Spontaneously Hypertensive Rats Exhibit Reduced Hypothalamic Noradrenergic Input After NaCl Loading

J. Michael Wyss, Yiu-Fai Chen, Hongkui Jin, Richard Gist, and Suzanne Oparil

SUMMARY Spontaneously hypertensive rats (SHR) of the Okamoto strain exhibit a significant exacerbation in severity of hypertension when fed diets high in NaCl. To examine the hypothesis that abnormalities in the monoaminergic innervation of the hypothalamus and brainstem contribute to the NaCl-induced exacerbation of hypertension, the monoamine and monoamine metabolite contents of specific hypothalamic and brainstem regions thought to be involved in the pathogenesis of hypertension were determined in SHR fed a diet containing 8% or 1% NaCl for either 2 or 6 weeks beginning at age 8 weeks. SHR maintained on the 8% NaCl diet for 2 weeks displayed significant decreases in norepinephrine in both the anterior and posterior hypothalamic regions but not in other brainstem or hypothalamic regions, as compared with animals consuming 1% NaCl. In addition, stores of the principal terminal norepinephrine metabolite 3-methoxy-4-hydroxyphenylglycol were reduced in the anterior hypothalamic region of SHR fed an 8% NaCl diet for 2 weeks. After 6 weeks on the diets, SHR fed 8% NaCl showed small but statistically nonsignificant reductions in norepinephrine stores of the anterior hypothalamic region as compared with SHR fed a basal diet, while WKY fed 8% NaCl had significantly elevated norepinephrine stores in the anterior hypothalamic region as compared with WKY fed a basal diet. There was a significant group x diet interaction ($p < 0.05$). After 6 weeks on the 8% NaCl diet, SHR (but not WKY) displayed a significant reduction in norepinephrine content of the posterior hypothalamic region. No NaCl-induced differences in norepinephrine stores were found in the pons or medulla of either strain. No alterations in serotonin, dopamine, or epinephrine content were correlated with the differential rise in blood pressure following 8% NaCl feeding in SHR as compared with WKY. These results support the hypothesis that diets high in NaCl elevate blood pressure in NaCl-sensitive SHR by reducing noradrenergic input to depressor neurons in the hypothalamus. (Hypertension 10: 313–320, 1987)

KEY WORDS • hypertension • catecholamines • salt sensitivity • neural control of hypertension

SPONTANEOUSLY hypertensive rats (SHR) of the Okamoto strain are frequently used for the study of genetically determined hypertension and its effects on the cardiovascular system.1-3 Many similarities between the pathogenesis of spontaneous hypertension in the SHR and of primary hypertension in humans have been found, and the SHR have often been examined in an attempt to obtain new insights into the pathogenesis of human essential hypertension.4 Much attention has been given to the possible roles of central and peripheral sympathetic mechanisms in the modulation of blood pressure in these animals. Among the lines of evidence that support a role for neurogenic mechanisms in the pathogenesis of hypertension in the SHR are the following: 1) adrenergic blocking drugs have been shown to be useful antihypertensive agents in these animals;2 2) central sympatholytic treatment with 6-hydroxydopamine prevents the development of hypertension in SHR;3 3) the hyperdynamic circulatory state found in immature SHR has been attributed to increased sympathetic activity7;8 4) physiological9 and biochemical10,11 evi-
An association between sympathetic nervous system activity, dietary NaCl, and genetically determined hypertension has been demonstrated in the SHR. In young SHR, the firing rate of sympathetic neurons increases during the developmental phase of hypertension, and ingestion of a high NaCl diet by young SHR enhances the severity of the hypertension, increases peripheral sympathetic nervous system activity (as compared with normotensive controls), and alters the norepinephrine (NE) content of hypothalamic nuclei known to be involved in the regulation of blood pressure.

Increases in plasma and urinary NE concentrations and an exaggerated depressor response to ganglionic blockade have been observed in young SHR maintained on high NaCl diets. There is a highly significant positive correlation between arterial plasma NE concentration and systolic blood pressure in conscious, unrestrained SHR. Further, the increase in plasma NE concentration in NaCl-loaded animals is exaggerated after stress induced by cold exposure. In contrast, oral NaCl loading does not affect blood pressure in normotensive Wistar-Kyoto rats (WKY) or in mature SHR. Taken together these findings suggest that, in the developmental phase of genetic hypertension in SHR, sympathetic nervous system activity is increased and acts as a trigger to set off a chain of events that leads to the development of systemic hypertension. In the presence of increased NaCl intake, sympathetic activity is further enhanced and the hypertension is earlier in onset and more severe. These mechanisms are operational only during the developmental phase and disappear once stable hypertension becomes established.

The present study tested the hypothesis that dietary NaCl loading elevates blood pressure in NaCl-sensitive SHR by altering the input of monoaminergic pathways to hypothalamic and brainstem regions involved in regulating sympathetic nervous system activity and blood pressure control. The results support the hypothesis that reduced release of NE to depressor neurons in the anterior hypothalamus may be an important mechanism underlying NaCl sensitivity in the SHR.

**Materials and Methods**

Male SHR (IBU3 Colony) and normotensive WKY were obtained from Taconic Farms (Germantown, NY, USA) at 7 weeks of age. All rats were maintained four per cage at constant humidity (60 ± 5%), temperature (24 ± 1°C), and light cycle (0600-1800). Three to 6 days after arrival, half of the rats in each genetic group (SHR or WKY) were placed on an 8% NaCl diet (Ralston Purina Diet 5883; St. Louis, MO, USA) while the other half remained on the basal 1% NaCl diet (Ralston Purina Diet 5001). Food and water were available ad libitum throughout the study. Twice per week between 0600 and 1100, systolic blood pressure was measured in conscious, prewarmed, restrained rats by tail plethysmography. The median of five successive measurements was used as the estimate of blood pressure for each animal. Body weight was determined on the same day as the blood pressure measurement.

In the first experiment, 10 SHR and eight WKY were maintained on the 8% NaCl diet for 2 weeks, while 10 SHR and eight WKY were maintained on a 1% NaCl diet for the same period. All rats were killed by decapitation without anesthesia (0600-1100), and the brains were quickly removed and dissected into the following regions: anterior hypothalamic region (AHR), posterior hypothalamic region (PHR), pons, and medulla. The dimensions of AHR were approximately 1 mm (rostrocaudal) × 2 mm (mediolateral) × 2 mm (dorsoventral). AHR dissected in this fashion includes the anterior hypothalamic area and segments of the ventral paraventricular, periventricular, and retrochiasmatic nuclei. The dimensions of the PHR dissections were approximately 1 mm (rostrocaudal) × 1.5 mm (mediolateral) × 3 mm (dorsoventral). PHR dissected in this fashion includes the posterior hypothalamic area and segments of the mammillary 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. After dissection, brain regions were immediately frozen in liquid nitrogen and stored at −80°C.

For analysis of monoamine and monoamine metabolite content, each region was homogenized in 1 ml of 0.1 M acetic acid (pH 5.0) containing ascorbate oxidase and glutathione, and the reaction was terminated by adding 1 ml of 0.1 M perchloric acid containing 0.5 mM glutathione. 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. The homogenates were centrifuged, and the resulting supernatants were filtered and assayed for catecholamines by high performance liquid chromatography with electrochemical detection. The chromatography system employed consisted of an LC-4B amperometric detector and cell (Bioanalytical Systems, Lafayette, IN, USA), an M-45 solvent delivery system and 710B automatic injector (Waters, Milford, MA, USA), a 3-μm C_{18} 10-cm column (IBM, Danbury, CT, USA), and an HP 3390A integrator (Hewlett-Packard, Atlanta, GA, USA). The column was maintained at 40 ± 1°C. The mobile phase conditions were 20 mM citrate/20 mM Na₂HPO₄ acetonitrile (650:250:40), 0.2% H₃PO₄, sodium acetyl sulfate, 120 mg/L, as the ion pairing agent and 1.5 mM tetra ethyl ammonium as a weak secondary ion pairing agent for serotonin.

The same protocol was followed in Experiment 2, but 11 SHR and 12 WKY were maintained on the 8% NaCl diet for 6 weeks, while 10 SHR and 11 WKY were maintained on the 1% NaCl diet for the same period. Six weeks after initiation of the diets, all rats were implanted with femoral arterial catheters as pre-
pressures in Table 2. Asterisk indicates significant difference (p < 0.05) for SHR fed 8% versus 1% NaCl diets. At 8 weeks of age, when the diets were initiated, the mean systolic blood pressure of the SHR was 44 mm Hg higher than that of the WKY (see Figure 1). After 1 week on the 8% NaCl diet, systolic blood pressure in the SHR was elevated significantly (+13 mm Hg) compared with SHR fed the 1% NaCl diet. Continued 8% NaCl feeding gradually increased this difference to 28 mm Hg (6 weeks). Blood pressure in the WKY did not increase significantly from baseline during the course of either experiment, but blood pressure rose significantly in both SHR groups during both experiments.

As shown in Table 2, body weights of 13-week-old SHR were significantly lower than those of WKY, but the 8% NaCl diet did not alter body weight in either group in either study. Similarly, heart rates of 13-week-old SHR were higher than those of WKY, but the high NaCl diet did not influence heart rate significantly in either study. In contrast, 8% NaCl feeding resulted in increases in both heart weight/body weight ratio (SHR only) and kidney weight/body weight ratio in both studies.

Figure 2 demonstrates the NaCl-induced alterations in regional brain norepinephrine levels in SHR and WKY following 2 weeks of 8% NaCl feeding. The 8% NaCl diet caused a significant reduction in NE stores in both AHR and PHR of SHR but had no discernible effect on NE stores in the brainstem (see Figure 2) or the ventral hypothalamic region (1% NaCl = 2333 ± 126 pg/mg tissue vs 8% NaCl = 2474 ± 84 pg/mg tissue) of SHR. In WKY 8% NaCl feeding did not alter NE stores in any of these regions. As shown, NE levels in the AHR were significantly lower in the WKY on either diet than in the SHR on the 1% NaCl diet. Further, the 8% NaCl diet reduced the concentration of the NE metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) in the AHR of SHR (265 ± 23 vs 437 ± 40 pg/mg tissue for 1% NaCl), suggesting that in SHR the 8% NaCl diet induces a lower release and/or higher presynaptic reuptake of NE by nerve terminals in this region. In contrast, in brainstem of SHR MHPG content was not altered by the 8% NaCl diet. MHPG data for the WKY in Experiment 1 are not available.

In SHR the 8% NaCl diet caused a significant reduction in serotonin content of the AHR (Table 3) but did not alter 5-hydroxyindoleacetic acid (5HIAA), dopamine, dihydroxyphenylacetic acid (DOPAC), or epinephrine content of the AHR or of any other brain region studied in SHR (Table 4). In WKY the diet did not produce any detectable change in these amines or metabolites in any brain region studied. In comparison to WKY, 5HIAA levels in SHR were higher in the AHR and PHR but lower in the pons. Similarly, serotonin levels were higher in the medulla but lower in the pons of SHR as compared with WKY, and dopamine contents were higher in the AHR of SHR as compared with WKY (see Table 4). Eight percent NaCl feeding did not affect any of these levels significantly.

Figure 3 summarizes the NE concentrations in AHR, PHR, pons, and medulla of SHR and WKY maintained on 8% and 1% diets for 6 weeks. In animals maintained on the basal (1% NaCl) diet, NE stores were not significantly different between strains in any region, although they tended to be elevated in the PHR of SHR as compared with WKY. The 8% NaCl diet caused a significant decrease in NE stores in the PHR of SHR but did not alter NE stores in the PHR of WKY. In the AHR, the 8% NaCl diet did not cause a significant change in NE content in the SHR, but did effect a significant rise in NE stores in WKY (p < 0.05) and a significant group × diet interaction (p < 0.05). No NaCl-induced differences in NE stores were found in the pons or medulla of either strain.

Figure 4 demonstrates that 8% NaCl feeding reduced the concentration of the MHPG in PHR of SHR but not of WKY. Thus, both NE and NE metabolite levels are reduced in the PHR by NaCl loading in SHR but not in WKY. No NaCl-induced differences in MHPG levels were seen in the pons or medulla of either strain following 6 weeks of the diet.

Stores of other monoamines and monoamine metab-
olites differed significantly between strains. In the PHR, levels of DOPAC were higher in SHR than in WKY (see Table 4). Dietary NaCl loading did not alter these levels. Significant group differences were also present in 5HIAA and serotonin levels in the PHR. Dietary NaCl loading did not alter these levels (see Table 3). Although 8% NaCl feeding elevated the serotonin content of the AHR in SHR, similar NaCl-induced elevations were present in WKY.

**Discussion**

Results of the present study demonstrate that significant alterations in noradrenergic projections to hypothalamic regions thought to be involved in blood pressure regulation and the pathogenesis of hypertension accompany the NaCl-induced exacerbation of hypertension in the SHR. The data indicate that 1) during the developmental phase of NaCl-exacerbated hypertension, NE stores are decreased in both the AHR and
TABLE 3. Serotonin and 5-Hydroxyindoleacetic Acid Contents in Brain Regions of Rats Fed 1% or 8% NaCl Diet for 2 (Experiment 1) or 6 (Experiment 2) Weeks

<table>
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<tr>
<th>Brain area</th>
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<th>8% NaCl</th>
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<tr>
<td>SHR</td>
<td>571 ± 82*</td>
<td>501 ± 52</td>
<td>522 ± 47†</td>
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<tr>
<td>WKY</td>
<td>401 ± 40</td>
<td>468 ± 54</td>
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<tr>
<td>PHR</td>
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<td>712 ± 38*</td>
<td>1520 ± 194</td>
<td>1409 ± 126</td>
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<tr>
<td>WKY</td>
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<tr>
<td>Pons</td>
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<td>488 ± 36</td>
<td>480 ± 35</td>
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<tr>
<td>Medulla</td>
<td>437 ± 89</td>
<td>360 ± 66</td>
<td>789 ± 124*</td>
<td>764 ± 127*</td>
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<tr>
<td>WKY</td>
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<td>329 ± 29</td>
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6-week diet

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Values are means ± SEM. 5HIAA = 5-hydroxyindoleacetic acid; AHR = anterior hypothalamic region; PHR = posterior hypothalamic region.

* p<0.05, compared with values for WKY on the same diet.
† p<0.05, compared with values for rats of the same strain fed 1% NaCl.

PHR compared with levels in SHR maintained on basal diets; 2) levels of MHPB, the major terminal NE metabolite, are reduced during this early developmental period of NaCl-exacerbated hypertension; 3) kidney weight/body weight and heart weight/body weight ratios are elevated after both 2 and 6 weeks of 8% NaCl feeding in the SHR, although absolute body weight is not affected by the diet, and 4) compared with WKY NE contents in the AHR and PHR of SHR are lower after 6 weeks of 8% NaCl feeding. These findings are consistent with the hypothesis that NaCl loading exacerbates the severity of hypertension in SHR by decreasing NE synthesis or release (or both) from noradrenergic nerve terminals in the anterior hypothalamus.

Central nervous system mechanisms appear to play an important role in the increase in peripheral sympathetic nervous system activity seen during the developmental phase of hypertension in SHR. Depletion of...
central NE and dopamine stores by intraventricular 6-hydroxydopamine treatment prevents the development but not the maintenance of hypertension in SHR, suggesting that central catecholaminergic pathways may be important in the initiation of the increases in blood pressure and sympathetic nervous system activity observed in developing SHR. Previous reports have suggested that, during the developmental phase of hypertension, two hypothalamic regions, the anterior and posterior hypothalamic areas, receive an abnormal noradrenergic projection in the SHR as compared with WKY controls. In addition, recent reports have demonstrated that release of NE from in vitro perfused anterior and posterior hypothalamic areas is altered in SHR. During the early phase of hypertension, NE release from the posterior hypothalamic area is elevated in SHR compared with WKY, while at a later stage of hypertension, NE release from the anterior hypothalamic area is reduced in SHR compared with WKY. In vivo, both alterations would tend to increase blood pressure by increasing sympathetic nervous system activity.

Several studies have demonstrated that neurons in the anterior hypothalamic area have a depressor function. Electrical stimulation of this area reduces blood pressure and heart rate, direct injection of α₂-adrenergic receptor agonists depresses the cardiovascular system, and injection of 6-hydroxydopamine or placement of electrolytic lesions leads to hypertension. Together these data demonstrate that excitation of NE input to the anterior hypothalamic area depresses the cardiovascular system. Conversely, reductions in NE input to the anterior hypothalamic area would be expected to decrease inhibition of the cardiovascular system and thereby allow blood pressure to increase. In the current study, SHR fed the 8% (compared with 1%) NaCl diet for 2 weeks showed a 22% reduction in NE content and a 39% reduction in MHPG content of the AHR in association with a significant increase in blood pressure. MHPG is the major terminal metabolite of NE in the rat brain, and its concentration has been shown to be directly related to the rate of NE turnover. The finding of reduced tissue stores of NE and its major metabolite in the AHR of salt-loaded SHR is consistent with the hypothesis that NaCl loading is associated with decreased NE synthesis or release (or both) by noradrenergic nerve terminals in the anterior hypothalamus.

After 6 weeks of the 8% NaCl diets, NE stores in the AHR of SHR were not significantly different than those in 1% NaCl-fed SHR. Conversely, the NE stores in the AHR of 8% (compared with 1%) NaCl-fed WKY were significantly elevated. The significant group x diet interaction suggests that there may be a failure of the NE levels in SHR to increase in relation to the high NaCl diet, which could contribute to a lack of sympathoinhibition. To demonstrate more definitively that the altered NE projections to the AHR are important to blood pressure regulation in the NaCl-loaded SHR, it will be necessary to demonstrate directly that the release of NE is decreased in these areas following NaCl loading in SHR. In preliminary studies we have demonstrated a reduction in the release of NE from terminals in the AHR of 8% (compared with 1%) NaCl-fed SHR and that similar changes do not occur in WKY or in SHR that are resistant to dietary NaCl loading. It will be important in future studies to examine the response of the NaCl-resistant SHR and of other non-NaCl-sensitive rats in order to demonstrate that the between-strain differences do not result from an abnormality in WKY. In this regard, a 1982 study by our laboratory demonstrated slightly increased NE stores in the anterior hypothalamic area of SHR fed a 8% NaCl diet. We are currently investigating whether the differences between the findings of that and the present study are the result of the use of different strains of SHR or of the use of different techniques (punch compared with regional dissections). Whatever the outcome, we are confident in the present results since they have been confirmed in three separate studies. Data from the 2-week study suggest that NE stores in AHR are lower in WKY than in SHR (see Figure 2). We have not found this difference in 9- to 10-week-old SHR as compared with age-matched WKY fed a 1% NaCl diet in two other studies, and thus the interpretation of this aspect of the data remains ambiguous.

The posterior hypothalamic area contains neurons that produce a pressor response when stimulated and that have previously been implicated in the genesis of hypertension in the SHR. Electrical stimulation of these neurons increases arterial pressure and heart rate by elevating sympathetic nervous system activity. Furthermore, electrical stimulation of this area in SHR elicits an exaggerated pressor response compared with WKY, and lesions in this area result in a hypotensive response that is greater in SHR than in WKY. The present results indicate that the NaCl-induced exacerbation of hypertension in SHR is associated with a decrease in NE stores in the PHR following both 2 and 6 weeks of 8% NaCl feeding and a reduction in MHPG stores following 6 weeks of the 8% NaCl feeding. The PHR dissection employed in the present study included the posterior hypothalamic area and axons from the A₁, A₂, and A₆ nuclei of the brainstem that pass near the posterior hypothalamic area en route to more rostral terminal fields. The reduction in NE content in the PHR of SHR fed the 8% NaCl diet for 2 weeks probably reflects reduced input both to the PHR and to more rostral areas (e.g., the anterior hypothalamic area). Conversely, the later (6 week) reduction in NE stores in the PHR probably reflects decreased NE input primarily to the posterior hypothalamic area itself, since NE stores in the AHR were not significantly reduced in SHR following 6 weeks of NaCl loading and since MHPG content in the PHR was decreased after 6 weeks of NaCl loading. We assume that the reduction in PHR NE at 6 weeks and some of the reduction at 2 weeks are an adaptive response to the elevated blood pressure in the SHR fed the 8% NaCl diet. It will be important in future studies to determine which of the NE alterations are secondary to the hypertension and which are primary.

In addition to the reductions in NE and MHPG, SHR...
fed an 8% NaCl diet also manifested alterations in stores of serotonin compared with SHR fed a basal diet, suggesting that serotoninergic input to the depressor neurons of the anterior hypothalamic area is altered by dietary NaCl loading. Dietary NaCl loading for 2 weeks decreased serotonin stores in the AHR of SHR. Koulu et al. recently demonstrated that cardiovascular control nuclei in the brainstem of SHR (compared with WKY) display significantly altered serotonin content and turnover before the development of hypertension (4 weeks) and that these increases are largely absent in 14-week-old SHR, suggesting that early increases in serotoninergic input to brainstem nuclei may contribute to the triggering of hypertension in SHR. Although the present data suggest that serotonin alterations may be important to the development of hypertension in the SHR fed an 8% NaCl diet, the direction and magnitude of the serotonin changes are equal in the 6-week-fed SHR compared with the WKY. Although dopamine and DOPAC stores were altered in the AHR of SHR compared with WKY, the 8% NaCl feeding did not change the regional content in either strain.

In summary, many studies have shown that the anterior hypothalamic area is a major cardiovascular depressor region in the central nervous system and that depressor responses elicited by stimulation of this area are exaggerated in SHR as compared with WKY. The present results demonstrate that dietary NaCl loading of SHR results in decreased NE and MHPG levels in the AHR during the development of the NaCl-induced exacerbation of hypertension in SHR. This finding is consistent with the hypothesis that decreased NE input to the anterior hypothalamus may be an important mechanism by which dietary NaCl loading elevates blood pressure. Current studies are focused on determining whether the decrease in NE in the AHR precedes the elevation in blood pressure, and whether this decrease is responsible at least in part for the exacerbation of hypertension in SHR fed high NaCl diets.

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