NaCl Does Not Affect Hypothalamic Noradrenergic Input in Deoxycorticosterone Acetate/NaCl and Dahl Salt-Sensitive Rats

Yiu-Fai Chen, Qingcheng Meng, J. Michael Wyss, Hongkui Jin, Caroline F. Rogers, and Suzanne Oparil

Previous studies from our laboratories demonstrated that dietary NaCl supplementation in NaCl-sensitive spontaneously hypertensive rats elevates blood pressure, increases peripheral sympathetic nervous system activity, and depresses endogenous norepinephrine stores and turnover in the anterior hypothalamus. These findings suggest that reduced noradrenergic input to sympathoinhibitory neurons in anterior hypothalamus contributes to NaCl-sensitive hypertension in spontaneously hypertensive rats. The current study tested the hypothesis that dietary NaCl supplementation depresses endogenous norepinephrine stores and turnover in anterior hypothalamus of two other NaCl-sensitive models of hypertension, the Dahl salt-sensitive rat and the deoxycorticosterone acetate/NaCl hypertensive rat, thus increasing blood pressure by reducing noradrenergic input to the anterior hypothalamus. Dahl salt-sensitive rats were fed a high (8%) NaCl diet, and deoxycorticosterone acetate/NaCl rats drank 1% NaCl solution ad libitum for 2 or 4 weeks. Age-matched Dahl salt-sensitive rats fed a basal 1% NaCl diet and uninephrectomized Sprague-Dawley rats drinking tap water were controls. Regional brain catecholamines were determined by high-performance liquid chromatography with electrochemical detection. Norepinephrine turnover in hypothalamus (anterior, posterior, and ventral regions) and brain stem (pons and medulla) was assessed using the dopamine β-hydroxylase inhibitor 1-cyclohexyl-2-mercapto-imidazole. High NaCl treatment caused significant elevations in blood pressure in Dahl salt-sensitive and deoxycorticosterone acetate/NaCl rats, but endogenous norepinephrine levels and turnover rates were not significantly different in anterior hypothalamus or any other brain region studied between the NaCl-supplemented and control groups. Noradrenergic input to the anterior hypothalamus is not reduced in Dahl salt-sensitive and deoxycorticosterone acetate/NaCl rats on a high NaCl intake, suggesting that the neural mechanisms of NaCl sensitivity are different in the Dahl salt-sensitive, deoxycorticosterone acetate/NaCl, and spontaneously hypertensive rat models of hypertension. Thus, the abnormalities in anterior hypothalamic norepinephrine handling observed in NaCl-supplemented, NaCl-sensitive hypertensive rats are strain-specific and not secondary to the NaCl-induced increase in blood pressure. (Hypertension 1990;16:55–62)

Both human studies and animal experiments indicate that, in genetically predisposed individuals, NaCl loading contributes to the development or exacerbation of hypertension accompanied by an increase in sympathetic nervous system activity.1,2 Previous studies from our laboratories have demonstrated that chronic NaCl loading (8%) in NaCl-sensitive spontaneously hypertensive rats (SHR-S) obtained from Taconic Farms (IBU3 Colony, Germantown, N.Y.) exacerbates hypertension, increases peripheral sympathetic nervous system activity, and reduces norepinephrine stores and turnover in the anterior hypothalamic area (AHA). NaCl-
resistant SHR (SHR-R), obtained from Charles River Breeding Laboratories, Wilmington, Mass., and normotensive control Wistar-Kyoto (WKY) rats, obtained from Taconic Farms, do not manifest these NaCl-induced changes.\(^3\)\(^4\) The afferent noradrenergic innervation of the AHA arises from three brain stem nuclei (A\(_1\), A\(_2\), and A\(_3\)) but primarily from A\(_2\).\(^5\)\(^-\)\(^7\) Effferent projections of the AHA are directed primarily to other hypothalamic nuclei,\(^8\)\(^9\) including regions containing primarily sympathoexcitatory neurons (the lateral and posterior hypothalamic areas and the ventromedial hypothalamic nucleus). The most prominent extrahypothalamic projection terminates in the central gray of the midbrain. Several lines of evidence, including electrical and chemical stimulation and lesion studies, suggest that the AHA has a sympathoinhibitory function and that stimulation of AHA leads to reductions in blood pressure and heart rate.\(^10\)\(^-\)\(^12\) We therefore hypothesize that in SHR-R and WKY rats fed a high NaCl diet, tonic norepinephrine release from projections of A\(_1\), A\(_2\), and A\(_3\) neurons to the anterior hypothalamic neurons results in tonic inhibition of pressor neurons in the lateral hypothalamic area, posterior hypothalamic area, and periaqueductal gray, thereby reducing excitation of sympathetic preganglionic neurons in the intermediolateral cell column. In SHR-S maintained on a high NaCl diet, reduced norepinephrine release from A\(_2\), A\(_3\), and A\(_4\) terminals in AHA reduces the tonic inhibition of pressor neurons in the lateral hypothalamic area, posterior hypothalamic area, and periaqueductal gray, thereby increasing sympathetic nervous system activity through the intermediolateral cell column. Thus, our data suggest that reduced noradrenergic input to depressor neurons in the AHA is an important mechanism underlying NaCl sensitivity in the SHR-S.

In the current study, we tested the hypothesis that dietary NaCl supplementation depresses endogenous norepinephrine stores and turnover in AHA of two other NaCl-sensitive models of hypertension, the Dahl salt-sensitive (DS) rat and the deoxycorticosterone acetate (DOCA)/NaCl hypertensive rat, thus increasing blood pressure by reducing stimulation of sympathoinhibitory neurons in AHA. Our results indicate that noradrenergic input to the AHA is not reduced in DS and DOCA/NaCl rats on a high NaCl intake, suggesting that the neural mechanisms of NaCl sensitivity are different in DS and DOCA/NaCl and SHR-S models of hypertension.

Methods

Male DS rats were obtained from the Brookhaven National Laboratory, Brookhaven, N.Y., at 4 weeks of age. Three days after arrival, half of the DS rats were placed on an 8% NaCl diet (ICN Biochemicals, Purina Chow with 8% NaCl, Cleveland, Ohio), while the other half (controls) remained on the basal 1% NaCl diet (diet 5001, Ralston Purina, St. Louis, Mo.). DS rats were maintained on the special diets for 2 weeks (to match the duration of NaCl loading of SHR-S) or 4 weeks (to match the level of blood pressure in 8% NaCl-fed SHR-S).

Male Sprague-Dawley rats were obtained from Charles River Breeding Laboratories at 3 weeks of age and were subjected to left nephrectomy at 4 weeks of age. After uninephrectomy, 14 days were allowed for compensatory renal hypertrophy to occur before DOCA/NaCl treatment was begun. DOCA (Sigma Chemical Co., St. Louis, Mo.) was administered by subcutaneous implantation of Silastic strips (Silicone rubber, Dow Corning, Midland, Mich.) containing 100 mg/kg DOCA. Salt was administered by substitution of 1% NaCl solution for drinking water. Normotensive controls were age-matched uninephrectomized rats sham-operated without DOCA implantation and allowed to drink tap water ad libitum (H\(_2\)O control rats). Both DOCA/NaCl and H\(_2\)O control rats were fed the basal 1% NaCl diet. DOCA/NaCl hypertensive and H\(_2\)O control rats were studied 2 weeks (to match the duration of NaCl loading) or 4 weeks (to match the blood pressure of 8% NaCl-fed SHR-S) after initiation of DOCA/NaCl treatment.

Throughout the study, rats were housed in a constant temperature (24±1°C) and humidity (60±5%) facility with a 12-hour light/dark cycle. Systolic blood pressure was measured weekly in conscious restrained rats by the tail-cuff method, using an electrophysgmonomanometer and physiograph recorder (Narco Biosystems, Houston, Tex.). To assess the effect of the NaCl supplements on brain noradrenergic neuronal activity, norepinephrine disappearance and dopamine accumulation were measured after inhibition of dopamine β-hydroxylase using the 1-cyclohexyl-2-mercaptoimidazole (CHMI) (Lilly Research Laboratories, Indianapolis, Ind.) method as previously described.\(^8\) CHMI (or LY10853), a specific inhibitor of dopamine β-hydroxylase, has been used to evaluate norepinephrine turnover in brain.\(^9\) After CHMI treatment, there are rapid decreases in norepinephrine concentration in regions of brain innervated by noradrenergic pathways. Norepinephrine disappearance rates are useful indexes of norepinephrine turnover in brain. In the current study, CHMI was given intraperitoneally in a dose of 50 mg/kg in 200 μl of 5% emulphore (Emulphore EL719P, GAF Corp., New York). Rats were killed 60 or 120 minutes later by decapitation without anesthesia. In the third subgroup, 200 μl of 5% emulphore was administered as a vehicle control, and the rats were killed 120 minutes later.

Brains were removed immediately after 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), and medulla (120–125 mg). The ventral hypothalamic dissection included the median eminence, arcuate nucleus, and the ventrolateral part of the ventromedial hypothalamic nucleus. The anterior hypothalamic dissection

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\(^1\) Hypertension Vol 16, No 1, July 1990
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 mammillary complex. Pons was separated from midbrain immediately caudal to the inferior colliculus and from 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 levels in brain regions were determined using high-performance liquid chromatography 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/1), and ascorbic acid oxidase (1 mg/ml; Boehringer, Mannheim, FRG) for 10 seconds on ice. An equal volume of 0.1N perchloric acid containing Na2EDTA (100 mg/1) and n-methyl-dopamine as the internal standard was added, and the sample was homogenized for another 30 seconds. Ascorbate oxidase reduces solvent front interferences with norepinephrine by significantly lowering the concentration of ascorbic acid, which normally elutes in the solvent front and partially obscures the norepinephrine peak. Homogenates were centrifuged (20,000g at 4°C for 10 minutes); supernatants were filtered through 0.2 μm membrane filters (nylon 66 filter, Rainin Instruments, Woburn, Mass.) and analyzed for monoamine and metabolite levels using HPLC with electrochemical detection.

The rate constant for norepinephrine turnover was calculated according to the method of Brodie et al.13 Values for tissue levels of norepinephrine and dopamine 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 mean±SEM.

Results

Blood Pressure and Body Weight

In DS rats, the 8% NaCl diet caused a significant increase in blood pressure compared with that of DS rats fed the 1% NaCl diet. The increase in systolic blood pressure was statistically significant after 2 weeks of 8% NaCl feeding. At 4 weeks of high NaCl diet, body weight and systolic blood pressure of 8% NaCl-diet DS rats were significantly greater than those of the 1% NaCl DS rats (Table 1).

Rats treated with DOCA and given 1% saline to drink showed a significant increase in systolic blood pressure as early as 7 days after the initiation of treatment (DOCA/NaCl, 137±3 mm Hg; H2O control, 120±2 mm Hg; p<0.05). At 2 and 4 weeks of treatment, body weight and systolic blood pressure of DOCA/NaCl-treated rats were significantly different from those of H2O controls (Table 1).

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

There were no significant changes in norepinephrine or dopamine stores in any brain region examined in DS or DOCA/NaCl rats after 2 or 4 weeks of high NaCl loading compared with their respective basal NaCl-fed normotensive control groups (Tables 2 and 3). CHMI administration caused significant disappearance of norepinephrine and accumulation of dopamine in all brain regions studied during the 2-hour experiment. NaCl supplementation had no significant effect on norepinephrine turnover or dopamine accumulation in AHA or any other brain region studied in high NaCl-treated DS or DOCA/NaCl rats compared with their respective basal NaCl-fed control groups (Tables 2 and 3). There was a slight decrease in turnover rate constant (k) and a slight increase in t1/2 of norepinephrine turnover in the AHA and posterior hypothalamic area at 4 weeks in 8% NaCl–treated DS rats (Table 2). However, these differences did not reach statistically significant levels (p=0.25, Figure 1).

In the AHA (Figure 1), the slope of the line (k[hr−1]), the rate constant of norepinephrine disap-
AHA.34 WKY rats obtained from Taconic Farms and SHR-R obtained from Charles River are resistant to dietary NaCl supplementation in SHR-S are strain-specific and do not contribute to NaCl-induced hypertension in any other brain region tested in 2- or 4-week NaCl-loading rats compared with their respective basal NaCl-fed control groups.

**Discussion**

Previous studies from our laboratory demonstrated that dietary NaCl supplementation in SHR-S obtained from Taconic Farms elevates blood pressure, increases peripheral sympathetic nervous system activity, and depresses endogenous norepinephrine stores and norepinephrine turnover in the AHA.3,4 WKY rats obtained from Taconic Farms and SHR-R obtained from Charles River are resistant to the NaCl-induced alterations in blood pressure and central and peripheral noradrenergic activity, suggesting that the alterations observed in the SHR-S during NaCl loading are strain-specific. Because local stimulation of α2-adrenergic receptors in AHA results in sympathoinhibition and reductions in blood pressure,14-16 we have proposed the hypothesis that a deficit in norepinephrine release from nerve terminals in the AHA of dietary NaCl-loaded SHR-S results in decreased sympathoinhibition and thereby increases peripheral sympathetic outflow and systemic arterial pressure. In the current study, we tested this hypothesis in a second genetically NaCl-sensitive hypertensive model, the DS rat, and in an acquired NaCl-sensitive hypertensive model, the DOCA/NaCl hypertensive rat.

We demonstrated that there were no differences in norepinephrine stores or turnover rates in AHA or any other brain region tested in 2- or 4-week NaCl-loaded DS and DOCA/NaCl rats compared with their respective basal NaCl-fed control groups. These results suggest that alterations in noradrenergic input to the AHA do not contribute to NaCl-induced hypertension in DS and DOCA/NaCl rats. Thus, the neuronal mechanisms of dietary NaCl sensitivity are different in DS, DOCA/NaCl, and SHR-S models of hypertension. Further, these data support the conclusion that the reductions in AHA norepinephrine release observed in NaCl-supplemented SHR-S are strain-specific and

### Table 2. Effects of 2 or 4 Weeks of NaCl Supplementation on Norepinephrine Turnover in Hypertensive Rats

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal NaCl</th>
<th>High NaCl</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Initial NE content (pg/mg tissue)</td>
<td>Calculated turnover rate (pg/mg/hr)</td>
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<tr>
<td><strong>AHA</strong></td>
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<td></td>
</tr>
<tr>
<td>DS (2 wk)</td>
<td>2,875±231</td>
<td>0.3853</td>
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<tr>
<td>DS (4 wk)</td>
<td>2,356±253</td>
<td>0.4051</td>
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<tr>
<td>DOCA/NaCl (2 wk)</td>
<td>1,740±104</td>
<td>0.2864</td>
</tr>
<tr>
<td>DOCA/NaCl (4 wk)</td>
<td>2,007±121</td>
<td>0.2591</td>
</tr>
<tr>
<td><strong>PHA</strong></td>
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<tr>
<td>DS (2 wk)</td>
<td>2,373±141</td>
<td>0.3429</td>
</tr>
<tr>
<td>DS (4 wk)</td>
<td>1,605±61</td>
<td>0.3630</td>
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<td>DOCA/NaCl (2 wk)</td>
<td>1,435±54</td>
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<td>1,990±99</td>
<td>0.4963</td>
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<td><strong>VHA</strong></td>
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<tr>
<td>DS (2 wk)</td>
<td>2,675±167</td>
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<tr>
<td>DS (4 wk)</td>
<td>2,410±167</td>
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<td>DOCA/NaCl (2 wk)</td>
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<td>DOCA/NaCl (4 wk)</td>
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<td><strong>Pons</strong></td>
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<td>DS (2 wk)</td>
<td>599±12</td>
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<tr>
<td>DS (4 wk)</td>
<td>632±14</td>
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<td>DOCA/NaCl (2 wk)</td>
<td>433±14</td>
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<td>DOCA/NaCl (4 wk)</td>
<td>477±38</td>
<td>0.4147</td>
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<tr>
<td><strong>Medulla</strong></td>
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</tr>
<tr>
<td>DS (2 wk)</td>
<td>548±32</td>
<td>0.4152</td>
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<td>DS (4 wk)</td>
<td>647±56</td>
<td>0.3247</td>
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<td>DOCA/NaCl (2 wk)</td>
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<tr>
<td>DOCA/NaCl (4 wk)</td>
<td>577±25</td>
<td>0.3931</td>
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Normal NaCl controls for deoxycorticosterone acetate (DOCA)/NaCl group are uninephrectomized rats without DOCA implantation and allowed to drink tap water ad libitum. Results represent mean±SEM for groups of six to seven rats assayed individually. NE, norepinephrine; AHA, anterior hypothalamic area; DS, Dahl salt-sensitive rats; PHA, posterior hypothalamic area; VHA, ventral hypothalamic area; k, turnover rate constant; t, time (in hours), the slope of log [NE]=log[NE]0-0.434k; t1/2, time (in hours) required for 50% decrease of initial NE content.5
### TABLE 3. Effects of 2 or 4 Weeks of NaCl Supplementation on Dopamine Accumulation in Hypertensive Rats

<table>
<thead>
<tr>
<th>Variable</th>
<th>Initial DA content (pg/mg tissue)</th>
<th>Normal NaCl</th>
<th>High NaCl</th>
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<tr>
<td></td>
<td></td>
<td>Calculated turnover rate (pg/mg/hr)</td>
<td>Calculated turnover rate (pg/mg/hr)</td>
</tr>
<tr>
<td><strong>AHA</strong></td>
<td></td>
<td>k (hr^-1)</td>
<td>t2 (hr)</td>
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<tr>
<td>DS (2 wk)</td>
<td>236±31</td>
<td>0.4270</td>
<td>100.7</td>
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<tr>
<td>DS (4 wk)</td>
<td>95±13</td>
<td>0.8650</td>
<td>83.4</td>
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<tr>
<td>DOCA/NaCl (2 wk)</td>
<td>121±9</td>
<td>0.5085</td>
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<td>DOCA/NaCl (4 wk)</td>
<td>162±25</td>
<td>0.2501</td>
<td>40.7</td>
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<tr>
<td><strong>PHA</strong></td>
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<tr>
<td>DS (2 wk)</td>
<td>326±35</td>
<td>0.3463</td>
<td>112.8</td>
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<tr>
<td>DS (4 wk)</td>
<td>95±16</td>
<td>0.6205</td>
<td>58.8</td>
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<td>DOCA/NaCl (2 wk)</td>
<td>151±13</td>
<td>0.3362</td>
<td>50.8</td>
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<td>DOCA/NaCl (4 wk)</td>
<td>251±11</td>
<td>0.3601</td>
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<td><strong>VHA</strong></td>
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<tr>
<td>DS (2 wk)</td>
<td>324±38</td>
<td>0.3535</td>
<td>114.7</td>
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<td>DS (4 wk)</td>
<td>145±44</td>
<td>0.7174</td>
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<td>DOCA/NaCl (2 wk)</td>
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<td>DOCA/NaCl (4 wk)</td>
<td>269±83</td>
<td>0.4313</td>
<td>116.1</td>
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<td><strong>Pons</strong></td>
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<td>DS (2 wk)</td>
<td>45±2</td>
<td>0.7241</td>
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<td>DS (4 wk)</td>
<td>49±3</td>
<td>0.8475</td>
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<td>DOCA/NaCl (2 wk)</td>
<td>168±52</td>
<td>0.4401</td>
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<td>DOCA/NaCl (4 wk)</td>
<td>40±6</td>
<td>0.6371</td>
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<tr>
<td><strong>Medulla</strong></td>
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<tr>
<td>DS (2 wk)</td>
<td>60±7</td>
<td>0.4696</td>
<td>28.2</td>
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<tr>
<td>DS (4 wk)</td>
<td>73±7</td>
<td>0.5430</td>
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<td>DOCA/NaCl (2 wk)</td>
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<tr>
<td>DOCA/NaCl (4 wk)</td>
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</table>

Normal NaCl controls for deoxycorticosterone acetate (DOCA)/NaCl group are uninephrectomized rats without DOCA implantation and allowed to drink tap water ad libitum. Results represent mean±SEM for groups of six to seven rats assayed individually. DA, dopamine; AHA, anterior hypothalamic area; DS, Dahl salt-sensitive rats; PHA, posterior hypothalamic area; VHA, ventral hypothalamic area; k, turnover rate constant; t, time (in hours), the slope of \( \log [NE] = \log [NE]_0 - 0.434 kt \); t2, time (in hours) required for 100% increase of initial DA content.5

### ANTERIOR HYPOTHALAMIC AREA

**FIGURE 1.** Plots showing disappearance of norepinephrine (NE) after inhibition of dopamine β-hydroxylase by 1-cyclohexyl-2-mercapto-imidazole (CHMI) in the anterior hypothalamus of Dahl salt-sensitive (Dahl S) and deoxycorticosterone acetate (DOCA)/ NaCl hypertensive rats after 2 weeks (top panels) or 4 weeks (bottom panels) of high NaCl diet compared with their respective basal NaCl-fed normotensive controls.
not secondary to the NaCl-induced increase in blood pressure. After inhibition of norepinephrine synthesis with CHMI, the decrease in tissue norepinephrine levels will be a first-order reaction, that is, the rate of norepinephrine release is proportional to the norepinephrine stores in the tissue. Accordingly, in this study the rate constant for norepinephrine turnover was calculated by the method of Brodie et al. Values of tissue levels of norepinephrine and dopamine were logarithmically transformed for calculation of linearity of regression. The current analysis (0 time plus 2 time points after CHMI treatment) revealed no major alterations in norepinephrine turnover, comparable with those seen in the AHA of SHR on 8% versus 1% NaCl diets, in any brain region of any group. Although the current data cannot rule out all possible changes in the short-term (less than 60 minutes) release of norepinephrine after CHMI administration, we doubt that these would attain a high level of statistical significance, comparable with those previously reported for the AHA of SHR-S fed 8% versus 1% NaCl diets.

The DS rat is a model of NaCl-induced hypertension in which both abnormal renal sodium handling and increased sympathetic nervous system activity are involved in the process by which increased dietary NaCl induces hypertension. Takeshita and associates have demonstrated that neurogenic vasoconstriction accounts for a large proportion of the increased vascular resistance and increased blood pressure in DS rats on a high NaCl diet and that high NaCl diet potentiate cardiovascular responses to sympathetic nerve stimulation in DS rats. Further, it has been demonstrated that the increase in sympathetic tone in DS rats on a high NaCl diet is associated with decreased baroreceptor-mediated regulation of blood pressure and with changes in hypothalamic regulation of sympathetic tone. Lesions of central nervous system structures can modify the development of NaCl-induced hypertension in the DS rat. Hypothalamic lesions involving either the periventricular tissue surrounding the anterovernal third ventricle or the paraventricular suprachiasmatic region prevent or attenuate the development of hypertension in the DS rats. It has been demonstrated that DS rats given a high NaCl diet show increases in epinephrine-forming enzyme phenylethanolamine-N-methyltransferase (PNMT) activity in the area postrema and nucleus commissuralis, compared with DS rats on normal NaCl diet. However, recent studies from our laboratory showed that high dietary NaCl intake did not influence hypothalamic or brain stem stores of monoamines (dopamine, norepinephrine, or serotonin) or their metabolites (DOPAC and 5HIAA). The present study confirmed these data by demonstrating that norepinephrine stores and turnover in the hypothalamic and brain stem regions of 2- or 4-week NaCl-loaded DS rats were not different from those of the normal NaCl DS rats. This suggests that the increased sympathetic nervous system activity in the DS model, unlike the SHR-S in which AHA norepinephrine turnover rate decreases (t = 2.27 hour in 1% NaCl rats and 6.34 hour in 8% NaCl rats) is not related to alterations in hypothalamic or brain stem noradrenergic system activity.

The DOCA/NaCl hypertensive rat is a model of acquired hypertension in which blood pressure elevations are induced by NaCl loading in normotensive Sprague-Dawley rats treated with the mineralocorticoid DOCA. Multiple lines of evidence indicate that alterations of central monoaminergic systems are involved in this model. Studies of norepinephrine metabolism in the DOCA/NaCl rat have revealed increased turnover in the heart and other peripheral tissues and a reciprocal decrease in brain stem turnover, elevated plasma levels, reduced tissue levels, and an apparent storage defect for norepinephrine. The decrease in brain stem norepinephrine turnover in DOCA/NaCl rats suggests that central sympathetic activity is altered during the maintenance phase (6-7 weeks of treatment) of hypertension in this model. Saavedra demonstrated that brain stem (area postrema, locus coeruleus, nucleus commissuralis, nucleus tractus solitarius, and A1 and A2 areas) norepinephrine levels in DOCA/NaCl hypertensive rats after 2 and 4 weeks of treatment were similar to those of matched controls. Only after 9 weeks of DOCA/NaCl treatment could these investigators detect significant increases in levels of norepinephrine in the nucleus commissuralis and epinephrine in A1 and A2, locus coeruleus, and nucleus commissuralis. These later (6-9 weeks of treatment) changes in catecholamine content of certain nuclei may merely reflect the chronic hypertension in this model. Recent studies from our laboratory showed that 4 weeks of treatment with DOCA/NaCl did not influence hypothalamic norepinephrine, dopamine, serotonin, or 5HIAA levels and produced small increases in norepinephrine and 5HIAA levels in whole pons-medulla tissue blocks. The present study confirmed these data by demonstrating that norepinephrine stores in the hypothalamic regions, pons, and medulla, of DOCA/NaCl hypertensive rats after 2 or 4 weeks NaCl loading were not different from those of H2O controls.

Studies of norepinephrine metabolism in the DOCA/NaCl rat have revealed increased norepinephrine turnover in the heart and other peripheral tissues and elevated plasma norepinephrine levels. Van Ameringen et al demonstrated reciprocal changes in norepinephrine turnover in the pons-medulla and heart of DOCA/NaCl hypertensive rats, namely, decreased norepinephrine turnover in the brain stem and increased turnover in the periphery. This observation led them to conclude that the lowering of noradrenergic activity in the depressor area of brain stem enhances peripheral sympathetic nervous activity. However, in the current study, norepinephrine turnover was unaltered in the hypothalamic areas, pons, and medulla. The discrepancy
between studies may be caused by the different brain dissections, ages of animals, and reagents used to study norepinephrine turnover. In Van Ameringen's study, the investigators used whole brain stem from DOCA/NaCl rats 5–7 weeks after the initiation of DOCA/NaCl treatment and α-methyl-p-tyrosine, a tyrosine hydroxylase inhibitor, to study norepinephrine turnover. The current study suggests that the increased sympathetic nervous system activity in the DOCA/NaCl hypertensive model, unlike the SHR-S, is not related to alterations in hypothalamic (anterior, posterior, and ventral) or brain stem regions (pons, medulla) noradrenergic neuronal activity.

In conclusion, the involvement of the central noradrenergic system in the pathogenesis of hypertension appears to be different in SHR-S, DS, and DOCA/NaCl models of hypertension. From our previous findings, it is evident that the NaCl-induced exacerbation of hypertension in SHR-S rats is related to reduced noradrenergic input to the AHA. This mechanism does not appear to contribute to the development of hypertension in DS and DOCA/NaCl rats after chronic NaCl loading.

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References


**KEY WORDS** • salt • deoxycorticosterone • sodium-dependent hypertension • hypothalamus • brainstem • catecholamines • Dahl rats
NaCl does not affect hypothalamic noradrenergic input in deoxycorticosterone acetate/NaCl and Dahl salt-sensitive rats.
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