rats obtained from an American supplier (Charles River) (data not shown). In all cases, rats were assessed at 10–12 weeks of age; that is, 6–8 weeks after the last injection of guanethidine. Hence, the SHR is the only strain of rat tested that was resistant to guanethidine. The data in Table 1 show the effect of neonatal guanethidine treatment on the mean arterial pressures in pentobarbital-anesthetized adult rats (at least 10 weeks old) of the four strains. Guanethidine treatment resulted in a decrease in blood pressure in all four strains. The decrease in the SHR (7%) was much smaller than the decrease (18–26%) seen in the other strains.

Two biochemical parameters were used to assess the degree of sympathectomy produced by guanethidine.
TABLE 2  Effect of Neonatal Guanethidine Treatment on the TOH Activity in Superior Cervical Ganglia of SHR and Other Strains of Rat

<table>
<thead>
<tr>
<th>Strain</th>
<th>Treatment</th>
<th>Enzyme activity (nmol/g pair per hr)</th>
<th>% Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-D</td>
<td>Saline, 3 wks</td>
<td>1.67 ± 0.18 (7)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Guan (50), 3 wks</td>
<td>0.07 ± 0.02 (7)</td>
<td></td>
</tr>
<tr>
<td>Wistar</td>
<td>Saline, 3 wks</td>
<td>3.49 ± 0.25 (5)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Guan (50), 3 wks</td>
<td>0.10 ± 0.04 (4)</td>
<td></td>
</tr>
<tr>
<td>SHR</td>
<td>Saline, 3 wks</td>
<td>2.05 ± 0.26 (6)</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>Guan (50), 3 wks</td>
<td>0.55 ± 0.15 (6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Guan (50), 2 wks + guan (75), 2 wks</td>
<td>1.05 ± 0.16 (3)</td>
<td>51</td>
</tr>
<tr>
<td>Kyoto Wistar</td>
<td>Saline, 3 wks</td>
<td>2.03 ± 0.22 (5)</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Guan (50), 3 wks</td>
<td>0.29 ± 0.07 (4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Guan (50), 3 wks k+ guan (75), 1 wk</td>
<td>0.12 ± 0.07 (4)</td>
<td>5</td>
</tr>
</tbody>
</table>

* Rats were treated as described in Methods with daily doses (mg/kg) of guanethidine (guan) shown in parentheses. Rats were killed at 10-13 weeks of age.
† Each value represents the mean ± SEM of number of observations shown in parentheses.

Guanethidine is unique among agents which destroy sympathetic neurons in that cytotoxic effects also are seen in animals treated as adults. 6-Hydroxydopamine destroys nerve terminals, but not cell perikarya, and, hence, regeneration rapidly occurs. In contrast to the dramatic effects of chronic treatment in adult S-D rats (Johnson and O'Brien, 1976), adult SHR are resistant to guanethidine. Adult SHR were treated with guanethidine for 5 weeks and the status of the sympathetic nervous system evaluated 4-5 weeks after stopping treatment. The increase in blood pressure resulting from stimulation of the vasomotor outflow in pithed rats was only slightly reduced (Fig. 3). This is in contrast to the 90% decrease in response seen in S-D rats (Johnson and O'Brien, 1976). Likewise, the biochemical parameters are reduced only by 40-50% (Table 4). Heart NE was reduced by 48% as compared to reduction to undetectable levels in S-D rats. Ganglionic TOH was reduced only by 43% as compared to an 85% decrease in S-D rats (Johnson and O'Brien, 1976).

An obvious possibility to explain resistance to

TABLE 3  Effect of Neonatal Guanethidine Treatment on the NE Concentration in Heart and Spleen of SHR and Other Strains of Rat

<table>
<thead>
<tr>
<th>Strain</th>
<th>Tissue</th>
<th>Control</th>
<th>Guanethidine†</th>
<th>% Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-D</td>
<td>Heart</td>
<td>317 ± 65 (7)</td>
<td>ND†</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Spleen</td>
<td>306 ± 45 (7)</td>
<td>ND</td>
<td>0</td>
</tr>
<tr>
<td>Wistar</td>
<td>Heart</td>
<td>253 ± 56 (4)</td>
<td>ND</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Spleen</td>
<td>1246 ± 142 (4)</td>
<td>35 ± 8 (4)</td>
<td>4</td>
</tr>
<tr>
<td>SHR</td>
<td>Heart</td>
<td>295 ± 55 (5)</td>
<td>62 ± 20 (6)</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Spleen</td>
<td>292 ± 57 (3)</td>
<td>70 ± 21 (4)</td>
<td>24</td>
</tr>
<tr>
<td>Kyoto Wistar</td>
<td>Heart</td>
<td>818 ± 137 (4)</td>
<td>12 ± 4 (4)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Spleen</td>
<td>748 ± 66 (4)</td>
<td>45 ± 11 (4)</td>
<td>6</td>
</tr>
</tbody>
</table>

* Each value represents the mean ± SEM of the number of observations shown in parentheses.
† Treatment (50 mg/kg per day for 3 weeks) carried out as described in Methods. Rats were killed at 10-13 weeks of age.
‡ ND = not detectable.
guanethidine-induced chemical sympathectomy in the SHR would be that guanethidine does not accumulate in the ganglia of SHR to attain concentrations reached in the ganglia of the other strains of rats. This does not appear to be the case. Guanethidine concentration was determined in superior cervical ganglia 24 hours after the last of three daily injections of guanethidine (50 mg/kg per day). Guanethidine reaches maximal levels after two injections (Johnson and Hunter, in press). The concentration (Table 5) was not statistically different in ganglia of SHR or Kyoto Wistar rats.

Because the cytotoxic effects of guanethidine on sympathetic neurons can be prevented by concomitant administration of NGF (Johnson and Aloe, 1974), we asked if the addition of small amounts of antibody of NGF (anti-NGF), combined with guanethidine, would lead to a complete sympathectomy in SHR. To the standard guanethidine treatment of neonatal SHR, a small amount (0.2-0.3 ml) of NGF antisera was added on the 4th day of each treatment week (i.e., day 11, 18, and 25 of age). The results of these experiments are shown in Figure 4 and Tables 6 and 7. The evaluation of functional innervation of the vasculature in pithed rats 15 shown in Figure 4. In contrast to the results seen in Figure 1, the guanethidine treatment alone produced a modest (about 50%) decrease in response to stimulation. Anti-NGF alone produced a similar decrease in response. The combined treatment of guanethidine and anti-NGF produced an almost complete functional denervation of the vasculature. The effects of the various treatments on blood pressure and heart rate in pentobarbital anesthetized SHR, before and after acute adrenalectomy, are shown in Table 6. Consistent with earlier results (Table 1), neonatal guanethidine treatment lowered blood pressure only slightly. Likewise, anti-NGF lowered pressure only slightly. The combined treatment, however, lowered blood pressure to nonhypertensive levels. The blood pressure dropped markedly after acute adrenalectomy, indicating that under these experimental conditions adrenal catecholamines are of major importance in the maintenance of the elevated blood pressure. Again, only in animals receiving combined anti-NGF/guanethidine did the blood pressure fall to a level lower than that in untreated rats.

The significantly more complete sympathectomy, produced by combined guanethidine/anti-NGF treatment over either agent alone, also is shown by the analysis of TOH in sympathetic ganglia (Table 7). In contrast to guanethidine or anti-NGF alone, either of which reduces TOH activity in superior cervical ganglia by about 50-60%, the combined treatment reduced TOH activity by more than 90%, thereby indicating a sympathectomy similar to that produced by guanethidine alone in the other strains. Similar reductions in TOH activity were produced in celiac ganglia.

![Figure 3](https://example.com/image3.png)

**Figure 3** Response (mean ± SEM) to stimulation of the vasomotor outflow in adrenalectomized pithed SHR treated as adults with saline (control) or guanethidine (as described in Methods). Initial mean arterial blood pressures were: control (211 ± 15 mm Hg) and guanethidine (200 ± 11 mm Hg). There was no statistical difference in the response of treated and control groups except at 1 Hz (P < 0.05).

### Table 5 Accumulation of Guanethidine in the Superior Cervical Ganglia of SHR and Kyoto Wistar Rats

<table>
<thead>
<tr>
<th>Strain</th>
<th>nmol guanethidine/pair</th>
<th>µg protein/pair</th>
<th>nmol/mg protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHR</td>
<td>0.50 ± 0.11</td>
<td>91 ± 3 (4)</td>
<td>5.52</td>
</tr>
<tr>
<td>Kyoto Wistar</td>
<td>0.46 ± 0.01</td>
<td>85 ± 4 (5)</td>
<td>5.38</td>
</tr>
</tbody>
</table>

* 7-day-old rats were treated with guanethidine (50 mg/kg per day) for three injections. Rats were killed 24 hours after last injection (11 days old), ganglia removed, and guanethidine determined as described in Methods. Each value is the mean ± SEM of three samples of three pairs each.

† Kyoto Wistar rats and SHR (11 days old) were killed, superior cervical ganglia removed, and protein content determined by the Lowry (15) method. Each value is the mean ± SEM of number of rats shown in parentheses.
suggested that the guanethidine-induced chemical
treatment of SHR treated neonatally (as described in
preparation of SHR treated neonatally (as described in
sympathectomy would provide a means of unam-
methods of
sympathectomy, as described in the introduction,
sympathectomy produced by gua-
early 1978), guanethidine produced significant
sympathetic nervous function in the development
modest decrease in function involved larger num-
Figure 4 Responses (mean ± SEM) to stimulation of
vasomotor outflow in the adrenalectomized pithed rat
with no drug (control, n = 27), guanethidine
(n = 7), anti-NGF (n = 13), or combined guanethidine
and anti-NGF (n = 12). Initial mean blood pressures
are shown in Table 6.

Discussion

The deficiencies of currently existing methods of
sympathectomy, as described in the introduction,
suggested that the guanethidine-induced chemical
sympathectomy would provide a means of unam-
biguously assessing the requirement for peripheral
sympathetic nervous function in the development
and maintenance of hypertension in the SHR.
Experiments carried out to test this idea produced the
unexpected observation that SHR are uniquely re-
sistant to the sympathectomy produced by gua-
ethidine. In our initial experiments (Fig. 1), we
found that guanethidine produced no functional
impairment of the innervation of the vasculature
and only a partial sympathectomy assessed by bio-
chemical criteria. Other strains of rats, including
Kyoto Wistar, were uniformly sensitive to guanethi-
dine. The sympathectomy produced in these other
strains was entirely consistent with those in our
previous reports (Johnson et al., 1976) on S-D rats.

The resistance of the SHR to guanethidine does
not appear related to failure of the neurons in the
SHR to accumulate guanethidine. Raising the dose
of guanethidine or prolonging treatment does not
improve the sympathectomy. Direct chemical
analysis shows no difference in the level of guanethidine
in ganglia of treated SHR or Kyoto Wistar rats. Also,
administration of a cytotoxic guanethidine
analog, which accumulates to a concentration twice
that of guanethidine, also fails to sympathectomize
SHR completely, whereas S-D rats are completely
sympathectomized (unpublished observation). Hence,
it appears that there is a distinct difference in the
neurons of the SHR that allows these neurons to
tolerate better high concentrations of guanethi-
dine.

We previously have reported that the cytotoxic
effects of guanethidine on sympathetic neurons can
be prevented by the concomitant administration of
NGF (Johnson and Aloe, 1974). Speculating that
perhaps there is an excess of NGF in SHR or that
SHR are particularly sensitive to NGF that antag-
ognizes the action of guanethidine, we attempted to
determine if low doses of anti-NGF would augment
the cytotoxicity of guanethidine. The results ob-
tained show that combined guanethidine/anti-NGF
treatment produced an essentially complete func
tional and biochemical sympathectomy, and in the
absence of a sympathetic nervous system, hyperten-
sion failed to develop in the SHR. Although the
biochemical results obtained in the initial and later
experiments are quite consistent (Table 2 and Table
7), differences were noted with respect to functional
sympathectomy produced by guanethidine alone
(Figs. 1 and 4). The reason for this is not clear. The
initial experiment (Fig. 1) showing no functional
deficit was carried out on a small group of animals,
whereas the later experiment (Fig. 4) showing a
modest decrease in function involved larger num-
bers of rats. These experiments were carried out
almost 3 years apart, and some change in the colony
may have occurred. This is also suggested by the
fact that we have observed, in our earlier experi-
ments (late 1974), that guanethidine was well tol-
erated by SHR, but in later experiments (1977,
early 1978), guanethidine produced significant
weight loss and mortality in SHR but not in S-D
rats. In any event, the level of hypertension in the

| TABLE 6 Blood Pressure and Heart Rates in SHR Treated Neonatally with
<p>| Guanethidine, Anti-NGF, or Combined Treatment |
|-------------------------------|----------------|----------------|----------------|----------------|----------------|----------------|
|                              | Initial         | Post-adrenalectomy |</p>
<table>
<thead>
<tr>
<th>Treatment*</th>
<th>BP (mm Hg)</th>
<th>HR</th>
<th>BP (mm Hg)</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>27±179*</td>
<td>4±27±385*</td>
<td>24±97*</td>
<td>5±24±347±8</td>
</tr>
<tr>
<td>Anti-NGF</td>
<td>13±167</td>
<td>5±13±439</td>
<td>13±99±6</td>
<td>13±396±111</td>
</tr>
<tr>
<td>Guanethidine</td>
<td>7±189</td>
<td>12±7±419</td>
<td>7±113±11</td>
<td>7±397±24</td>
</tr>
<tr>
<td>Guanethidine + anti-NGF</td>
<td>12±129</td>
<td>8±12±414</td>
<td>9±69±58</td>
<td>9±369±6</td>
</tr>
</tbody>
</table>

BP = blood pressure; HR = heart rate.
* Rates (15 weeks of age) were examined during pithing procedure as described in Methods.
† Significantly different from mean of guanethidine + anti-NGF-treated rats (P < 0.01).
‡ Significantly different from mean in control rats (P < 0.01).
§ Significantly different from mean in control rats (P < 0.05).
Consistent with other reports, deprivation of pemo SHR (Follkow et al., 1972; Cutilletta et al., 1977) is not clear. Although our rationale for the combined use of guanethidine and anti-NGF was a 30,000 molecular weight protein. Proc Natl Acad Sci USA 64: 787-794

The mechanism underlying the unique resistance of the SHR to guanethidine-induced hypertension is not clear. Although our rationale for the combined use of guanethidine and anti-NGF was a possible “enhanced” NGF system in SHR, our data are insufficient to provide a strong argument for such a phenomenon. A much more systematic study, using various doses of the agents and involving other strains of rats, would be required to demonstrate synergism as opposed to additive effects. It does, however, suggest that the possibility that some anomaly of the NGF response, either peripherally or centrally, may play a role in the enhanced sympathetic nervous activity which appears to participate in the development of hypertension in the SHR.

Acknowledgments

We would like to thank Brian Greenberg, Ferdinand O’Brien, and Sarah Oldham for their excellent technical assistance. Statistical analysis in Tables 6 and 7 was carried out by Barbara Hixon, Division of Biostatistics, Washington University Medical School.

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Table 7: TOH Activity in Sympathetic Ganglia of SHR Treated Neonatally with Guanethidine, Anti-NGF, or Combined Treatment

<table>
<thead>
<tr>
<th>Treatment*</th>
<th>n</th>
<th>Mean</th>
<th>SEM</th>
<th>n</th>
<th>Mean</th>
<th>SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>29</td>
<td>2.06</td>
<td>0.13</td>
<td>18</td>
<td>1.35</td>
<td>0.20†</td>
</tr>
<tr>
<td>Anti-NGF</td>
<td>20</td>
<td>0.86</td>
<td>0.08‡</td>
<td>13</td>
<td>0.82</td>
<td>0.07†</td>
</tr>
<tr>
<td>Guanethidine</td>
<td>11</td>
<td>0.93</td>
<td>0.14‡</td>
<td>9</td>
<td>0.72</td>
<td>0.16</td>
</tr>
<tr>
<td>Guanethidine + anti-NGF</td>
<td>21</td>
<td>0.17</td>
<td>0.03‡</td>
<td>11</td>
<td>0.18</td>
<td>0.06‡</td>
</tr>
</tbody>
</table>

* Rats were treated as described in Methods and killed at 15 weeks of age.
† Significantly different from guanethidine + anti-NGF group (P < 0.01) by Kruskal-Wallis test.
‡ Significantly different from control group (P < 0.01) by Kruskal-Wallis test.
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E M Johnson, Jr and R A Macia

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