Sodium Responsiveness of Central $\alpha_2$-Adrenergic Receptors in Spontaneously Hypertensive Rats

JOHN P. KOEPKE, SUSAN JONES, AND GERALD F. DIBONA

SUMMARY The responsiveness of central nervous system $\alpha_2$-adrenergic receptors in the neural control of renal function was compared in conscious spontaneously hypertensive rats (SHR) and normotensive Wistar-Kyoto rats (WKY) on normal or high sodium intake (3-4 weeks of 1% NaCl for drinking). The responsiveness of central $\alpha_2$-adrenergic receptors was determined by comparing among groups the dose-response curves for the effects of cumulative intracerebroventricular injections of guanabenz (5, 25, and 125 $\mu$g) on changes in mean arterial pressure, renal sympathetic nerve activity, and urinary sodium excretion. Guanabenz altered mean arterial pressure similarly in SHR on normal or high sodium intake and in WKY on normal or high sodium intake. High sodium intake shifted the guanabenz-renal sympathetic nerve activity and guanabenz-urinary sodium excretion dose-response curves to the left in SHR and to the right in WKY. The dose-response curves between SHR and WKY on normal sodium intake were similar. Surgical renal denervation or pretreatment with an $\alpha_2$-adrenergic receptor antagonist (rauwolscine, 30 $\mu$g i.c.v.) attenuated the ability of guanabenz to inhibit renal sympathetic nerve activity or increase urinary sodium excretion in SHR and WKY on either normal or high sodium intake. We conclude that the responsiveness of central nervous system $\alpha_2$-adrenergic receptors regarding the neural control of renal function is increased by high sodium intake in conscious SHR, but not in conscious normotensive WKY. (Hypertension 11: 326–333, 1988)

KEY WORDS • renal function • sodium intake • central nervous system • guanabenz

INJECTION of the $\alpha_2$-adrenergic receptor agonists guanabenz or clonidine into the lateral cerebral ventricle or central amygdaloid nucleus prevents the increased renal sympathetic nerve activity and antinatriuretic responses to environmental stress in conscious spontaneously hypertensive rats (SHR).$^1,2$ The ability of these $\alpha_2$-adrenergic receptor agonists to block the renal responses to environmental stress is reversed by $\alpha_2$-adrenergic receptor antagonists, indicating a specific $\alpha_2$-adrenergic receptor mechanism.$^1,2$

High dietary sodium intake (15 days of isotonic saline for drinking) enhances the increased renal sympathetic nerve activity and antinatriuretic responses to environmental stress in conscious SHR.$^3$ Thus, high sodium intake increases the responsiveness of the central nervous system to environmental stress as relates to the neural control of renal function. Consistent with this finding, long-term isotonic saline ingestion in Sprague-Dawley rats results in enhanced increases in peripheral sympathetic nerve activity in response to electrical stimulation of the ventromedial hypothalamus relative to water ingestion.$^4$ Other recent data show that stimulation of $\alpha_2$-adrenergic receptors in the anterior hypothalamus decreases mean arterial pressure more in SHR on high than on normal sodium intake, suggesting that high sodium intake increases the responsiveness of anterior hypothalamic $\alpha_2$-adrenergic receptors with regard to mean arterial pressure.$^5$

In light of these reports, we examined whether the responsiveness of central nervous system $\alpha_2$-adrenergic receptors is altered by high dietary sodium intake in conscious SHR and WKY with regard to the neural control of renal function.

Materials and Methods

Male SHR ($n = 52$) and WKY ($n = 40$), 12 to 13 weeks of age, were used for experiments (Harlan, Indianapolis, IN, USA). Three to 4 weeks before experi-
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Rats were anesthetized with ketamine HCl (Ketaset; 150 mg/kg), and catheters were surgically implanted into the jugular vein, carotid artery, and lateral cerebroventricle 1 to 3 days before experimentation. The venous and arterial catheters (Tygon, U.S. Stoneware, Akron, OH, USA) were tunneled to the back of the neck, filled with heparinized saline (100 U/ml; Elkins-Sinn), and plugged with stainless steel pins. With the skull surface level between bregma and lambda, a stainless steel cannula (23 gauge) was stereotaxically implanted into the right lateral cerebral ventricle according to the coordinates of Paxinos and Watson: 0.3 mm posterior to bregma, 1.4 mm lateral to midline, and 4.5 mm below skull surface. Verification of cannula location in the cerebroventricular system was accomplished by either observing spontaneous flow of cerebrospinal fluid after removal of the obturator (30-gauge stainless steel wire) or injecting dye into the lateral cerebroventricular cannula with subsequent postmortem brain section. The venous catheter was used for saline infusions, the arterial catheter was used for arterial pressure recordings, and the cerebroventricular cannula was used for intracerebroventricular (i.c.v.) drug injections. Renal denervation was performed in some rats through bilateral flank incisions by surgically stripping the renal arteries and veins of adventitia and cutting all visible renal nerve bundles under a dissecting microscope (25 ×) and coating the vessels with a solution of 10% phenol in 95% ethanol, as previously described. A period of 7 to 10 days was allowed for recovery from the operation. This renal denervation procedure prevents the antinatriuretic response to stress, prevents the vasoconstrictor response to supra-renal lumbar sympathetic nerve stimulation, reduces renal catecholamine histofluorescence to nondetectable levels, and reduces renal norepinephrine concentration to less than 10% of control.

On the experimental day, rats were anesthetized with methohexital sodium (Brevital; 20 mg/kg i.v., supplemented by 10 mg/kg i.v. as needed; Eli Lilly) and a bladder cannula and an electrode for recording renal sympathetic nerve activity were implanted. Through a suprapubic incision, a polyethylene cannula (PE-240) was sutured into the urinary bladder, exteriorized, and secured by suturing to adjacent muscle, subcutaneous tissue, and skin. To implant the electrode for recording renal sympathetic nerve activity, the left kidney was exposed through a left flank incision using a retroperitoneal approach. With the aid of a dissecting microscope (25 ×), a renal nerve branch was dissected from the aortorenal ganglion and placed on a bipolar silver or platinum wire (Cooner Wire, Chatsworth, CA, USA) electrode. Renal sympathetic nerve activity was amplified (10,000–50,000 times) and filtered (low, 30 Hz; high, 3000 Hz) using a high impedance probe and bandpass amplifier (Models HIP511 and PS11, Grass, Quincy, MA, USA). The amplified and filtered signal was channeled to a Tektronix 5113 oscilloscope (Beaverton, OR, USA) and Grass Model 7DA polygraph for visual evaluation, to an audio amplifier/loudspeaker (Grass Model AM 8 audio monitor) for auditory evaluation, and to a rectifying voltage integrator (Grass Model 7P10). The integrated voltage and renal neurogram signals were displayed on the Grass polygraph. The quality of the renal sympathetic nerve signal was assessed intraoperatively by examining the magnitude of decrease in recorded renal sympathetic nerve activity during sinoaortic baroreceptor unloading with an intravenous (i.v.) injection of norepinephrine (3 μg) and the magnitude of increase in recorded renal sympathetic nerve activity during sinoaortic baroreceptor unloading with an i.v. injection of acetylcholine (1 μg). The renal nerve activity remaining after maximum inhibition following norepinephrine administration (3 μg i.v.) was similar to the background noise observed 30 to 45 minutes postmortem (<1 integrator reset/min); this value was subtracted from all experimental values of renal sympathetic nerve activity. When an optimal renal sympathetic nerve activity signal was observed, the recording electrode was fixed to the renal nerve branch with a silicone cement (Wacker Sil-Gel 604, Wacker-Chemie, Munich, FRG). The electrode cable was tunneled to the back of the neck and exteriorized, and the flank incision was closed in layers.

Rats were then placed in Lucite cylinders, and a 5% dextrose Ringer’s solution was infused (30 μl/min) for 30 minutes. Four to 6 hours after surgical preparation, an isotonic saline infusion was started (50 μl/min), the arterial catheter was flushed and attached to a pressure transducer (Model P23Db, Statham, Oxnard, CA, USA), and a 3-cm polyethylene catheter was attached to the urinary bladder cannula and led to a collection beaker. The quality of the renal sympathetic nerve activity recording was tested with an i.v. injection of norepinephrine (3 μg) as already described to ensure the absence of noise due to mechanical movement, respiration, or heart rate. If the quality of the renal sympathetic nerve activity recording was the same as that observed when the electrode was implanted, then the experiment commenced.

After urine flow rate and urinary sodium excretion stabilized (60 minutes), a 10-minute control collection period was followed by three experimental collection periods during which cumulative doses of guanabenz were injected at 5, 25, and 125 μg i.c.v. Fifteen minutes was allowed after each guanabenz injection before a collection period was begun. In some experiments rauwolscine (30 μg; 2 μl vehicle) was injected i.c.v. or i.v. 15 minutes before the control period. Vehicle
was isotonic saline (1 μl for 5 μg, 1 μl for 25 μg, and 5 μl for 125 μg of guanabenz). The i.c.v. injection of 7 μl of isotonic saline alone had no effect on mean arterial pressure, urinary sodium excretion, or renal sympathetic nerve activity. Urine volume was determined gravimetrically. Urinary sodium concentration was measured by flame photometry (Model 143, Instrumentation Laboratories, Lexington, MA, USA).

Data are expressed as means ± SE. Statistical analyses\textsuperscript{10,11} were conducted with parametric and nonparametric methods, as appropriate. Methods used included repeated-measures analyses of variance for main effects and interactions, Tukey's Honestly Significant Difference test for pairwise comparisons among means, and Kruskal-Wallis one-way and Friedman two-way analyses of variance. Statistical significance was defined as a p level below 0.05.

**Results**

Baseline mean arterial pressures were similar between SHR-NNa and SHR-HNa (173 ± 8 vs 178 ± 6 mm Hg) and between WKY-NNa and WKY-HNa (109 ± 4 vs 110 ± 3 mm Hg). Body weight was higher (p < 0.01) in SHR-HNa than in SHR-NNa (312 ± 8 vs 284 ± 8 g); however, kidney weight was similar between SHR-HNa and SHR-NNa (2.29 ± 0.07 vs 2.31 ± 0.14 g). Body weight was also higher (p < 0.05) in WKY-HNa than in WKY-NNa (298 ± 5 vs 291 ± 6 g). Kidney weight (KW) was higher (p < 0.01) in WKY-HNa than in WKY-NNa (2.51 ± 0.09 vs 2.35 ± 0.09 g). Baseline urinary sodium excretion was higher (p < 0.01) in SHR-HNa than in SHR-NNa (3.1 ± 0.3 vs 2.0 ± 0.4 μEq/min/g KW) and in WKY-HNa than in WKY-NNa (3.3 ± 0.4 vs 1.9 ± 0.2 μEq/min/g KW).

The guanabenz–renal sympathetic nerve activity dose–response curve was shifted to the left (p < 0.01) in SHR-HNa compared with SHR-NNa (Figure 1). Both absolute and percent changes from control renal sympathetic nerve activity were greater (p < 0.05) at each dose of guanabenz in SHR-HNa than in SHR-NNa. In contrast, in WKY-HNa the guanabenz–renal sympathetic nerve activity dose–response curve was shifted to the right (p < 0.01) of that of WKY-NNa (see Figure 1). The lowest dose of guanabenz (5 μg) had no effect on renal sympathetic nerve activity in WKY-NNa and WKY-HNa and in WKY-NNa and WKY-HNa (Table 1).

The guanabenz–urinary sodium excretion dose–response curve was shifted to the left (p < 0.01) in SHR-HNa compared with SHR-NNa (Figure 2). Both the absolute and percent changes from control were greater (p < 0.05) at each dose of guanabenz in SHR-HNa than in SHR-NNa. In contrast, in WKY-HNa the absolute and percent changes from control in urinary sodium excretion at the two higher doses of guanabenz (25 and 125 μg) were smaller (p < 0.05) than those in WKY-NNa; the lowest dose of guanabenz (5 μg) had no effect on urinary sodium excretion in WKY-NNa or WKY-HNa (see Figure 2). The urine flow rate responses to guanabenz among these groups were similar to the urinary sodium excretion responses (Table 2).

In the absence of guanabenz i.c.v. injections mean arterial pressure, urine flow rate, and urinary sodium excretion remained stable. In conscious SHR (n = 4), during consecutive 20-minute recordings for 2 hours, no changes occurred in mean arterial pressure (range,

### Table 1. Mean Arterial Pressure After i.c.v. Injections of Guanabenz

<table>
<thead>
<tr>
<th>Group</th>
<th>Control G, 5 μg</th>
<th>G, 25 μg</th>
<th>G, 125 μg</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHRN Na (n = 8)</td>
<td>173 ± 8</td>
<td>175 ± 8</td>
<td>167 ± 9</td>
</tr>
<tr>
<td>SHRN Na (n = 7)</td>
<td>178 ± 6</td>
<td>176 ± 6</td>
<td>168 ± 6*</td>
</tr>
<tr>
<td>SHRN Na (n = 6)</td>
<td>109 ± 4</td>
<td>105 ± 4</td>
<td>98 ± 4*</td>
</tr>
<tr>
<td>WKY-NNa (n = 7)</td>
<td>110 ± 3</td>
<td>111 ± 2</td>
<td>106 ± 2*</td>
</tr>
<tr>
<td>WKY-HNa (n = 7)</td>
<td>108 ± 4</td>
<td>108 ± 6</td>
<td>102 ± 2*</td>
</tr>
<tr>
<td>DNX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHRN Na (n = 5)</td>
<td>158 ± 4</td>
<td>156 ± 4</td>
<td>153 ± 3</td>
</tr>
<tr>
<td>SHRN Na (n = 5)</td>
<td>159 ± 4</td>
<td>159 ± 4</td>
<td>157 ± 5</td>
</tr>
<tr>
<td>WKY-NNa (n = 6)</td>
<td>117 ± 3</td>
<td>116 ± 4</td>
<td>113 ± 3</td>
</tr>
<tr>
<td>WKY-HNa (n = 8)</td>
<td>124 ± 4</td>
<td>122 ± 5</td>
<td>118 ± 4*</td>
</tr>
</tbody>
</table>

Values are means ± SE. Because of the failure of arterial catheters in some rats, the number of rats in some groups may be less than in the figures. G = guanabenz; NNa = normal sodium intake; HNa = high sodium intake; DNX = renal denervation; Rau = rauwolscine pretreatment, 30 μg i.c.v.

* p < 0.05, compared with control.

**Figure 1.** Dose-response effects of cumulative i.c.v. injections of guanabenz, an α₂-adrenergic receptor agonist, on renal sympathetic nerve activity in conscious SHR and normotensive WKY on normal or high sodium intake. CONT = control period. Asterisk indicates significant difference (p < 0.05) compared with control. Dagger indicates significant difference (p < 0.05) compared with rats on a normal sodium diet. Number of rats is shown in parentheses.
Baseline mean arterial pressure was lower ($p < 0.01$) in renal-denervated than in renal- innervated SHR-NNa and SHR-HNa (see Table 1). Mean arterial pressure changed similarly in renal-denervated SHR-NNa and SHR-HNa during guanabenz i.c.v. injections (see Table 1).

Surgical renal denervation attenuated the natriuretic and diuretic responses to i.c.v. injections of guanabenz in WKY-NNa and WKY-HNa relative to those in WKY-NNa and WKY-HNa with intact renal nerves (Figure 4; see Table 1). Mean arterial pressure changed similarly in renal denervated WKY-NNa and WKY-HNa during i.c.v. injections of guanabenz (see Table 1).

The rauwolscine i.c.v. injection caused a shift ($p < 0.01$) to the right in the guanabenz–urinary sodium excretion and urine flow rate dose-response curves in SHR-NNa and in SHR-HNa compared with the respective SHR-NNa and SHR-HNa without rauwolscine (see Figure 4 and Table 2). A similar shift to the right was observed for urine flow rate after rauwolscine (see Table 2). The rauwolscine i.c.v. injection had no effect on baseline urinary sodium excretion in either SHR-NNa or SHR-HNa (Figure 5). Baseline mean arterial pressure was not affected by rauwolscine. Before rauwolscine administration, mean arterial pressure was $154 \pm 9$ mm Hg in SHR-NNa and $169 \pm 10$ mm Hg in SHR-HNa. When administered, rauwolscine ($30 \mu g$ i.v.) had no effect on the guanabenz–urinary sodium excretion dose-response curve in SHR-NNa or SHR-HNa. For SHR-NNa ($n = 5$), urinary sodium excretion after i.v. injection of rauwolscine ($30 \mu g$) was $1.7 \pm 0.3 \mu Eq/min/g KW$ for control, $2.3 \pm 0.2 \mu Eq/min/g KW$ for $5 \mu g$, $3.3 \pm 0.1 \mu Eq/min/g KW$ for $25 \mu g$, and $5.5 \pm 0.2 \mu Eq/min/g KW$ for $125 \mu g$. For SHR-HNa ($n = 5$), urinary sodium excretion after i.v. administration of rauwolscine ($30 \mu g$) was $5.3 \pm 1.0 \mu Eq/min/g KW$ for control, $8.7 \pm 1.1 \mu Eq/min/g KW$ for $5 \mu g$, $12.6 \pm 1.7 \mu Eq/min/g KW$ for $25 \mu g$, and $17.6 \pm 2.0 \mu Eq/min/g KW$ for $125 \mu g$.

### Table 2. Urine Flow Rate After i.c.v. Injections of Guanabenz

<table>
<thead>
<tr>
<th>Group</th>
<th>Control</th>
<th>G, 5 µg</th>
<th>G, 25 µg</th>
<th>G, 125 µg</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHR-NNa ($n = 8$)</td>
<td>13.5 ± 2.8</td>
<td>20.4 ± 4.6</td>
<td>35.5 ± 5.0*</td>
<td>44.8 ± 7.6*</td>
</tr>
<tr>
<td>SHR-HNa ($n = 8$)</td>
<td>17.4 ± 1.7†</td>
<td>29.9 ± 3.2* †</td>
<td>52.6 ± 7.2* †</td>
<td>73.7 ± 14.5* †</td>
</tr>
<tr>
<td>WKY-NNa ($n = 8$)</td>
<td>14.9 ± 2.7</td>
<td>22.1 ± 2.5*</td>
<td>40.3 ± 9.7*</td>
<td>57.1 ± 14.6</td>
</tr>
<tr>
<td>WHY-HNa ($n = 8$)</td>
<td>21.5 ± 3.7†</td>
<td>23.5 ± 5.7</td>
<td>35.1 ± 4.6*</td>
<td>40.0 ± 5.1*</td>
</tr>
<tr>
<td>DNX</td>
<td></td>
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</tr>
<tr>
<td>SHR-NNa ($n = 7$)</td>
<td>24.3 ± 5.0</td>
<td>28.7 ± 7.1</td>
<td>32.0 ± 6.0</td>
<td>37.2 ± 3.6*</td>
</tr>
<tr>
<td>SHR-HNa ($n = 7$)</td>
<td>29.8 ± 6.4</td>
<td>30.0 ± 3.8</td>
<td>32.4 ± 3.2</td>
<td>37.9 ± 2.8*</td>
</tr>
<tr>
<td>WKY-NNa ($n = 6$)</td>
<td>11.7 ± 1.7</td>
<td>13.2 ± 1.7</td>
<td>15.5 ± 2.6</td>
<td>19.0 ± 4.2*</td>
</tr>
<tr>
<td>WKY-HNa ($n = 8$)</td>
<td>20.8 ± 2.8</td>
<td>23.1 ± 3.1</td>
<td>32.2 ± 1.5*</td>
<td>33.3 ± 4.2*</td>
</tr>
<tr>
<td>Rau</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHR-NNa ($n = 7$)</td>
<td>21.5 ± 4.9</td>
<td>19.9 ± 4.0</td>
<td>29.4 ± 5.2</td>
<td>42.8 ± 7.3*</td>
</tr>
<tr>
<td>SHR-HNa ($n = 5$)</td>
<td>26.9 ± 2.9</td>
<td>27.3 ± 4.2</td>
<td>33.4 ± 6.5</td>
<td>38.7 ± 5.7*</td>
</tr>
<tr>
<td>WKY-NNa ($n = 5$)</td>
<td>19.6 ± 3.9</td>
<td>21.4 ± 6.1</td>
<td>23.0 ± 4.5</td>
<td>33.6 ± 6.5*</td>
</tr>
<tr>
<td>WHY-HNa ($n = 5$)</td>
<td>27.9 ± 4.0</td>
<td>26.8 ± 5.2</td>
<td>28.8 ± 5.0</td>
<td>36.1 ± 7.2*</td>
</tr>
</tbody>
</table>

Values are means ± SE. KW = kidney weight; G = guanabenz; NNa = normal sodium intake; HNa = high sodium intake; DNX = renal denervation; Rau = rauwolscine pretreatment, 30 µg i.c.v.

* $p < 0.05$, compared with control; † $p < 0.05$, compared with NNa.
The i.v. rauwolscine injection had no effect on baseline urinary sodium excretion: Before rauwolscine pretreatment urinary sodium excretion was 1.6 ± 0.3 μEq/min/g KW in SHR-NNa and 4.8 ± 0.9 μEq/min/g KW in SHR-HNa. In WKY-NNa or WKY-HNa, urinary sodium excretion did not change after i.c.v. injection of rauwolscine, except at the high dose (125 μg) in WKY-NNa (Figure 6). Mean arterial pressure changed similarly between WKY-NNa and WKY-HNa during i.c.v. guanabenz administration after rauwolscine i.c.v. pretreatment (see Table 1). The guanabenz–renal sympathetic nerve activity dose-response curves were shifted (p < 0.01) to the right by rauwolscine pretreatment, more in SHR-HNa than in SHR-NNa (Figure 7). Before rauwolscine pretreatment (i.e., vehicle), the dose-response curve for SHR-HNa was shifted to the left of that for SHR-NNa; after rauwolscine pretreatment, the dose-response curve was shifted to the right by rauwolscine pretreatment.
Our results indicate that high dietary sodium intake increased the responsiveness of the central nervous system α₂-adrenergic receptor control of renal sympathetic nerve activity and urinary sodium excretion. This conclusion is based on the following observations: 1) guanabenz decreased renal sympathetic nerve activity and increased urinary sodium excretion to a greater degree in conscious SHR on high than on normal sodium intake; 2) the i.c.v. administration of an α₂-adrenergic receptor antagonist (rauwolscine) into the central nervous system inhibited the effects of guanabenz on renal sympathetic nerve activity and urinary sodium excretion in SHR on normal or high sodium intakes; and 3) chronic renal denervation inhibited the effects of guanabenz on urinary sodium excretion in SHR on normal or high sodium intakes. However, at the highest dose of guanabenz (125 µg i.c.v.), renal denervation or i.c.v. administration of rauwolscine did not completely block the natriuretic response. Thus, factor(s) in addition to renal sympathetic nerve activity contributed to the natriuretic response at the highest dose of guanabenz. One possible factor may be central inhibition of vasopressin release. A peripheral effect on diuresis or natriuresis of the high dose of guanabenz is unlikely since 1) the diuretic and natriuretic responses to guanabenz are the same in SHR on normal sodium intake with and without i.v. administration of rauwolscine and 2) i.v. rauwolscine administration in SHR on high sodium intake does not reduce the diuretic or natriuretic responses to guanabenz (125 µg). The localization of the action of guanabenz to the central nervous system is indicated by the finding that only the central administration of rauwolscine, not the peripheral (i.e., i.v.) administration, inhibited the natriuretic effects of guanabenz. The mean arterial pressure responses to guanabenz do not explain the different renal sympathetic nerve activity and urinary sodium excretion responses, since mean arterial pressure changed similarly in SHR on normal or high sodium intake.

In conscious WKY, high dietary sodium intake decreased the responsiveness of the central nervous system α₂-adrenergic receptor control of renal sympathetic nerve activity. As in SHR, the renal sympathetic nerve activity and natriuretic responses to guanabenz in WKY on normal and high sodium intake were inhibited by central administration of an α₂-adrenergic receptor antagonist (rauwolscine) or chronic renal denervation. The greater decreases in renal sympathetic nerve activity resulting from guanabenz pretreatment in WKY on normal rather than on high sodium intake cannot be attributed to different mean arterial pressure responses, since mean arterial pressure changed similarly in the two groups. In addition, the renal sympathetic nerve activity and natriuretic responses to guanabenz were similar in SHR and WKY on normal sodium intake. Thus, the responsiveness of central α₂-adrenergic receptors was similar between SHR and WKY on normal sodium intake. However, high dietary sodium intake increased the responsiveness of central α₂-adrenergic receptors in SHR and decreased the sensitivity of central α₂-adrenergic receptors in WKY with regard to the neural control of renal function.

These results do not support the hypothesis of...
Gavras that high dietary sodium intake contributes to hypertension by decreasing the responsiveness of central nervous system α2-adrenergic receptors. Increased dietary sodium intake is hypothesized to decrease the affinity of brainstem α2-adrenergic receptors, which tonically inhibit sympathetic nervous system-mediated vasoconstrictor tone, thereby resulting in sympathoexcitation and elevated mean arterial pressure. Support for this hypothesis comes from studies showing: 1) Microinjection of hypertonic saline into the nucleus tractus solitarii of rats increases mean arterial pressure more than does isotonic saline or other non-NaCl equiosmolar solutions; the pressor response to hypertonic saline is abolished by i.v. administration of phentolamine, suggesting an α-adrenergic receptor mechanism. 2) Saline infusion attenuates the pressor response to i.v. clonidine administration in rats; this effect is prevented by i.v. administration of the α2-adrenergic receptor antagonist yohimbine, suggesting an α2-adrenergic receptor mechanism. 3) Increased sodium concentration inhibits the binding of α2-adrenergic receptor agonists to α2-adrenergic receptors in vitro. In support of their hypothesis, Gavras and colleagues showed that high dietary sodium intake (1% NaCl to drink for 1 week) in prehypertensive SHR or young WKY has no effect on α2-adrenergic receptor binding density or affinity in the hypothalamus, but in the brainstem, high dietary sodium intake increases receptor density and affinity in young WKY and decreases receptor density and affinity in prehypertensive SHR. Whether this relationship is sustained as hypertension progresses in adult animals or with longer exposure to high dietary sodium intake is not yet known.

The main differences between the present study and those used to support the hypothesis of Gavras are the following. First, to assess central α2-adrenergic receptor sensitivity, the present study focused on changes in renal sympathetic nerve activity and urinary sodium excretion, whereas Gavras and associates focused on mean arterial pressure. Indeed, if mean arterial pressure were the only measurement in the present study, the conclusion would be that high dietary sodium intake does not affect the sensitivity of central α2-adrenergic receptors. Second, the present study increased dietary sodium intake chronically (3–4 weeks of isotonic saline for drinking); this does not change extracellular sodium concentration, whereas Gavras cited in vivo and in vitro studies that acutely alter extracellular sodium concentration (e.g., hypertonic saline injection or infusion). Third, the present study used i.c.v. injection of selective α2-adrenergic receptor agonists and antagonists known to directly affect central α2-adrenergic receptors, whereas Gavras administered agents intravenously with attendant uncertainty as to peripheral versus central site of action.

The present study is consistent with several other studies. In prehypertensive SHR (2 weeks of age), high dietary sodium intake (8% NaCl) decreased norepinephrine concentrations in the anterior and posterior hypothalamus. The decreased hypothalamic norepinephrine concentration in SHR persisted after 6 weeks of high dietary sodium intake as the SHR entered the more stable phase of hypertension. In addition, the dose-response curve for the effects of clonidine injected into the anterior hypothalamus on mean arterial pressure in SHR (9 weeks of age) on high dietary sodium intake (8% NaCl) was shifted to the left of SHR on normal sodium intake (1% NaCl), suggesting that high dietary sodium intake increases the responsiveness of anterior hypothalamic α2-adrenergic receptors. The importance of the hypothalamus in the neural control of renal function is represented by a recent study showing that electrical stimulation of the hypothalamus decreases urinary sodium excretion. Radioligand binding studies have shown that high dietary sodium intake increases renal α2-adrenergic receptor density in SHR and Dahl salt-sensitive rats, but not in WKY or Dahl salt-resistant rats. This finding supports the possibility of high sodium intake increasing central nervous system α2-adrenergic receptor number. However, in prehypertensive SHR, 1 week of saline ingestion had no effect on hypothalamic α2-adrenergic receptors. Whether high dietary sodium intake increases the radioligand binding density of central nervous system α2-adrenergic receptors in adult hypertensive SHR is not yet known.

The control of renal function by the renal sympathetic nerves is influenced by an interaction among environmental stress, dietary sodium intake, and genetic predisposition to hypertension. Environmental stress in conscious SHR increases renal sympathetic nerve activity and decreases urinary sodium excretion. High dietary sodium intake, another environmental factor, enhances the increased renal sympathetic nerve activity and antinatriuretic responses to environmental stress in conscious SHR, but it has no additional effects in WKY. The importance of the renal sympathetic nerves in the antinatriuretic response to environmental stress in SHR on either normal or high sodium intake is indicated by studies showing that chronic renal denervation abolishes the antinatriuretic responses. Moreover, stimulation of central nervous system α2-adrenergic receptors with clonidine or guanabenz prevents the antinatriuretic response to environmental stress in conscious SHR. Together with the data showing that high dietary sodium intake reduces hypothalamic norepinephrine concentration and increases hypothalamic α2-adrenergic receptor responsiveness, these studies suggest that high dietary sodium intake reduces the normal activation of neurons that mediate sympathetic inhibition in SHR.

The development of hypertension is also influenced by an interaction among stress, sodium intake, and genetics. The development of hypertension in rats with a genetic predisposition to hypertension is accelerated by high sodium intake alone or by environmental stress alone, but the combination of high sodium intake and environmental stress results in a more severe hypertension than does either factor alone. Surgical renal denervation delays the onset of spontaneous hypertension and chronic stress hyperten-
A hypothesis stemming from these studies is that high dietary sodium intake contributes to the pathophysiology of hypertension by reducing the steady state level of stimulation of central nervous system sympathoinhibitory α₂-adrenergic receptors (as reflected by decreased hypothalamic norepinephrine concentration and increased responsiveness of central α₂-adrenergic receptors), leading to an enhanced responsiveness of renal sympathetic nerve activity and renal sodium retention to environmental stress.

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