SUMMARY The current study tested the hypothesis that high NaCl diets elevate blood pressure in NaCl-sensitive spontaneously hypertensive rats (SHR-S) by reducing noradrenergic input to depressor neurons in the anterior hypothalamus. SHR-S were studied at 7 weeks of age, and age-matched salt-resistant SHR (SHR-R) and normotensive Wistar-Kyoto rats (WKY) were controls. Rats were fed either high (8%) NaCl or control (1% NaCl) diets for 2 weeks, following which norepinephrine turnover in hypothalamus (anterior, posterior, and ventral regions), brainstem (pons and medulla), and thoracic spinal cord was assessed using the dopamine β-hydroxylase inhibitor 1-cyclohexyl-2-mercapto-imidazole (CHMI). Regional brain catecholamines were measured by high performance liquid chromatography with electrochemical detection following intraperitoneal injection of CHMI or vehicle. Disappearance of norepinephrine following CHMI was used as an index of noradrenergic neuronal activity. The 8% NaCl diet caused a significant elevation in blood pressure in SHR-S but not in SHR-R or WKY. Endogenous norepinephrine levels and turnover were lower in the anterior hypothalamus of SHR-S fed 8% NaCl than in those fed 1% NaCl but were not significantly different in other groups. Endogenous norepinephrine levels and turnover were greater in pons of 8% NaCl-fed SHR-S than in those fed 1% NaCl but were not significantly different in other groups. These observations support the hypothesis that reduced noradrenergic input to depressor neurons in the anterior hypothalamus and increased noradrenergic input to neurons in the pons are related to NaCl sensitivity in the SHR-S. (Hypertension 11: 55–62, 1988)
hampered by the fact that the rats obtained from Charles River were no longer NaCl-sensitive. These NaCl-resistant SHR (SHR-R) were used as hypertensive controls in the current study. In a search for NaCl-sensitive SHR (SHR-S), we found that SHR from Taconic Farms (IBU3 colony, Germantown, NY, USA) exhibited significant increases in blood pressure when fed diets high in NaCl. SHR-S maintained on an 8% NaCl diet for 2 weeks displayed significant decreases in NE stores in anterior and posterior hypothalamus but not in other brainstem or hypothalamic regions compared with rats consuming 1% NaCl. The present studies 1) assessed noradrenergic activity by measuring NE turnover in hypothalamic and brainstem regions of NaCl-loaded and control SHR-S and 2) compared the sympathetic nervous system activity of these rats with that in WKY controls.

Our hypothesis was that dietary NaCl loading increases blood pressure in SHR-S by altering the input of noradrenergic pathways and thus turnover of NE in hypothalamic and brainstem areas that regulate sympathetic nervous system activity and blood pressure control. Our results support the hypothesis that reduced noradrenergic input to depressor neurons in the anterior hypothalamus and increased turnover of NE in the pons are important mechanisms underlying NaCl sensitivity in the SHR-S.

Materials and Methods

Male SHR-S of the Okamoto strain (IBU3 colony) and normotensive control Wistar-Kyoto rats (WKY) were obtained from Taconic Farms at 7 weeks of age. Male SHR-R were obtained from Charles River Breeding Laboratories at the same age. All rats were maintained four per cage at constant humidity (60 ± 5%), temperature (24 ± 1°C), and light cycle (0600-1800). Three days after arrival, half of the rats in each group (SHR-S, SHR-R, or WKY) were placed on an 8% NaCl diet (ICN Biochemicals Purina chow with 8% NaCl, Costa Mesa, CA, USA) while the other half remained on the basal 1% NaCl diet (Ralston Purina diet 5001, St. Louis, MO, USA). Food and water were available ad libitum throughout the study. Systolic blood pressure (SBP) was measured twice weekly in conscious, prewarmed, restrained rats by the tail-cuff method using an electrophysmomanometer and physiograph recorder (Narco Bio-Systems, Houston, TX, USA). The median of five successive measurements was used as the estimate of blood pressure. Body weight was determined on the same day.

To assess the effect of the NaCl supplement on brain noradrenergic neuronal activity, NE disappearance and dopamine (DA) accumulation were measured after inhibition of DA β-hydroxylase using the CHMI (1-cyclohexyl-2-mercapto-imidazole) method. CHMI (or LY 10853) is a specific inhibitor of DA β-hydroxylase that has been used to evaluate NE turnover in brain. After CHMI treatment, there are rapid increases in DA concentration and decreases in NE concentration in brain and peripheral tissues innervated with noradrenergic nerves. NE disappearance rates are useful indices of NE turnover in brain, and DA accumulation rates are useful indices of NE turnover in peripheral organs.

Two weeks after initiation of the special diets, rats from each experimental group (SHR-S, SHR-R, WKY fed 1% NaCl or 8% NaCl diet) were randomly assigned to three subgroups with seven to eight animals in each. In two subgroups, CHMI (Lilly Research Laboratories, Indianapolis, IN, USA) was given intraperitoneally (i.p.) in a dose of 50 mg/kg in 200 μL of 5% emulphor (Emulphore EL719P, GAF Corporation, New York, NY, USA). Rats were killed 60 or 120 minutes later by decapitation without anesthesia. In the third subgroup, 200 μL of 5% emulphor was administered as a vehicle control, and the rats were killed 120 minutes later.

Brains were removed immediately following decapitation and dissected on an ice-cold plate into the following regions in sequence: ventral (7.5–9 mg), anterior (10–11 mg), and posterior hypothalamic areas (9–10 mg), pons (115–125 mg), medulla (120–125 mg), and spinal cord (190–220 mg). The ventral hypothalamic dissection included the median eminence, arcuate nucleus, and the ventrolateral part of the ventromedial hypothalamic nucleus. The anterior hypothalamic dissection included the anterior hypothalamic area and segments of the ventral paraventricular, periventricular, suprachiasmatic, and rostromedial part of the ventromedial hypothalamic nuclei. The posterior hypothalamic dissection included the dorsomedial and posterior hypothalamic nuclei and segments of the mamillary complex. Pons was separated from the midbrain immediately caudal to the inferior colliculus and from the medulla at the level of the lateral aperture of the fourth ventricle. The medulla dissection included the entire medulla from the pontine separation to the spinomedullary junction. Tissue samples were frozen in liquid nitrogen and stored at −80°C until assay.

Catecholamine and metabolite levels in brain regions were determined using high performance liquid chromatography (HPLC) with electrochemical detection as described previously. Tissue samples were homogenized in 0.1 M acetic acid (pH 5.0) containing glutathione (1 mM), Na2EDTA (100 mg/L) and ascorbic acid oxidase (1 mg/ml; Boehringer, Mannheim, FRG) for 10 seconds on ice. An equal volume of 0.1 N perchloric acid containing Na2EDTA (100 mg/L) and n-methyl-DA as the internal standard was added, and the sample was homogenized for another 30 seconds. Ascorbate oxidase reduces solvent front interactions with NE by significantly lowering the concentration of ascorbic acid, which normally elutes in the solvent front and partially obscures the NE peak. Homogenates were centrifuged (20,000 g at 4°C for 10 minutes); supernatants were filtered through 0.2-μm membrane filters (nylon 66 filter, Rainin Instruments, Woburn, MA, USA) and analyzed for monoamine and metabolite levels using HPLC with electrochemical detection.

The rate constant for NE turnover was calculated according to the method of Brodie et al. Values for
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tissue levels of NE and DA were logarithmically transformed for calculation of linearity of regression and significance of differences between regression coefficients. Two-way analysis of variance (NaCl treatment × CHMI treatment) was performed on the neurochemical data to assess the effects of NaCl and CHMI on regional catecholamine levels. Groups exhibiting a significant F ratio were subjected to the Duncan's multiple-range test. Differences were reported as significant if the p value was less than 0.05. Values are given as means ± SEM.

**Results**

**Blood Pressure and Body Weight**

In SHR-S, the 8% NaCl diet caused an increase in blood pressure compared with rats fed the 1% NaCl diet (Table 1). The blood pressure increase was statistically significant after 5 days of 8% NaCl feeding (8% NaCl group = 154 ± 2 mm Hg; 1% NaCl group = 143 ± 2 mm Hg; p<0.05). After 2 weeks on the special diets, SBP in the 8% NaCl group averaged 23 mm Hg greater than that in the 1% NaCl-fed group (p<0.005). In contrast, blood pressure in the SHR-R and the WKY showed no change in response to dietary NaCl supplementation. The 8% NaCl diet did not influence heart rate significantly in any experimental group.

Body weights of 1% NaCl–treated SHR-S and SHR-R were significantly greater than those of the WKY (see Table 1). The body weights of 8% NaCl–treated SHR-S and SHR-R were significantly lower than those of their respective 1% NaCl–fed controls, while body weights of 8% NaCl–treated WKY were significantly greater than those of 1% NaCl–treated controls.

**Effects of NaCl Loading on Norepinephrine and Dopamine Content in Brain Regions**

**NaCl-Induced Changes**

The 8% NaCl diet caused a significant reduction in NE stores in the anterior hypothalamic area and a significant increase in NE stores in the pons in vehicle-treated SHR-S (Tables 2 and 3). NaCl loading had no significant effect on NE stores of any other brain region studied in SHR-S. Further, NaCl loading had no significant effect on NE stores in any brain region of vehicle-treated SHR-R or WKY. There were no significant changes in DA levels in any brain region examined in vehicle-treated SHR-S, SHR-R, or WKY following 2 weeks of 8% NaCl loading compared with 1% NaCl–fed controls.

**Strain-Related Changes**

A number of strain-related differences in regional brain NE and DA stores appeared when SHR-S, SHR-R, and WKY were compared at 2 weeks on the special diets (see Tables 2 and 3). These tended to be the same whether the rats were maintained on 1% or 8% NaCl diets.

In 1% NaCl–fed rats, the NE content of the anterior hypothalamic area in vehicle-treated SHR-S was greater than that in vehicle-treated SHR-R. NE stores in the anterior hypothalamic area of 1% NaCl–fed SHR-R were significantly lower than those in WKY. In the posterior hypothalamic area, NE stores in both SHR-S and SHR-R were significantly lower than those in WKY. In the ventral hypothalamic area, NE stores in SHR-R were greater than those in SHR-S. However, in both medulla and spinal cord, NE stores in SHR-S and SHR-R were significantly greater than those in WKY. DA stores in the pons of SHR-S were significantly greater than those in SHR-R, but there were no differences in DA content of any other brain region studied among 1% NaCl–treated SHR-S, SHR-R, and WKY.

In 8% NaCl–fed rats, the NE content of the anterior hypothalamic area in vehicle-treated SHR-S was significantly lower than that in vehicle-treated SHR-R and WKY. In the posterior hypothalamic area, NE stores in both SHR-S and SHR-R were significantly lower than those in WKY. In the ventral hypothalamic area, NE stores in SHR-R were greater than those in SHR-S. In both medulla and spinal cord, NE stores in SHR-S and SHR-R were significantly greater than those in WKY. DA stores in the pons of SHR-S were significantly greater than those in SHR-R, but there were no differences in DA content of any other brain region studied among 8% NaCl–treated SHR-S, SHR-R, and WKY.

**Effects of NaCl Loading on Norepinephrine and Dopamine Turnover**

In the anterior hypothalamic area (Figure 1), the slope of the line (k [hr⁻¹], the rate constant of NE disappearance after CHMI injection) of NE turnover was significantly (p<0.05) decreased in the 8%

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**Table 1. Effects of NaCl Supplementation (2 Weeks) on SBP, Heart Rate, and Body Weight in SHR-S, SHR-R, and WKY**

<table>
<thead>
<tr>
<th>Group</th>
<th>1% NaCl</th>
<th>8% NaCl</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SBP (mm Hg)</td>
<td>HR (beats/min)</td>
</tr>
<tr>
<td>SHR-S</td>
<td>171 ± 4 (22)*</td>
<td>471.8 ± 8.4 (22)</td>
</tr>
<tr>
<td>SHR-R</td>
<td>167 ± 2 (23)*</td>
<td>457.5 ± 8.1 (23)</td>
</tr>
<tr>
<td>WKY</td>
<td>144 ± 3 (25)</td>
<td>463.8 ± 12.6 (25)</td>
</tr>
</tbody>
</table>

Results represent means ± SEM. Number of animals is shown in parentheses. HR = heart rate; SHR-S = SHR NaCl-sensitive strain; SHR-R = SHR NaCl-resistant strain.

* p<0.05, compared with respective values of WKY; † p<0.05, compared with respective values of 1% NaCl–fed control group; †† p<0.05, compared with respective values of SHR-R and WKY.
NaCl–treated SHR-S ($t_{50} = 6.34$ hours) compared with 1% NaCl–treated SHR-S ($t_{50} = 2.27$ hours; see 1a in Figure 1 and Table 2). In contrast, in the pons (Figure 2), the NE turnover rate was significantly ($p < 0.05$) decreased in the 8% NaCl–treated SHR-S ($t_{50} = 1.82$ hours) compared with 1% NaCl–treated SHR-S ($t_{50} = 2.66$ hours; 1a in Figure 2; see Table 2). Thus, NaCl supplementation induced changes in NE turnover that were opposite in direction in the anterior hypothalamic area compared with the pons. NaCl supplementation had no significant effect on NE turnover in any other brain region in SHR-S or in any brain region in 8% NaCl–treated SHR-R or WKY compared with their respective 1% NaCl–fed control groups (see Table 2). When SHR-S, SHR-R, and WKY were compared, turnover rates of NE in the posterior hypothalamic area of either the 1% NaCl–treated or 8% NaCl–treated WKY ($t_{50} = 1.91$ hours and $t_{50} = 1.75$ hours, respectively) were significantly greater than those of the respective SHR-S and SHR-R (1c in Figure 3; see Table 2).

NaCl supplementation had no significant effect on DA accumulation in any brain region in 8% NaCl–treated SHR-S, SHR-R, or WKY compared with their respective 1% NaCl–fed control groups (see Table 3). In the posterior hypothalamic area, the slopes of the lines ($k$ [hr$^{-1}$], the rate constant of DA accumulation after CHMI injection) were significantly greater in 1% NaCl–treated and 8% NaCl–treated WKY ($t_{50} = 1.14$ hours and $t_{50} = 1.48$ hours, respectively) than those of the respective SHR-S and SHR-R (see 2c in Figure 3 and Table 3).

**Discussion**

The current study had four principal findings. First, high NaCl intake in the young SHR-S but not in SHR-R or WKY produced an increase in the severity of hypertension. Second, NaCl-induced exacerbation of hypertension in SHR-S was associated with decreased NE stores and turnover in the anterior hypothalamus, a region that mediates depressor responses and suppresses central sympathetic outflow when stimulated electrically or chemically, and with increased NE turnover in the pons. These changes were not seen in NaCl–loaded SHR-R or WKY. Third, NE stores and turnover in the posterior hypothalamus, a region that mediates pressor responses and enhances central sympathetic outflow when stimulated, were lower in both 1% NaCl–fed and 8% NaCl–fed SHR-S and SHR-R than in WKY. Fourth, NE stores in medulla and spinal cord of both 1% and 8% NaCl–fed SHR-S and SHR-R were greater than those in WKY. These findings are consistent with the hypothesis that NaCl loading exacerbates the severity of hypertension in SHR-S by decreasing...
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TABLE 3. Effects of NaCl Supplementation on Dopamine Accumulation in SHR-S, SHR-R, and WKY

<table>
<thead>
<tr>
<th>Variable</th>
<th>1% NaCl</th>
<th>8% NaCl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial DA content (pg/mg tissue)</td>
<td>k (hr(^{-1}))</td>
<td>Calculated turnover rate (pg/mg/hr)</td>
</tr>
<tr>
<td>AHA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHR-S</td>
<td>336 ± 111</td>
<td>0.4835</td>
</tr>
<tr>
<td>SHR-R</td>
<td>224 ± 16</td>
<td>0.3078</td>
</tr>
<tr>
<td>WKY</td>
<td>192 ± 78</td>
<td>0.4871</td>
</tr>
<tr>
<td>PHA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHR-S</td>
<td>254 ± 26</td>
<td>0.2972*</td>
</tr>
<tr>
<td>SHR-R</td>
<td>218 ± 21</td>
<td>0.3881*</td>
</tr>
<tr>
<td>WKY</td>
<td>213 ± 22</td>
<td>0.6081</td>
</tr>
<tr>
<td>VHA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHR-S</td>
<td>387 ± 78</td>
<td>0.3058</td>
</tr>
<tr>
<td>SHR-R</td>
<td>300 ± 20</td>
<td>0.2739</td>
</tr>
<tr>
<td>WKY</td>
<td>363 ± 35</td>
<td>0.2431</td>
</tr>
<tr>
<td>Pons</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHR-S</td>
<td>69 ± 6</td>
<td>0.4724</td>
</tr>
<tr>
<td>SHR-R</td>
<td>49 ± 4</td>
<td>0.5059</td>
</tr>
<tr>
<td>WKY</td>
<td>54 ± 6</td>
<td>0.5862</td>
</tr>
<tr>
<td>Medulla</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHR-S</td>
<td>64 ± 6</td>
<td>0.4154</td>
</tr>
<tr>
<td>SHR-R</td>
<td>77 ± 6</td>
<td>0.4329</td>
</tr>
<tr>
<td>WKY</td>
<td>63 ± 6</td>
<td>0.5459</td>
</tr>
<tr>
<td>Spinal cord</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHR-S</td>
<td>41 ± 3</td>
<td>0.3442</td>
</tr>
<tr>
<td>SHR-R</td>
<td>52 ± 5</td>
<td>0.4257</td>
</tr>
<tr>
<td>WKY</td>
<td>46 ± 2</td>
<td>0.4565</td>
</tr>
</tbody>
</table>

Results represent means ± SEM for groups of seven to eight animals assayed individually. DA = dopamine; SHR-S = SHR NaCl-sensitive strain; SHR-R = SHR NaCl-resistant strain; AHA = anterior hypothalamic area; PHA = posterior hypothalamic area; VHA = ventral hypothalamic area; k = turnover rate constant, t = time (in hr); the slope of log[DA] = log[DA] \(_0\) + 0.434 kt; \(t_2\) = time (in hr) required for 100% increase of initial DA content.

*p < 0.05, compared with respective values of WKY; \(t_p < 0.05\), compared with respective values of SHR-R.

FIGURE 1. The disappearance of norepinephrine (NE) and accumulation of dopamine (DA) after inhibition of DA \(\beta\)-hydroxylase by 1-cyclohexyl-2-mercapto-imidazole (CHMI) in the anterior hypothalamus of NaCl-sensitive SHR (SHR-S), NaCl-resistant SHR (SHR-R), and WKY fed a 1% NaCl or 8% NaCl diet for 2 weeks. Data are plotted as means ± SEM of seven to eight animals in each group. Asterisk indicates significant difference (p < 0.05) compared with values for 1% NaCl control group.

the synthesis or release, or both, of NE from noradrenergic nerve terminals in the anterior hypothalamus and by increasing the release of NE from noradrenergic nerve terminals in cardiovascular control centers in the brainstem. NaCl-resistant SHR and WKY were genetically resistant to these effects of dietary NaCl.

Our findings suggest that alterations in noradrenergic pathways in anterior hypothalamus and pons may
play a role in the NaCl-induced increases in peripheral sympathetic activity and severity of hypertension in SHR-S. Although the design of the current study does not permit us to exclude the possibility that the reduction in anterior hypothalamic NE turnover in 8% NaCl-fed SHR-S was secondary to the blood pressure elevation, this interpretation seems unlikely. Patel and Kline demonstrated that acute hypertension caused by intravenous infusion of phenylephrine did not alter NE turnover in anterior hypothalamus of conscious, normotensive rats. Further, in the current study, there were no significant differences in anterior hypothalamic NE turnover between SHR-R and WKY, despite large (~23 mm Hg) differences in blood pressure. The difference in blood pressure between 8% NaCl-fed and 1% NaCl-fed SHR-S was no greater than that between SHR-R and WKY. Therefore, if the reduction in anterior hypothalamic NE turnover in SHR-S were secondary to the pressor effect of the 8% NaCl diet, one would expect similar differences in anterior hypothalamic NE turnover between SHR-R and WKY. These were not observed.

Noradrenergic projection from A1, A2, and A6 regions of brainstem to the anterior hypothalamus participate in cardiovascular regulation. Administration of NE or clonidine into the anterior hypothalamus produces a dose-dependent, α1-adrenergic receptor-mediated decrease in arterial blood pressure and heart rate, and electrical stimulation of anterior hypothalamus also reduces blood pressure and heart rate.
Chemical (6-hydroxydopamine) destruction of the ventral noradrenergic pathway of male Wistar rats selectively depletes NE stores in the anterior hypothalamus and increases blood pressure and heart rate. These rats are hypersensitive to the depressor effects of NE and clonidine administered into the anterior hypothalamus. These data demonstrate that excitation of NE inputs to the anterior hypothalamic area has a depressor effect. Reductions in NE activity in the anterior hypothalamic area would be expected to decrease inhibition of sympathetic outflow and thereby cause blood pressure to rise.

The posterior hypothalamus contains neurons that have a pressor function when stimulated and that are implicated in the pathogenesis of hypertension in the SHR. Biochemical or electrical stimulation of these neurons leads to local release of catecholamines, elevates sympathetic outflow, and increases arterial blood pressure and heart rate. Further, electrical stimulation of the posterior hypothalamic area in SHR elicits an exaggerated pressor response compared with WKY, and lesions in this area result in a depressor response that is greater in SHR than in WKY.

In the present study, we observed that in the posterior hypothalamic area NE stores and turnover (indicated by both the NE disappearance and DA accumulation rates) in both 1% NaCl-fed and 8% NaCl-fed SHR-S and SHR-R were significantly lower than those of the respective 1% NaCl-fed and 8% NaCl-fed WKY. There was no NaCl diet × CHMI interaction in either NE stores or NE turnover within any strain. These results indicate that the alterations in noradrenergic activity in the posterior hypothalamus observed in the current study are not associated with dietary NaCl.

Several reports have demonstrated increased turnover of NE in the posterior hypothalamus in response to a decrease in arterial pressure and decreased turnover of NE in response to an increase in arterial pressure in the rat. Patel and Kline demonstrated that acute hypotension caused by intravenous infusion of nitroprusside produces a significant increase in NE turnover in the posterior hypothalamus, kidney, intestine, and skeletal muscle, indicative of reflexly increased sympathetic activity, in conscious, normotensive rats. Conversely, administration of phenylephrine elicits the expected pressor response, which is associated with a significant decrease in NE turnover in the posterior hypothalamus. In addition, it has been reported that transection of aortic depressor nerves increases hypothalamic NE turnover and blood pressure in normal rats and that renal denervation decreases hypothalamic NE content and blood pressure in one-kidney, one-clip Goldblatt hypertensive rats. These results suggest that afferent nerves may influence the activity of noradrenergic neurons in the hypothalamus and thus influence central sympathetic outflow. Therefore, it is reasonable to assume that the reduction of NE stores and turnover in the posterior hypothalamic area of SHR-R and SHR-S observed in the present study may be an adaptive response to the elevated pressure.

Our findings demonstrated increased NE stores and turnover in pons of SHR-S fed the 8% NaCl diet. No similar NaCl diet × CHMI interaction was observed in either SHR-R or WKY. Thus, the NaCl-induced increase in blood pressure in SHR-S was associated with hyperactivity of noradrenergic neurons in the pons. The pontine region dissected out in our study included the locus ceruleus. Stimulation of the locus ceruleus by electrical or biochemical means (microinjection of arginine vasopressin) enhances sympathetic outflow. Our finding of increased NE turnover in pons is consistent with the interpretation that noradrenergic activity in cardiovascular control centers (e.g., locus ceruleus) in the pons may be involved in the activation of sympathetic outflow and thus contribute to NaCl-sensitive hypertension in SHR-R.

The NE content of medulla and spinal cord was significantly increased in 1% NaCl-fed and 8% NaCl-fed SHR-S and SHR-R compared with their respective WKY controls. No strain × NaCl × CHMI interactions of NE turnover were detected among the experimental groups. Thus, the increased stores of NE in the medulla and spinal cord of SHR-S and SHR-R appear to be related to genetically induced hypertension rather than to dietary NaCl supplementation.

The cellular and molecular mechanisms by which dietary NaCl supplementation elevates blood pressure in genetically susceptible persons are poorly understood. Most current theories suggest that an increase in either intravascular volume or sodium concentration in the blood or cerebrospinal fluid, or both, could trigger abnormalities in monoaminergic neurons. Gavras hypothesized that NaCl loading slightly elevates extracellular sodium in the brain, leading to decreased affinity of α2-adrenergic receptors and concomitant up-regulation of α2-adrenergic receptor density. In addition, Na+-K+ pump–mediated regulation of intracellular sodium and calcium may be altered in NaCl-sensitive persons, leading to greater sympathetic nerve activity.

The sodium ion can produce effects on nerve terminals by altering calcium handling by the cell. Calcium is important for the uptake and binding of NE by nerve endings and for the release of catecholamines from nerve endings and the adrenal medulla. There may be a direct sodium–calcium counterexchange system in which sodium concentration gradients influence the movement of calcium across cell membranes. Perturbations of this countertransport system could alter intracellular calcium levels, with resultant changes in retention, storage, and reuptake of catecholamines. Other mechanisms that have been postulated to link sodium, the sympathetic nervous system, and the pathogenesis of systemic hypertension include alterations in baroreceptor reflex sensitivity, vascular reactivity to α-adrenergic agonists and central and peripheral sympathetic stimulation, renal sodium handling, sensitivity of presynaptic and postsynaptic mechanisms that govern the release and reuptake of biogenic amines, and the synthesis, storage, and turnover of biogenic amines in central and peripheral neurons.
In summary, the anterior hypothalamus is a major cardiovascular depressor region, and depressor responses elicited by stimulation of this area are exaggerated in SHR versus WKY. We observed that dietary NaCl loading in SHR-S decreased endogenous NE stores and turnover in the anterior hypothalamus and increased endogenous NE stores and turnover in pons. This finding is consistent with the hypothesis that decreased noradrenergic activity of the depressor neurons in the anterior hypothalamus and increased turnover of NE in the brainstem cardiovascular control centers may mediate the exacerbation of hypertension that occurs in NaCl-sensitive animals during dietary NaCl supplementation. The exacerbation of hypertension and changes in central noradrenergic activity are observed only in NaCl-loaded SHR-S, not in SHR-R or WKY, indicating that these NaCl-induced alterations in central noradrenergic activity are genetically mediated.

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High NaCl diet reduces hypothalamic norepinephrine turnover in hypertensive rats.

Y F Chen, Q C Meng, J M Wyss, H Jin and S Oparil

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