High Urinary Dopa and Low Urinary Dopamine-to-Dopa Ratio in Salt-Sensitive Hypertension

John R. Gill Jr., Ehud Grossman, and David S. Goldstein

Dopamine in urine is derived substantially from renal uptake and decarboxylation of 3,4-dihydroxyphenylalanine (dopa), and increases in excretion of dopa normally parallel increases in excretion of dopamine during salt loading. Since patients with salt-sensitive hypertension may have decreased urinary excretion of dopamine during dietary salt loading, the present study was designed to evaluate the response of dopa to salt loading. Sixteen inpatients with normal-renin essential hypertension ate a constant metabolic diet containing 9 mmol/day sodium for 7 days, followed by the same diet but containing 249 mmol/day sodium for 7 days. Salt sensitivity was defined as an increase in mean arterial pressure of 8 mm Hg between the diets; on this basis, nine patients were salt-sensitive and seven, salt-resistant. The rate of urinary dopa excretion was significantly higher in the salt-sensitive patients throughout the study (mean rates 132±13 nmol/day in the salt-sensitive group and 78±9 nmol/day in the salt-resistant group for the 14 days of observation, \(p<0.01\)). When dietary sodium intake was increased to 249 mmol/day, urinary dopa excretion increased significantly more in salt-sensitive patients than salt-resistant patients. At the end of the high salt diet, dopamine excretion was significantly attenuated in the salt-sensitive patients, despite higher rates of dopa excretion. Thus, the urinary ratio of dopamine to dopa was decreased in salt-sensitive patients, regardless of salt intake. Among individual patients, cumulative sodium retention during the first 3 days of salt loading was unrelated to the magnitude of the pressor response; however, the dopa excretion rate was positively correlated with the magnitude of the pressor response (\(r=0.62, \ p=0.015\)). The results suggest that salt-sensitive patients have decreased renal uptake or decarboxylation of dopa and that this deficiency is associated with enhanced delivery of dopa to renal uptake sites during dietary salt loading. A high rate of urinary excretion of dopa and a low urinary dopamine/dopa ratio appear to be markers of salt-sensitive hypertension in humans. (Hypertension 1991;18:614–621)

Blood pressure responses to acute salt loading or restriction vary markedly among hypertensive patients. The prevalence of salt-sensitive hypertension depends on the criterion used to define it. When salt-sensitive patients were defined as those whose mean arterial pressure increased by 8 mm Hg or more during a sodium intake of 249 mmol/day after 7 days on a 9 mmol/day sodium intake, about half of the hypertensive study group were classified as salt-sensitive.1

Many mechanisms have been proposed to explain salt-sensitive hypertension. One suggests that it may, in part, be caused by an attenuated response of dopamine, with subnormal sodium excretion and failure to suppress release of norepinephrine, during dietary salt loading. Urinary excretion of dopamine normally increases in people on a high salt diet.2 Since administration of dopamine produces natriuresis,3 and blockade of dopamine receptors or of production of dopamine from its precursor, 3,4-dihydroxyphenylalanine (dopa), may blunt the natriuretic response,4,5 dopamine may contribute to sodium homeostasis. Conversely, plasma levels and urinary excretion of norepinephrine, the sympathetic neurotransmitter synthesized from dopamine, tend to decrease during dietary salt loading,6 and renal sympathetic stimulation has an antinatriuretic effect.7,8 Studies of salt-sensitive humans and laboratory animals have indicated decreased responses of urinary excretion of dopamine,1,9–13 no decrease in norepinephrine levels,14–17 or both1 when dietary salt intake is increased.

Urinary dopamine appears to be derived substantially from renal uptake and decarboxylation of
dopa. Changes in dietary salt intake normally produce similar proportionate changes in urinary
dopa and dopamine, consistent with the view that the rate of delivery of dopa to proximal tubular cells
of the kidney largely determines the rate of urinary excretion of dopamine. If this were true, then during
dietary salt loading, salt-sensitive patients with attenuated dopamine excretory responses would be expected also to have attenuated dopa excretory responses. Alternatively, if there were an abnormality in the uptake of dopa into the tubule cells or in the intracellular conversion of dopa to dopamine, then salt-sensitive patients would have normal (or even increased) urinary excretion of dopa, and the urinary dopamine/dopa ratio would be low.

The present study examined these possibilities in inpatients. Measurements of daily, 24-hour urinary excretion rates of catechols in each subject allowed quantitative assessments of trends of catechol excretion over time both within subjects and between salt-sensitive and salt-resistant groups.

Normal values for urinary excretion of dopa and dopamine have not been established as a function of normal aging. To examine possible effects of aging mismatch between hypertensive and normotensive groups, 24-hour urine collections were obtained from a large number of outpatient volunteers ranging in age from 18 to 65 years, and the urinary contents of catechols and sodium were assayed.

**Methods**

**Patients and Procedure**

The clinical protocols were approved by the Intramural Research Board, National Heart, Lung, and Blood Institute. All subjects gave written informed consent.

Sixteen patients with mild or moderate, uncomplicated, normal-renin essential hypertension were admitted to the Clinical Center, National Institutes of Health, at least 2 weeks after they had discontinued antihypertensive medications. Clinical characteristics of the subjects on the first day of the study diet are summarized in Table 1.

Throughout the study, the subjects ate a constant, isocaloric diet containing 9 mmol/day sodium. After 7 days of a low salt diet (9 mmol/day), the diet was supplemented with 240 mmol/day sodium as sodium chloride (high salt diet) for 7 days. Measurements of urinary sodium excretion confirmed that the subjects had attained a stable sodium balance by the fourth day of each diet. Fluid intake was constant throughout the study.

Blood pressure was measured every 4 hours using a cuff and sphygmomanometer after at least 5 minutes of rest; mean arterial pressure was calculated by adding one third of the pulse pressure to the diastolic pressure. The values for mean arterial pressure were averaged for each day in each subject.

Urine was collected daily throughout the study in 24-hour aliquots and equally divided between a container with 30 ml of 6N HCl and one without preservative.

On the last day of each diet, forearm venous blood for assay of plasma catechols was obtained from each subject in the fasting state. This was performed after overnight bed rest and at least 20 minutes after insertion of an indwelling needle, first with the subject supine and then after the subject had been standing for 5 minutes.

Ten normal volunteers (six women and four men, aged 20–24 years) with no family history of hypertension underwent the same testing protocol as inpatients. Some results from this group have been published previously.

In 36 healthy normotensive outpatients (15 women and 21 men, aged 18–65 years), 24-hour collections of urine were obtained for measurement of sodium, dopa, dopamine, and norepinephrine levels.

**Assays**

Urinary sodium excretion was determined by flame photometry.

Aliquots of 100 μl urine and 1 ml plasma were assayed for catechols, including dopa, dopamine, norepinephrine, adrenaline, the dopamine metabolite dihydroxyphenylacetic acid (DOPAC), and the norepinephrine metabolite dihydroxyphenylglycol (DHPG), using liquid chromatography (Waters Associates, Milford, Mass.) with electrochemical detection (ESA, Bedford, Mass.), according to previously published methods. The limits of detection were about 60 pmol/l (10 pg/ml) each for plasma norepinephrine and dopa, 150 pmol/l (25 pg/ml) for DHPG and dopamine, and about 600 pmol/l (100 pg/ml) for urinary norepinephrine, dopa, and dopamine. Levels of adrenaline were below limits of detection in several samples, and those data are not reported.

**Data Analysis**

Subjects were categorized as salt-sensitive if their mean arterial pressure increased by a mean of 8 mm Hg or more between the 9 and 249 mmol/day diets. Subjects with increments in mean arterial pressure of less than 8 mm Hg were categorized as salt-resistant. As indicated in Table 1, when this criterion was used, about half the patients were salt-sensitive and half were salt-resistant.

The statistical significance of changes in rates of excretion and in plasma levels of catechols as a
All but one subject demonstrated increased urinary dopa excretion during dietary salt loading (p<0.001). Regardless of dietary salt intake, salt-sensitive patients had a significantly higher mean rate of urinary dopa excretion than salt-resistant patients.

function of day and diagnosis was assessed by analyses of variance for repeated measures. Differences in mean excretion rates and plasma levels also were averaged for each dietary condition and compared by t tests for dependent or independent means. Linear regression analysis was applied to scatter plots relating changes in the biochemical values to changes in mean arterial pressure during the dietary manipulation.

Mean values were expressed ±1 SEM. A value of p<0.05 defined statistical significance.

Results

Blood Pressure and Sodium Excretion

Mean daily diastolic blood pressure for each of the hypertensive patients was greater than 90 mm Hg at the time of the study. Changes in mean arterial pressure during dietary salt loading varied widely among the subjects. In the salt-resistant group, the change in mean arterial pressure averaged −0.3±1.6 mm Hg, whereas in the salt-sensitive group, the change in mean arterial pressure averaged 11.6±0.8 mm Hg (p<0.001), with virtually all of the increase occurring during the first 3 days of the high salt diet.

In all subjects, urinary sodium excretion was about the same as dietary sodium intake by day 3 after initiation of each dietary manipulation (data not shown). Cumulative sodium retention was unrelated to the magnitude of the pressor response.

Dopa

In all but one subject, urinary excretion of dopa increased during dietary salt loading (Figure 1). Whereas dopa excretion was similar in salt-resistant and control subjects during the low salt diet and increased similarly in the two groups during salt loading, urinary dopa excretion was significantly higher in the salt-sensitive group than in the other groups throughout the study (Figure 2), and increased markedly during the first few days of high salt intake. For instance, on the last day of the low salt diet, urinary dopa excretion averaged 89±10 nmol/day in the salt-sensitive group and 53±6 nmol/day in the salt-resistant group (p<0.01). On the second day of the high salt diet, urinary dopa excretion averaged 174±20 nmol/day in the salt-sensitive group and 80±9 nmol/day in the salt-resistant group (p<0.01).

On the last day of the low salt intake, the urinary clearance of dopa (expressed per 100 ml creatinine clearance to correct for any difference in excretion that may have occurred as a result of a difference in glomerular filtration rate) was 8.05±0.85 ml/min in the salt-sensitive patients, significantly higher than in the normal subjects (4.15±0.73 ml/min) and in the salt-resistant patients (5.19±0.74 ml/min). In all three groups, urinary clearance of dopa increased significantly between the last day of the low salt diet and the last day of the high salt diet. At the end of the high salt diet, the dopa clearance was higher in the salt-sensitive group (12.99±2.35 ml/min per 100 ml creatinine clearance) than in the salt-resistant group (9.11±1.22 ml/min) or in the normal subjects (7.46±1.46 ml/min) but was significant only if the salt-resistant hypertensive patients and the normal subjects were considered as a single group.

During the first 3 days of the high salt diet, the rate of increase in mean urinary dopa excretion was much greater in the salt-sensitive group than in the salt-resistant group or the normal subjects. This rate of increase correlated with the change in mean arterial pressure during this period of time (r=0.62, p=0.015) (Figure 3). Urinary dopa excretion was unrelated to cumulative sodium retention during either the first 3 days or all 7 days of the high salt diet (r=−0.05, and r=−0.08).
Dopamine were considered as a single group, the mean urinary dopamine excretion was significantly positively correlated with the magnitude of the pressor response (p=0.015). When the hypertensive patients considered as a single group, the mean plasma dopa level decreased during dietary salt loading. Each point indicates the mean value for the 3 days after initiation of the high salt diet. Urinary dopa excretion was significantly positively correlated with the mean arterial pressure (AMAP) during dietary salt loading. Each point indicates the mean value for the 3 days after initiation of the high salt diet. Urinary dopamine excretion did not differ significantly among the groups on either diet. In hypertensive patients considered as a single group, the mean plasma dopa level decreased slightly but significantly during salt loading (Table 2). For instance, on the last day of the low salt diet, the plasma dopa concentration averaged 10.0±1.3 nmol/l in the control subjects, 8.2±1.1 nmol/l in the salt-resistant patients, and 9.7±0.8 nmol/l in the salt-sensitive patients; on the last day of the high salt diet, the mean values were 9.1±1.5, 7.3±0.8, and 9.2±0.8 nmol/l, respectively.

**Dopamine**

Urinary dopamine excretion did not differ significantly between the salt-resistant and salt-sensitive groups (Figure 4). When the hypertensive patients were considered as a single group, the mean urinary dopamine excretion in the hypertensive patients was significantly higher than that in the normotensive control subjects. The higher urinary dopamine excretion was most apparent during the low salt diet.

Urinary excretion of dopamine increased in most but not all subjects during dietary salt loading. The increases in urinary dopamine excretion were similar in the groups during the first few days of salt loading, but by the end of the high salt diet, differences emerged. By the last 2 days of the high salt diet, urinary dopamine excretion in the control subjects and the salt-resistant patients had increased significantly by 60±26% and 50±17%, respectively, compared with the last 2 days of the low salt diet. These increases in dopamine were associated with increases in dopa excretion, averaging 75±22% and 79±14%, respectively. By contrast, in the salt-sensitive patients, the increases in urinary excretion of dopamine averaged only 10±5% (p=NS), whereas dopa excretion was increased by 60±16% (Figure 5).

**Dopamine/Dopa Ratio**

Since in the salt-sensitive patients the responses of urinary excretion of dopamine were smaller and the responses of urinary excretion of dopa larger during dietary salt loading than in patients in the other groups, the ratio of dopamine/dopa in urine was markedly decreased in the salt-sensitive group. The ratio was lower in this group than in the other groups during both the low and high salt diets (Figure 6). When the mean dopamine/dopa ratio for the 14 days of observation was calculated for each subject, the values were significantly lower in the salt-sensitive than in the salt-resistant group (8.77±0.82 for salt-resistant patients versus 14.29±2.88 for salt-sensitive patients, p<0.01). In all three groups, the urinary dopamine/dopa ratio decreased significantly during the high salt diet (Figure 6), reflecting an increase in dopa excretion that was larger than the increase in dopamine excretion.

**Norepinephrine**

Plasma norepinephrine decreased significantly in the supine and upright positions during the high salt diet.

**Table 2.** Plasma Concentrations of Catechols (nmol/l) in Salt-Resistant and Salt-Sensitive Hypertensive Patients After 7 Days of Low Salt Diet (LSD) and 7 Days of High Salt Diet (HSD)

<table>
<thead>
<tr>
<th>Catechol</th>
<th>Posture*</th>
<th>LSD</th>
<th>HSD</th>
<th>LSD</th>
<th>HSD</th>
</tr>
</thead>
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<tr>
<td>DHPG</td>
<td>Supine</td>
<td>5.29±0.76</td>
<td>5.06±0.61</td>
<td>6.95±0.85</td>
<td>6.08±0.46</td>
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<td>Norepinephrine</td>
<td>Supine</td>
<td>1.28±0.19</td>
<td>1.04±0.29†</td>
<td>2.04±0.37</td>
<td>1.36±0.19†</td>
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<tr>
<td></td>
<td>Upright</td>
<td>4.01±0.38</td>
<td>2.76±0.31†</td>
<td>4.04±0.69</td>
<td>3.55±0.69</td>
</tr>
<tr>
<td>Dopa</td>
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<td>8.22±1.11</td>
<td>7.34±0.80†</td>
<td>9.66±0.82</td>
<td>9.20±0.81†</td>
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<tr>
<td></td>
<td>Upright</td>
<td>8.03±1.03</td>
<td>7.29±0.75†</td>
<td>9.81±0.81</td>
<td>9.12±0.80†</td>
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<tr>
<td>DOPAC</td>
<td>Supine</td>
<td>16.30±3.61</td>
<td>16.56±4.36</td>
<td>15.92±3.43</td>
<td>14.40±3.30</td>
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<td></td>
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<td>17.07±3.19</td>
<td>16.52±4.07</td>
<td>16.57±3.54</td>
<td>14.98±3.33</td>
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<tr>
<td>Dopamine</td>
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<td>0.29±0.23</td>
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<td>0.40±0.36</td>
<td>0.17±0.05</td>
<td>0.16±0.05</td>
</tr>
</tbody>
</table>

DHPG, dihydroxyphenylglycol; Dopa, 3,4-dihydroxyphenylalanine; DOPAC, dihydroxyphenylacetic acid.

*Supine defined as after overnight bed rest; upright defined as after standing or walking 5 minutes.
†Significant difference between low and high salt diet when hypertensive patients were considered as one group.
FIGURE 4. Line graph shows mean urinary dopamine (DA) excretion as a function of day during low and high salt diets. Each point represents the mean daily excretion rate of the salt-sensitive, salt-resistant, and normotensive control groups. Hypertensive patients had higher dopamine excretion than normotensive control subjects; this difference was most apparent during the low salt diet. Mean dopamine excretion did not differ between the salt-sensitive and salt-resistant groups.

FIGURE 5. Bar graph shows changes in urinary excretion of dopa and dopamine (DA) during low and high salt diets. Each bar shows the mean ±SEM value for the percentage of change between the last 2 days of each diet. Proportional increase in urinary dopamine excretion during salt loading was significantly smaller in the salt-sensitive group than in the salt-resistant or normotensive control groups, whereas the proportional increases in urinary dopa excretion were similar in the three groups. + Significant difference from low salt diet, p<0.01; * significant differences from salt-sensitive and normotensive groups, p<0.05.

FIGURE 6. Line graph shows daily mean ratio of urinary dopamine (DA) to dopa during low and high salt diets. Dopamine/dopa ratio was significantly decreased in salt-sensitive patients compared with salt-resistant patients and normotensive control subjects, regardless of dietary salt intake (p<0.01).

Discussion
Dopamine in urine appears to be derived substantially from renal uptake and decarboxylation of dopa, and dietary salt loading normally elicits proportionately similar increases in the rates of urinary excretion of dopa and dopamine. Since we and others have reported attenuated responses of urinary dopamine excretion during dietary salt loading in salt-sensitive hypertension, we thought that patients with deficient dopamine excretory responses would also have either deficient dopa excretory responses or impaired renal uptake or decarboxylation of dopa during dietary salt loading.

In the present study, dietary salt loading during an otherwise constant diet elicited rapid increases in urinary excretion of dopa in virtually all subjects. Urinary dopa excretion was significantly increased in the salt-sensitive patients on both the low and high salt diets, and dopa excretory responses during salt loading were exaggerated in salt-sensitive patients.
compared with salt-resistant patients and normotensive control subjects. In contrast, responses of urinary dopamine excretion were blunted in salt-sensitive patients, so that, regardless of dietary salt intake, the urinary dopamine/dopa ratio was highly significantly decreased in the salt-sensitive patients.

The rate of urinary excretion of dopa was significantly positively correlated with the magnitude of the pressor response during the first 3 days of the high salt diet. These relations did not appear to be due to effects of high blood pressure itself on dopa excretion because during the low salt diet, when their blood pressure was lower, the salt-sensitive group still had a significantly higher mean rate of dopa excretion than did the salt-resistant group. Also, dopa excretion in the hypertensive patients as a group did not differ significantly from that in the control subjects. The results suggest that a high rate of urinary dopa excretion and a low urinary dopamine/dopa ratio in urine may be markers of salt-sensitive hypertension. This was not the case for dopamine excretion or norepinephrine excretion alone, or for the magnitude of the increase in dopamine excretion or of the decrease in norepinephrine excretion during salt loading.

Previous reports about urinary catecholamine responses during alterations of dietary salt intake generally have not reported results in each subject for each day during the dietary manipulation. The present results show that the extent to which responses of urinary dopamine were attenuated in salt-sensitive hypertensive patients depended on the day on which the urine collection was obtained, since in the first few days of salt loading, salt-sensitive patients had normal increases in urinary dopamine excretion, apparently due to supernormal increases in delivery of dopa to the kidney.

The high rate of urinary excretion of dopa without a correspondingly high rate of excretion of dopamine is consistent either with deficient uptake of dopa into proximal tubular cells of the kidney — a process that is sodium-dependent or with deficient intracellular conversion of dopa to dopamine in salt-sensitive patients. Dopa is taken up by many cell types in the body and converted to dopamine intracellularly. Whether the present findings in salt-sensitive patients reflect a generalized abnormality or one confined to the kidney is unknown.

There are several potential explanations for high urinary excretion rates of dopa in salt-sensitive patients. It is possible that the renal synthesis of dopamine is subject to feedback regulation and that release of dopa into the bloodstream is enhanced in a compensatory fashion in salt-sensitive patients. In rats, we recently observed that dietary salt loading resulted in significantly increased spillover of dopa into arterial plasma, and this response was exaggerated in rats with bilateral renal denervation. Conversion of tyrosine to dopa by tyrosine hydroxylase occurs mainly, if not only, in catecholamine-synthesizing cells. Increases in urinary excretion of dopamine, therefore, could reflect increased tyrosine hydroxylase activity, increased efficiency of uptake of tyrosine into dopa-synthesizing cells, or increased release of dopa from or decreased removal of dopa into nonneuronal storage pools.

During the low salt diet, the group of hypertensive patients had a significantly higher mean rate of urinary dopamine excretion than did the normotensive control group. Although the patients in the hypertensive group were older than those in the normotensive group, this age mismatch does not explain the observation that dopamine excretion was higher in the hypertensive subjects than in normotensive subjects, because dopamine excretion did not change with age in a large group of healthy outpatients aged 20–65 years. It should be noted, however, that a preliminary publication indicates that very old subjects, aged 70–89 years, may have lower dopamine excretion than young subjects aged 18–26 years. Urinary dopa excretion tended to decrease with age (Figure 8), consistent with age-related decrease in plasma dopa, and in contrast to plasma and urinary norepinephrine levels, which tend to increase. Hypertensive patients on a low salt diet previously were found to have a higher mean rate of dopamine excretion than normotensive control subjects of unspecified age. Normotensive subjects with a family history of hypertension have been reported to lack the usual positive relation between dopamine and sodium excretion, because of relatively high values for urinary dopamine excretion in some subjects with relatively low values for sodium excretion, and patients with borderline hypertension had higher urinary dopamine excretion rates than did normotensive control subjects or patients with established hypertension.

Our findings that salt-sensitive patients tended to have decreased plasma dopamine concentrations and blunted dopamine excretory responses to dietary salt loading are similar to results reported for "non-mod-
ulating hypertensive patients who as a group tend to be salt-sensitive. These changes in plasma and urinary dopamine of the salt-sensitive group were minor compared with the abnormalities in dopa excretion.

The extents of suppression of plasma levels of norepinephrine and of urinary excretion of norepinephrine during 1 week of dietary salt loading did not differ in salt-sensitive and salt-resistant patients. In other studies, Fujita et al11 noted suppression of plasma norepinephrine levels in salt-sensitive patients at 3 days but not 4 days of salt loading. Campese et al12 reported no suppression of plasma norepinephrine levels in salt-sensitive patients after 1 week of salt loading. Koolen and van Brummelen13 found normal suppression of norepinephrine levels at the end of 1 week but not at the end of 2 weeks of salt loading. We previously1 reported that plasma norepinephrine levels in salt-sensitive patients were more suppressed on day 4 than on day 8 of high salt intake. Dustan,4 Masuo et al,11 and Shikuma et al10 reported that the extent of suppression of plasma norepinephrine levels or urinary norepinephrine excretion did not distinguish salt-sensitive and salt-resistant groups. Thus, although most studies have indicated that plasma norepinephrine levels do not decrease normally in salt-sensitive patients during dietary salt loading, the pattern of response has been variable.

In conclusion, dietary salt loading increased the rate of urinary excretion of dopa. Patients with salt-sensitive hypertension, who as a group tend to have blunted responses of urinary dopamine excretion to salt loading, had exaggerated responses of urinary dopa excretion to salt loading. Urinary dopa excretion during the first 3 days of salt loading was related to the magnitude of the pressor response. Since patients with salt-sensitive hypertension had a low ratio of dopamine to dopa in urine, regardless of dietary salt intake, a high urine excretion of dopa and a low urinary dopamine/dopa ratio may indicate salt-sensitive hypertension.

Acknowledgment

We acknowledge the technical assistance of Robin Stull.

References


**Key Words** • dopamine • salt • sodium • norepinephrine • salt-sensitive hypertension • dopa
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Hypertension. 1991;18:614-621
doi: 10.1161/01.HYP.18.5.614

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1991 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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