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)
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.

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 (7.46±1.46 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 magnitude of the pressor response (p=0.015).

Dopamine excretion and change in 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 between the salt-resistant and salt-sensitive groups (Figure 3). When the hypertensive patients were considered as a single group, the mean plasma dopa level decreased significantly during the high salt diet. Plasma dopa levels did not differ 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).

**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 in the hypertensive patients 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 were significantly larger than the increase in dopamine excretion that was observed 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/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-sensitive patients versus 14.29±2.88 for salt-resistant 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>
<thead>
<tr>
<th>Catechol</th>
<th>Posture*</th>
<th>Salt-resistant group</th>
<th>Salt-sensitive group</th>
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<tr>
<td></td>
<td>LSD</td>
<td>HSD</td>
<td>LSD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HSD</td>
</tr>
<tr>
<td>DHPG</td>
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<td>5.29±0.76</td>
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<td>Supine</td>
<td>1.28±0.19</td>
<td>1.04±0.29</td>
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<td>DOPAC</td>
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<tr>
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<td>Upright</td>
<td>0.24±0.17</td>
<td>0.40±0.36</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.
diet in the salt-resistant patients and control subjects, and urinary excretion of norepinephrine was decreased similarly in all three groups (Figure 7). In the salt-sensitive patients, plasma levels of norepinephrine in the upright position were not suppressed at the end of the high salt diet compared with the levels at the end of the low salt diet (Table 2).

Age and Excretion Rate of Dopa and Dopamine

Among normotensive outpatients, urinary dopa excretion tended to decline as a function of subject age ($r=0.34, 0.05<p<0.01$) (Figure 8). Urinary dopamine excretion was unrelated to subject age.

Discussion

Dopamine in urine appears to be derived substantially from renal uptake and decarboxylation of dopa,18-20 and dietary salt loading normally elicits proportionately similar increases in the rates of urinary excretion of dopa and dopamine.20 Since we1 and others9-13 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 normoten-
sive 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 signifi-
cantly 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 pres-
ent 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. Dopamine is taken up by many cell types in the
body and converted to dopamine intracellularly. Whether
the present findings in salt-sensitive pa-

patients reflect a generalized abnormality or one con-
fined 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 dopa
mine is subject to feedback regulation and that release
of dopa into the bloodstream is enhanced in a com-
pen-satory fashion in salt-sensitive patients. In rats,
we recently observed that dietary salt loading re-
sulted 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 dopa, there-
fore, could reflect increased tyrosine hydroxylase ac-
tivity, 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 normoten-
sive 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 normoten-
sive subjects, because dopamine excretion did not
change with age in a large group of healthy outpa-
tients 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 sub-
jects 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 sub-
jects with relatively low values for sodium excretion;
and patients with borderline hypertension had higher
urinary dopamine excretion rates than did normoten-
sive 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-

FIGURE 8. Scatter plot shows urinary dopa and dopamine
(DA) excretion (on a log scale) in relation to subject age in 36
healthy volunteers. Dopa excretion tended to decrease with
increasing subject age (r=0.34, 0.05<p<0.01). Dopamine
excretion was unrelated to subject age.
spontaneously 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 al. noted suppression of plasma norepinephrine levels in salt-sensitive patients at 3 days but not 4 days of salt loading. Campese et al. reported no suppression of plasma norepinephrine levels in salt-sensitive patients after 1 week of salt loading. Koolen and van Brummelen found normal suppression of norepinephrine levels at the end of 1 week but not at the end of 2 weeks of salt loading. We previously reported that plasma norepinephrine levels in salt-sensitive patients were more suppressed on day 4 than on day 8 of high salt intake. Dustan, Masuo et al., and Shikuma et al. 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 urinary excretion of dopa and a low urinary dopamine/dopa ratio may indicate salt-sensitive hypertension.

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References


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