Dopaminergic Abnormalities in Borderline Essential Hypertensive Patients

Shuichi Shigetomi, Nguyen T. Buu, and Otto Kuchel

To explore whether an altered metabolic pathway of dihydroxyphenylalanine (DOPA) may be related to some previously observed dopamine abnormalities in borderline hypertension, we measured basal and DOPA-induced (500 mg orally) changes in blood pressure and pulse rate as well as in three hourly plasma and urine samples. We found that borderline hypertensive patients compared with controls 1) showed a higher baseline urinary excretion of methoxytyramine, a marker of exocytotic dopamine release, with a greater DOPA-induced decrease of systolic blood pressure without reflex tachycardia; 2) had in response to DOPA a blunted plasma DOPA and free dopamine increase but an accentuated plasma dopamine sulfate and urinary DOPAC excretion; and 3) eliminated comparable quantities of dopamine in urine despite a lower rise in the glomerular DOPA load. Furthermore, although DOPA elicited natriuresis in both groups, its effect was greater in borderline hypertensive patients, who lacked the urinary sodium correlation with urinary dopamine excretion seen in control subjects. These data are compatible with increased basal exocytotic dopamine release and accelerated neuronal and renal (extraneuronal) dopamine generation from administered DOPA in borderline hypertension. The DOPA-induced hypernatriuresis exceeding augmented dopamine in borderline hypertensive patients, contrasting with the urinary sodium and dopamine correlation in control subjects, suggests that DOPA induced an additional natriuresis in borderline hypertensive patients by a decrease in renal sympathetic tone because of its central inhibition of sympathetic outflow, which also may account for the absence of reflex tachycardia. (Hypertension 1991;17:997-1002)

The role of dopamine in essential hypertension (EH) is controversial because concentrations of plasma free dopamine are almost unmeasurable, urinary dopamine measurements are of limited value, and EH is a heterogeneous syndrome. Some evidence suggests a renal dopaminergic defect in low renin and stable EH. However, such a defect cannot be found in borderline EH patients, who present an opposite profile, that is, higher, occasionally episodic plasma dopamine release and higher urinary excretion of dopamine and some of its metabolites. Because most of these patients have an increased sympathetic activity, an accelerated dopamine generation may partly reflect their increased sympathetic tone.

Recently, plasma 3,4-dihydroxyphenylalanine (DOPA), an immediate product of the rate-limiting catecholamine biosynthesis enzyme tyrosine hydroylase, was considered to be an alternative marker of sympathetic nerve activity, the tyrosine hydroxylase activity in particular. It was suggested that DOPA released into plasma by the heart, brain, limbs, and adrenomedullary cells is taken up from the circulation and may be a source of catecholamine biosynthesis in tissues devoid of tyrosine hydroxylase and may be removed from the bloodstream by the kidneys. Most urinary dopamine is derived from renal uptake and decarboxylation of plasma DOPA. DOPA did not receive much attention in the past because it was considered to be a dietary contaminant, but this does not appear to be the case. Because borderline EH patients had higher indexes of dopaminergic activity and dopamine generation is augmented in early spontaneously hypertensive rats (which correspond best to borderline EH patients), one might expect that DOPA in the circulation, as a substrate for its renal conversion to dopamine and its metabolites, may be increasingly transformed to dopamine in borderline EH patients.

In the present study, we explore this hypothesis by comparing basal conditions with those after exogenous DOPA administration. Even if drawing conclusions from exogenous DOPA administration to en-
dogenous DOPA pathways is difficult, it nevertheless may be possible to detect subtle differences in cardiovascular, renal, and catecholamine biosynthetic and feedback responses to DOPA between borderline EH patients and control subjects.

Methods

Patients and Study Protocol

We studied 10 borderline EH patients (six men and four women) with an average age of 34.6 years (range, 24–51) and 10 control subjects (eight men and two women) with an average age of 25.5 years (range, 19–29) who had no family history of hypertension. Patients were considered to be borderline EH when their blood pressure decreased, off medication, to normotensive values after 4 days of bed rest. They received a diet containing 150 mmol/day sodium, 100 mmol/day potassium, and 90 g protein. Citrus fruit, cereals, and coffee were excluded for at least 3 days before the test. Patients who previously had been treated with antihypertensive drugs stopped medication at least 10 days before the examination, and none of the women had taken oral contraceptives at any time. On the day preceding the test, a 24-hour urine sample was collected. After an overnight fast, which appears to be long enough for the effects of meals to be discarded, the subjects arrived at the clinical investigation center and assumed a supine position until completion of the study. At 8:00 AM, a heparin lock for blood sampling was placed in the right antecubital vein, and baseline blood was taken at 8:30 AM and 9:00 AM (time 0). At 9:00 AM, 500 mg DOPA (levodopa, Larodopa, Roche Laboratories, Nutley, N.J.) was administered orally, and consecutive blood samples were obtained at 60-minute intervals for the remainder of the study (60, 120, and 180 minutes). Urine was collected at 60-minute intervals (hours 1, 2, and 3). At 9:00 AM and at 90 minutes, tap water (250 ml) was administered orally. Blood pressure and pulse rate were monitored every 30 minutes before and after DOPA administration, and body weight before and after the test.

This study was approved by the Clinical Research Institute of Montreal Ethics Committee, and patients gave their informed consent.

Analytical Methods

Blood samples collected in tubes were placed on ice and immediately centrifuged at 5,000g for 15 minutes at 4°C. Plasma and urine were poured into cooled plastic vials containing 0.5 mg/ml sodium metabisulfite as antioxidant and were frozen and stored at -80°C until assay.

Free and sulfoconjugated catecholamines (norepinephrine and dopamine) in plasma and urine were determined radioenzymatically using catechol-O-methyl-transferase before and after sulfate hydrolysis. Plasma and urinary 3-O-methyl-DOPA, 3,4-dihydroxylphenylacetic acid (DOPAC) and homovanillic acid, plasma tyrosine, plasma and urinary DOPA and its sulfates, and urinary normetanephrine and 3-methoxytyramine were measured by high-performance liquid chromatography with electrochemical detection. The interassay variability of these methods was between 7% and 12%.

Serum and urinary sodium and potassium were measured by flame photometry, and creatinine by colorimetry.

Calculation

Creatinine clearance (Ccr) corrected for body surface area was calculated from urinary and plasma creatinine concentrations and urinary volume (UV). Na+ clearance (CNa+), fractional Na+ excretion (FeNa+), DOPA clearance (CDOPA), and glomerular DOPA load (LDOPA) were determined by the following formulas: 1) CNa+ = (urinary Na+ concentration x UV)/plasma Na+ concentration; 2) FeNa+ = (CNa+ / Ccr) x 100; 3) CDOPA = (urinary DOPA concentration x UV)/plasma DOPA concentration; 4) LDOPA = plasma DOPA concentration x Ccr; and 5) CDA sulfate = (urinary dopamine sulfate concentration x UV)/plasma dopamine sulfate.

Statistics

The mean absolute values, their changes, and the area under the curve for control subjects and borderline EH patients were analyzed by unpaired Student’s t test. DOPA-induced modifications in each parameter containing two factors (time and the value change) were analyzed by two-way analysis of variance with repeated measures on one factor.

Results

Baseline Values

As shown in Table 1, urinary 3-methoxytyramine excretion in borderline EH patients was greater than in control subjects (p<0.05). The other values in plasma and urine were not significantly different between the two groups.

Effect of DOPA on Blood Pressure, Pulse Rate, and Renal Sodium Excretion

As shown in Table 2, DOPA induced a fall in systolic blood pressure in both control subjects and borderline EH patients. The decrease in the latter was significantly greater than in their controls. Diastolic blood pressure fell after DOPA administration in both groups but without any significant differences. Pulse rate changes were not significant in either group.

DOPA induced significant increases in urinary volume, urinary Na+ concentration, Na+ clearance, and fractional Na+ excretion in both groups. The DOPA-induced enhancement of Na+ clearance was significantly greater in borderline EH patients (p<0.05), whereas changes in urinary Na+ concentration and fractional Na+ excretion were at limits of
DOPA, dihydroxyphenylalanine.

essential hypertension (EH) patients, respectively; baseline diastolic blood pressure was 76.7 ± 1.2 and 96.9 ± 3.0 mm Hg, respectively.

DOPA, dihydroxyphenylalanine.

Tyrosine, DOPA, Dopamine, and their Metabolites in Plasma and Urine After DOPA Administration

Plasma and Urine After DOPA Administration

<table>
<thead>
<tr>
<th>TABLE 2. Changes in Blood Pressure, Pulse Rate, and Renal Clearance of Na⁺ After DOPA Administration in Control Subjects and Borderline Essential Hypertensive Patients</th>
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<td>Baseline</td>
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<td>Systolic blood pressure (mm Hg)</td>
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<td>Na⁺ clearance (ml/min)</td>
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<td>Borderline</td>
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Values are mean ± SEM. Systolic blood pressure at baseline was 118.5 ± 2.5 and 146.9 ± 3.3 mm Hg in control subjects and borderline essential hypertension (EH) patients, respectively; baseline diastolic blood pressure was 76.7 ± 1.2 and 96.9 ± 3.0 mm Hg, respectively.

DOPA, dihydroxyphenylalanine.

*p < 0.01, compared with baseline values.
†p < 0.05, ‡p < 0.01, comparison between control and borderline EH patients.
Figure 1. Increases in urinary 3,4-dihydroxyphenylacetic acid excretion (U-DOPAC, fold increase), plasma dopamine sulfate (P-DA-S), and plasma free dopamine (P-DAFREE) in control subjects (control) and borderline essential hypertensive (b-EH) patients. U-DOPAC, P-DA-S, and P-DAFREE were significantly increased after DOPA administration in both groups (p<0.001). Time is expressed in minutes.

Fate clearance was significantly reduced (33.6±9.0 ml/min in borderline EH patients versus 79.8±20.9 ml/min in control subjects, p<0.05). Plasma 3-O-methyl-DOPA was markedly increased in both groups after DOPA administration, with no differences between control subjects and borderline EH patients. There also were no significant differences in increases of urinary 3-O-methyl-DOPA and homovanillic acid between the two groups after DOPA administration, whereas the increase in urinary 3-methoxytyramine excretion (from increased baseline values) was significantly lower (p<0.02) in borderline EH patients than in control subjects.

Correlation Between Renal Dopamine Generation and Natriuresis After DOPA Administration

There was a significant correlation between urinary dopamine excretion and the glomerular DOPA load in both control subjects (r=0.593, p<0.02) and borderline EH patients (r=0.753, p<0.001). The regression slope, however, indicated that the same amount of glomerular DOPA load corresponds to a urinary dopamine excretion that is greater in borderline EH patients than in control subjects. Urinary Na⁺ excretion after DOPA administration in control subjects was correlated with urinary dopamine excretion (r=0.52, p<0.02), but there was no significant correlation between both parameters in borderline EH patients; the DOPA-induced hypernatriuresis exceeded the urinary dopamine increase.
Discussion

DOPA administration decreases blood pressure by dopamine generation. The absence of sympathetic activation in response to blood pressure decrease may be due to a sympathetic outflow inhibiting central actions of dopamine (possibly also norepinephrine generated from DOPA) in the brain. In the kidney, the correlation between an increase in urinary free dopamine and natriuresis after DOPA administration in control subjects and its absence in borderline EH patients due to excessive natriuresis indicates that in borderline EH patients, natriuresis is promoted after DOPA administration not only by renal free dopamine generation but probably also by central inhibition of renal nerve activity by DOPA entering the brain, as observed in spontaneously hypertensive rats with renal nerve activity measurements. The blunted rise in plasma DOPA (which may be partly accounted for by different baseline values) and dopamine in borderline EH patients in itself is difficult to explain, because we do not have more precise indexes showing that the intestinal absorption, decarboxylation, and sulfocojugation of DOPA were different in hypertensive versus normotensive subjects. Because DOPAC generation requires not only DOPA decarboxylation to dopamine but also the action of monoamine oxidase, the site of which are the mitochondria close to the vesicles of the nerve endings, we can only indirectly conclude from the increase in DOPAC that the neural turnover of dopamine generated from DOPA was elevated in borderline EH patients. This suggests that after oral DOPA administration, accelerated DOPA decarboxylation and generation of dopamine, which was rapidly metabolized by monoamine oxidase, probably occurred in the nerve terminals and may account for the blunted rise in plasma DOPA in borderline EH patients. The elevated dopamine sulfate levels in borderline EH patients are difficult to attribute exclusively to increased dopamine sulfate generation, because we found, in accordance with a previous report, a decreased renal clearance of dopamine sulfate in borderline EH patients. However, the lower free dopamine increase after DOPA administration in borderline EH patients, coupled with excessive dopamine sulfate generation, also is compatible with an accentuated sulfocojugation pathway after DOPA administration, which had been previously observed in rats. The baseline augmentation of 3-methoxytyramine in borderline EH patients suggests an enhanced basal exocytotic dopamine release in this form of hypertension. When exposed to exogenous DOPA, DOPAC in urine becomes the main dopamine metabolite. This indicates that, in the presence of a lower rise in 3-methoxytyramine, the DOPA and dopamine uptake by neuronal tissues is accelerated in borderline EH patients. A lower increase in the glomerular DOPA load due to a smaller elevation of plasma DOPA in borderline EH patients, in the presence of a comparable urinary free dopamine increase and the change in the regression slope between glomerular DOPA load and urinary dopamine, suggests that probably more dopamine also is generated from DOPA in tubules in borderline EH patients than in control subjects. Because tubular dopamine is rapidly metabolized to DOPAC, this conclusion also is supported by the increased urinary DOPAC without augmented plasma DOPAC levels.

The suppression of tyrosine by DOPA administration in both groups appears to be a feedback effect on the main precursor of catecholamine synthesis rather than a consequence of overnight fasting, because overnight is not long enough to affect tyrosine concentration. Phenylalanine hydroxylase, which catalyzes phenylalanine conversion to tyrosine, mainly in the liver, has properties similar to those of tyrosine hydroxylase. It is conceivable that oral DOPA administration, increasing DOPA concentration in the portal vein, may suppress phenylalanine hydroxylase and lower plasma tyrosine. The weakened suppressibility of tyrosine 3 hours after DOPA administration indicates that DOPA was administered in borderline EH patients against a background in which there is a more generous supply of tyrosine to neuronal sites of its hydroxylation.

In conclusion, several subtle baseline and DOPA-induced feedback and biosynthetic pattern abnormalities occur in borderline EH patients. These modifications are compatible with increased basal exocytotic dopamine release (as part of the general increase in sympathetic tone) as well as enhanced neuronal DOPA uptake and turnover and an increased dopamine generation from DOPA in the kidney in borderline EH patients. Further studies of more precise intermediate steps in baseline and DOPA-induced changes are required.

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