The Pathophysiological Role of Renal Dopaminergic Activity in Patients with Essential Hypertension

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To evaluate the role of the renal dopaminergic system on renal water-sodium metabolism patients with essential hypertension (EHT), urinary excretion of dopamine, urinary excretion of sodium (UNaV) and fractional excretion of sodium (FENa) were all investigated before and after the administration of dopamine (3 μg/kg/min, intravenous infusion for 60 minutes), dopamine antagonist, metoclopramide (8 mg/m² BSA, intravenous injection) or mild sodium loading in both normotensive subjects and benign EHT.

In the basal values, no significant difference in urinary excretion of free (u-fDA), conjugated (u-cDA) or total dopamine (u-tDA) was found between normotensives and hypertensives. However, low renin EHT showed a pronounced reduction in u-fDA compared with normotensives subject and (NT) normal renin EHT. In this study, a significant reduction of u-cDA and of u-tDA was also found in those patients with low renin essential hypertension. In the normotensive and essential hypertensive groups UNaV or FENa showed a positive correlation with f-DA (measured simultaneously), but not with t-DA or c-DA. The regression line between u-fDA and UNaV or FENa in EHT was shifted towards a lower u-fDA level than in NT.

UNaV and FENa were increased by dopamine infusion and were decreased by metoclopramide injection in both NT and EHT. Changes of UNaV and FENa following dopamine or metoclopramide, showed a negative correlation with u-fDA measured immediately before the administration of these drugs. The enhanced natriuretic response to infused dopamine and the attenuated antinatriuretic response to injected metoclopramide were significant in low renin EHT, when compared with NT or normal renin EHT patients.

Mild sodium loading brought about significant increases of UNaV, FENa and u-fDA, while no change took place in u-tDA or u-cDA in EHT.

These findings suggest that the renal dopaminergic activity, which might play an important role in sodium handling of the kidney, was attenuated in EHT particularly in low renin EHT. This attenuation may contribute to the water-sodium expansion in the pathophysiological mechanisms of EHT and in particular low renin EHT.

Key words:
Essential hypertension
Low-renin-essential hypertensives
Renal dopaminergic system
Renal sodium handling
Natriuretic response to dopamine

It is well recognized1–3 that an abnormality of the renal sodium handling exists in patients with essential hypertension (EHT). This abnormality should be considered as an important fac-
tor in the pathogenesis of this disease. Furthermore, some studies have revealed that compared with normal or high renin EHT, a more pronounced suppression of renal blood flow or natriuretic ability and augmentation of renal vascular resistance, expansion of body fluid volume or sodium retention are observed in the patients with low renin EHT. However, the mechanism underlying the attenuation of renal vasodilation or natriuresis, which is particularly pronounced in low renin EHT, still remains unclear.

Alexander et al. observed parallel increases in urinary excretion of sodium and dopamine following sodium loading in normal subjects. Cuche et al. noted a positive correlation between urinary excretion of dopamine and urinary excretion of sodium in man. Recently, it has also been reported that dopamine has a potent vasodilative and natriuretic action in the kidney. Intravenous infusion or intra-renal arterial infusion of dopamine causes vasodilation in the kidney as well as natriuresis. These effects of dopamine on renal function are most pronounced at a dose of 3 μg/kg/min i.v. and are almost completely inhibited by dopamine-receptor blocking agents alone. In our previous studies, the enhanced diuretic and natriuretic responses to infused dopamine at this dose were reproduced in EHT, and low renin essential hypertensives showed particularly pronounced responses. Thus, it was suggested from these findings that there is a suppression of dopaminergic activity in the kidney and is considered to be one of the possible mechanisms causing sodium retention and expansion of body fluid volume in EHT, particularly in low renin EHT.

In order to further clarify the role of renal dopaminergic activity on renal water-sodium metabolism in EHT, the effect of infused dopamine, injected dopamine antagonist, metoclopramide or mild sodium loading on urinary excretion of dopamine and of water-sodium were investigated in normotensive subjects and benign EHT.

SUBJECTS AND METHODS

Twenty-five patients with mild to moderate EHT, 9 females and 16 males, aged 23 to 56 (41.6 ± 2.2, mean ± SEM) years, and fifteen normotensive subjects (NT), 15 males, aged 17 to 25 (20.8 ± 0.7) years, were included in this study. Patients complicated with cerebrovascular disease, ischemic heart disease, diabetes mellitus or congestive heart failure, and with an endo-
TABLE 1  EFFECT OF MILD SODIUM LOADING ON $U_{Na}V$, $FE_{Na}$, $u\cdot fDA$, $u\cdot tDA$ AND 
$u\cdot cDA$ IN ESSENTIAL HYPERTENSIVES (n = 7)

<table>
<thead>
<tr>
<th></th>
<th>120 mEq</th>
<th>200 mEq</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>$U_{Na}V$ (µEq/min)</td>
<td>80.9 ± 11.6</td>
<td>147.2 ± 14.7</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>$FE_{Na}$ (%)</td>
<td>0.68 ± 0.09</td>
<td>1.09 ± 0.09</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>$u\cdot fDA$ (ng/min)</td>
<td>130.9 ± 9.5</td>
<td>156.2 ± 8.4</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>$u\cdot tDA$ (ng/min)</td>
<td>193.9 ± 28.0</td>
<td>264.6 ± 30.4</td>
<td>n.s.</td>
</tr>
<tr>
<td>$u\cdot cDA$ (ng/min)</td>
<td>74.5 ± 16.6</td>
<td>103.3 ± 18.2</td>
<td>n.s.</td>
</tr>
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</table>

$U_{Na}V$ = urinary excretion of sodium; $FE_{Na}$ = fractional excretion of sodium; $u\cdot fDA$ = urinary excretion of free dopamine; $u\cdot tDA$ = urinary excretion of total dopamine; and $u\cdot cDA$ = urinary excretion of conjugated dopamine.

Fig.2. Correlation between Urinary Excretion of Sodium ($U_{Na}V$) or Fractional Excretion of Sodium ($FE_{Na}$) and Urinary Excretion of Free Dopamine ($u\cdot fDA$) in Normotensive Subjects (NT) and Patients with Benign Essential Hypertension (EHT).

Genus creatinine clearance of less than 60 ml/ min, grade 3 to 4 hypertensive retinopathy or secondary hypertension were excluded by the appropriate diagnostic procedures. EHT were divided into two renin-subgroups: 16 cases of normal renin group and 9 cases of low renin group, according to our criteria by using both supine and upright plasma renin activity. High renin patients were excluded from this study because of their small number. All NT and EHT were admitted to our hospital, and received a constant diet including 120 mEq/day of sodium, 75 mEq/day of potassium and 2400 calories/day. The study was carried out with the absence or discontinued use of antihypertensive drugs for a period of at least two weeks prior to the examinations. Seven out of 25 EHT were given a constant diet including 120 mEq/day of sodium for the first two weeks of admission and then a mild sodium loaded diet, containing 200 mEq/day of sodium, 75 mEq/day of potassium and 2400 calories/day for the subsequent two weeks.

Studies were performed after fourteen days of hospitalization. In the early morning, after overnight fasting, the patients remained in a supine state and were examined for renal clearance. The control clearance period started at 7:00 a.m. after emptying the bladder and lasted for two hours. Ten NT and eighteen EHT, composed of age-matched 9 normal renin and 9 low renin patients were examined for their natriuretic response to infused dopamine, suc-
TABLE II  RELATIONSHIP BETWEEN U-fDA, U-tDA OR U-cDA AND $U_{Na}V$ OR $FE_{Na}$ IN NORMOTENSIVE SUBJECTS (NT) AND PATIENTS WITH ESSENTIAL HYPERTENSION (EHT)

<table>
<thead>
<tr>
<th></th>
<th>NT (n = 15)</th>
<th>EHT (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$U_{Na}V$</td>
<td>$FE_{Na}$</td>
</tr>
<tr>
<td>u-fDA</td>
<td>$r = 0.550$, $p &lt; 0.005$</td>
<td>$r = 0.535$, $p &lt; 0.05$</td>
</tr>
<tr>
<td>u-tDA</td>
<td>$r = 0.161$, n.s.</td>
<td>$r = 0.122$, n.s.</td>
</tr>
<tr>
<td>u-cDA</td>
<td>$r = -0.289$, n.s.</td>
<td>$r = -0.325$, n.s.</td>
</tr>
</tbody>
</table>

$u-fDA$ = urinary excretion of free dopamine; $u-tDA$ = urinary excretion of total dopamine; $u-cDA$ = urinary excretion of conjugated dopamine; $U_{Na}V$ = urinary excretion of sodium; and $FE_{Na}$ = fractional excretion of sodium.

cessively. In these NT and EHT, dopamine was infused into an antecubital vein at 3 μg/kg/min, for 60 minutes and in the absence of α or β-adrenergic effects. Blood pressure was measured repeatedly, at least ten times, at supine position by the auscultatory method, immediately before and at the mid-point of the clearance period. Blood was sampled at the mid-point and urine was collected by spontaneous voiding at the end-point of each clearance period.

Intravenous injection of the dopamine receptor antagonist, metoclopramide (MCP: 8 mg/m² BSA) was performed in ten NT and eighteen EHT (12 normal renin and 6 low renin EHT). In this examination, clearance periods before and after MCP injection were 60 minutes, respectively.

The mean arterial pressure (MAP) was calculated as the diastolic pressure plus 1/3 pulse pressure. Urinary excretion of free dopamine (u-fDA) was measured by HPLC-ECD method and urinary excretion of total dopamine (u-tDA) was measured by the same method after deconjugation by acidification and boiling. The value of urinary excretion of conjugated dopamine (u-cDA) was obtained by subtracting u-fDA from u-tDA. PRA was estimated by radioimmunoassay according to the method of Haber et al. Blood and urinary sodium, and creatinine were measured by the method of ion electrode Fiske-Saffbarow and Jaffe respectively. Fractional excretion of sodium ($FE_{Na}$) was calculated from values of blood and urine samples, using the formula: $FE_{Na}$ (%) = ($C_{Na}/C_{Cr}$) × 100, where the $C_{Na}$ refers to the percentage of filtered sodium appearing in the urine, $C_{Cr}$ the clearance of sodium, and $C_{Cr}$ endogenous creatinine clearance. Urine volume (UV), urinary excretion of dopamine, urinary excretion of sodium ($U_{Na}V$), $Cr$, and $FE_{Na}$ were determined in each clearance period.

The mean value was expressed with the standard error of the mean (SEM). All statistical analysis was carried out using the Student’s t-test.

RESULTS

1. Urinary Excretion of Free, Conjugated and Total Dopamine.

As shown in Fig. 1, u-fDA in the low renin EHT (139.2 ± 9.4 ng/min) was significantly lower than those in NT (193.5 ± 14.9 ng/min, p < 0.05) or normal renin EHT (193.5 ± 10.5 ng/min, p < 0.01). Similarly, u-tDA in the low renin EHT (230.7 ± 22.1 ng/min) was lower than those in NT (352.7 ± 17.7 ng/min, p < 0.001) or normal renin EHT (337.5 ± 22.0 ng/min, p < 0.025), and u-cDA in the low renin EHT (91.5 ± 19.3 ng/min) was lower than that in NT (159.2 ± 17.9 ng/min, p < 0.05).

Following mild sodium loading in seven EHT, $U_{Na}V$ (from 80.9 ± 11.6 to 147.2 ± 14.7 μEq/min, p < 0.005), $FE_{Na}$ (from 0.68 ± 0.09 to 1.09 ± 0.09%, p < 0.005) and u-fDA (from 130.9 ± 9.5 to 156.2 ± 8.4 ng/min, p < 0.005) increased significantly. However, no significant change was found in u-cDA (from 74.5 ± 16.6 to 103.3 ± 18.2 ng/min) or u-tDA (from 193.9 ± 28.0 to 264.6 ± 30.4 ng/min) (Table I).

2. Relationship between Urinary Excretion of Dopamine and Renal Sodium Metabolism.

As shown in Fig. 2, u-fDA showed a positive correlation with $U_{Na}V$ or $FE_{Na}$ measured simultaneously in both NT ($r = 0.550$, p < 0.005 or $r = 0.535$, p < 0.05) and EHT ($r = 0.617$, p < 0.005 or $r = 0.512$, p < 0.05). The regression
line between u-fDA and UNaV or FEna in EHT shifted towards a lower u-fDA level compared with NT. While, no significant relationship was observed between u-tDA and UNaV or FEna, and between u-cDA and UNaV or FEna in both NT and EHT (Table II).

3. Natriuretic Response to Infused Dopamine and Antinatriuretic Response to Injected Metoclopramide.

The natriuretic response to infused dopamine was examined in 10 NT, age-matched 9 normal renin and 9 low renin EHT. In addition, the antinatriuretic response to injected MCP was estimated in 10 NT and in 18 EHT, including 12 normal renin and 6 low renin EHT.

The natriuretic response to dopamine was more marked in low renin EHT (ΔUNaV and ΔFEna; 477 ± 57 μEq/min and 2.64 ± 0.31%), moderate in normal renin EHT (357 ± 81 and 1.48 ± 0.31) and most mild in NT (202 ± 39 and 0.91 ± 0.23, respectively) (Fig. 3-a). On the other hand, the antinatriuretic response to MCP was most mild in low renin EHT (ΔUNaV and ΔFEna; −9.5 ± 7.4 μEq/min and −0.03 ± 0.04%), moderate in normal renin EHT (−34.9 ± 10.5 and
Fig. 4. Correlations between Urinary Excretion of Free Dopamine (u-fDA) immediately before Drug Administration and Change of Urinary Excretion of Sodium (ΔU_{Na}V) or Change of Fractional Excretion of Sodium (ΔF_{Na}) by Dopamine or Metoclopramide in Essential Hypertensives.

TABLE III  STATISTICALLY SIGNIFICANT CORRELATIONS AMONG VARIABLES IN BENIGN ESSENTIAL HYPERTENSIVES

<table>
<thead>
<tr>
<th>Log PRA</th>
<th>pNE</th>
<th>NE-R</th>
<th>ANG II-R</th>
<th>PV</th>
<th>ECFV</th>
<th>Nae</th>
<th>F_{Na}</th>
<th>uDA</th>
<th>uKAL</th>
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</thead>
<tbody>
<tr>
<td>Log PRA</td>
<td></td>
<td>0.423</td>
<td>-0.594</td>
<td>-0.564</td>
<td>-0.476</td>
<td>-0.611</td>
<td>-0.625</td>
<td>0.233</td>
<td>0.454</td>
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<tr>
<td></td>
<td></td>
<td>(156)</td>
<td>(68)</td>
<td>(57)</td>
<td>(101)</td>
<td>(77)</td>
<td>(81)</td>
<td>(97)</td>
<td>(23)</td>
</tr>
<tr>
<td>pNE</td>
<td>0.423</td>
<td></td>
<td>-0.629</td>
<td>-0.615</td>
<td>-0.390</td>
<td>-0.388</td>
<td>-0.403</td>
<td>0.338</td>
<td>0.714</td>
</tr>
<tr>
<td></td>
<td>(156)</td>
<td></td>
<td>(79)</td>
<td>(34)</td>
<td>(98)</td>
<td>(107)</td>
<td>(105)</td>
<td>(42)</td>
<td>(44)</td>
</tr>
<tr>
<td>NE-R</td>
<td>-0.594</td>
<td>-0.629</td>
<td></td>
<td>0.478</td>
<td>0.562</td>
<td>0.632</td>
<td>0.696</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(68)</td>
<td>(79)</td>
<td></td>
<td>(41)</td>
<td>(42)</td>
<td>(30)</td>
<td>(28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PV</td>
<td>-0.475</td>
<td>-0.390</td>
<td>0.562</td>
<td>0.674</td>
<td></td>
<td>0.452</td>
<td>0.382</td>
<td>-0.277</td>
<td>N.S.</td>
</tr>
<tr>
<td></td>
<td>(101)</td>
<td>(98)</td>
<td>(42)</td>
<td>(46)</td>
<td></td>
<td>(199)</td>
<td>(199)</td>
<td>(96)</td>
<td></td>
</tr>
<tr>
<td>F_{Na}</td>
<td>0.235</td>
<td>0.338</td>
<td>-0.277</td>
<td>-0.332</td>
<td>-0.308</td>
<td></td>
<td>0.512</td>
<td>0.619</td>
<td></td>
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<tr>
<td></td>
<td>(97)</td>
<td>(42)</td>
<td>(96)</td>
<td>(91)</td>
<td>(93)</td>
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Correlation Coefficients (p < 0.05).
( ) = number of patients; = not determined; PRA = plasma renin activity; pNE = plasma norepinephrine; ANG II-R = pressor response to infused norepinephrine; PV = plasma volume; ECFV = extracellular fluid volume; Nae = total exchangeable sodium; F_{Na} = fractional excretion of sodium; uDA = urinary excretion of free dopamine; uKAL = urinary excretion of kallikrein.

-0.21 ± 0.08) and more pronounced in NT (-41.6 ± 10.9 and -0.26 ± 0.06, respectively) (Fig. 3-b). 4. The Relationship of U-fDA with Natriuretic Response to Dopamine and Antinatriuretic Response to Metoclopramide. A significant negative correlation was found
between u-fDA just prior to dopamine infusion and the change of $\text{U}_{\text{Na}} V$ ($r = -0.727, p < 0.05$) or $\text{FE}_{\text{Na}}$ ($r = -0.676, p < 0.05$) in EHT. A significant negative correlation was observed between u-fDA immediately before MCP injection and the change of $\text{U}_{\text{Na}} V$ ($r = -0.533, p < 0.025$) or $\text{FE}_{\text{Na}}$ ($r = -0.544, p < 0.025$) in EHT (Fig. 4).

**DISCUSSION**

Previous studies$^1-10$ have shown that an attenuation of natriuretic ability, causing an expansion of body fluid volume and sodium, may contribute significantly to the hypertensive mechanism in EHT, particularly in the case of low renin EHT.

It has been recognized that dopamine exists in the central nervous system and in sympathetically innervated organs including renal tissue.$^{27}$ Dopamine exists not only as a metabolic precursor of the sympathetic neurotransmitter, norepinephrine, but also as an active hormone. In addition, the possibility has been emphasized that dopamine may act as a potent vasodilative and natriuretic hormone in the kidney$^{28}$ and play an important role in the regulation of renal hemodynamics and water-sodium metabolism.$^{11-22}$

In regard to the source of dopamine in the kidney, Cuche et al. have described the presence of dopa decarboxylase in the proximal tubules.$^{12}$ The production of urinary dopamine from plasma dopa by dopa decarboxylase in the kidney has also been studied.$^{12,29-31}$ Kuchel et al.$^{32}$ suggested that dopamine originates in the dopaminergic neurons of the kidney. Dinerstein et al.$^{27}$ demonstrated the presence of dopamine-containing neural elements in the canine kidney by the histo-fluorescence technique.

In the present study u-fDA as well as u-tDA and u-cDA was lower in the low renin EHT than in NT or normal renin EHT in subjects receiving the standard diet containing 120 mEq/day sodium and 75 mEq/day potassium, however, u-fDA increased significantly, unlike u-tDA or u-cDA, parallel with the increases of $\text{U}_{\text{Na}} V$ and $\text{FE}_{\text{Na}}$ following mild sodium loading (200 mEq/
day) in EHT. In addition, u-fDA showed a positive correlation with $U_{Na}V$ or $FE_{Na}$ measured simultaneously in both NT and EHT, while there was no significant relationship between u-tDA, u-cDA in $U_{Na}V$ or $FE_{Na}$. These results were consistent with previous reports\textsuperscript{11–22,32} suggesting that the renal dopaminergic system plays an important role in water-sodium metabolism in both NT and EHT.

The response to infused dopamine and injected MCP was compared among NT, normal renin and low renin EHT. Natriuretic response to dopamine was most pronounced in low renin EHT and antinatriuretic response to MCP was the least pronounced in low renin EHT. In contrast, however, antinatriuretic response to MCP was more pronounced and natriuretic response to dopamine was less pronounced in NT. In low renin EHT exogenous stimulation of renal dopaminergic activity has a pronounced effect on natriuresis. Exogenous suppression of renal dopaminergic activity, however, was least pronounced in the low renin EHT. In addition, there was a negative correlation between natriuretic response to infused dopamine or antinatriuretic response to injected MCP and u-fDA just prior to the administration of these drugs in EHT. The negative correlation indicates that a down regulation exists in the renal dopaminergic system. The responses to dopamine and MCP described above, indicate that the activity of endogenous renal dopaminergic system might be attenuated in EHT, and in particular in low renin EHT.

The collated results from our previous studies\textsuperscript{4–7,33,34} included 156 benign EHT who were placed on a diet containing 120 or 200 mEq/day of sodium and 75 mEq/day of potassium two weeks before examination. The following relationships between the variables measured in these patients were observed. As shown in Table III, statistically significant correlations were found between plasma renin activity (PRA), plasma norepinephrine concentration (pNE), blood pressure responses to infused nor-epinephrine (NE-R) and to angiotensin II (ANG II-R), plasma volume (PV), extravascular fluid volume (ECFV), total exchangeable sodium (Nae), $FE_{Na}$, u-fDA, and urinary excretion of kallikrein (uKAL). Correlations were considered as significant at values of $p = 0.05$. The significant relationships of log PRA as shown by the regression lines with pNE, NE-R, PV, ECFV, Nae, $FE_{Na}$ to infused dopamine ($FE_{Na}$ to DA), u-fDA and uKAL are illustrated in Fig. 5. All of these regression lines are from Table III, except $FE_{Na}$ to DA\textsuperscript{23} Furthermore, the progression of PRA suppression was significantly correlated with the age of the subjects ($r = -0.380$, $p < 0.025$), duration of hypertension ($r = -0.338$, $p < 0.05$) and progression of clinical stage of this disease (PRA higher in the order of borderline hypertension, WHO stage I, and stage II).

An interesting conclusion can be drawn from the facts obtained in our comprehensive study of benign EHT. Firstly, PNE decreases and PV increases, with suppression in PRA, suggesting either progression of stage, aging, or duration of hypertension. Secondly, the process of change from normal PRA to low PRA might be caused by the disturbance of urinary sodium excretion, to which a lowered activity of renal kallikrein system and a suppression of renal dopaminergic activity may contribute.

Thus, it can be concluded that the renal dopaminergic activity, related to natriuresis, might be attenuated in EHT, and in particular in the low renin EHT. This attenuation may play an important role in the hypertensive mechanism due to water-sodium expansion in the low renin EHT.

The cause or mechanism of suppression of renal dopaminergic activity has yet to be sufficiently clarified. It largely depends upon future multilateral studies involving the interrelationships of dopaminergic system, kallikrein system, prosaglandins and other systems in the kidney.

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