Dopaminergic Abnormalities in Hypertension Associated With Moderate Renal Insufficiency

Otto G. Kuchel, Shuichi Shigetomi

Abstract To evaluate the additive effect of moderate chronic renal failure to the abnormal dopamine generation and action observed in stable hypertension, we investigated 22 age-matched patients with a comparable degree of hypertension with and without chronic renal failure. Both groups were compared with each other and with an age-matched control group after a single oral dose of dihydroxyphenylalanine (DOPA) while cardiorenal responses and DOPA, dopamine, and their metabolites were measured. The hypertensive patients with chronic renal failure shared with their hypertensive counterparts without chronic renal failure an impaired DOPA decarboxylation to dopamine. However, patients with chronic renal failure had decreased hemodynamic and normal natriuretic responses compared with the hypernatriuresis of hypertensive patients with normal renal function; patients with chronic renal failure had elevated basal plasma concentrations of DOPA and dopamine sulfates as well as increased plasma and urinary DOPA sulfate but blunted urinary dopamine sulfate increases after DOPA administration; they presented augmented plasma atrial natriuretic factor concentrations. Thus, hypertensive patients with moderate chronic renal failure exhibit a decreased hemodynamic responsiveness to DOPA administration-induced dopamine elevation but with the natriuretic effect of dopamine maintained (possibly because of its permissive interaction with increased atrial natriuretic factor levels). Hypertensive patients with chronic renal failure have a heightened DOPA and dopamine sulfoconjugating propensity. Dopamine sulfate attenuates the biologic action of free dopamine. This may contribute (possibly via glomerular hypertension and hyperfiltration due to decreased postglomerular vasodilatation) to progressive hypertensive renal damage, particularly in groups predisposed to dopamine deficiency, such as diabetics, blacks, and the elderly. (Hypertension. 1994;23[suppl 1]:I-240-I-245.)

Key Words • DOPA • dopamine • hypertension, renovascular • kidney failure

In physiological concentrations, dopamine is a vasodilating, natriuretic and, thus essentially, antihypertensive catecholamine generated by dihydroxyphenylalanine (DOPA) decarboxylation in several neuronal and nonneuronal tissues, particularly the kidney. Patients with renal insufficiency have an abnormal renal dopamine response to salt loading, impaired renal hemodynamic reactions to exogenous dopamine, and elevated concentrations of conjugated catecholamines, especially dopamine sulfate, which decrease to approximately half of their original 20-fold increase in severe chronic renal failure (CRF) after hemodialysis. Because hypertension, which is often associated with CRF, exhibits similar dopaminergic abnormalities, it is important to distinguish their respective roles in the observed changes of dopamine generation and action.

We have previously reported that patients with stable hypertension (HBP), the form of HBP usually associated with CRF, have defective dopamine generation from exogenous L-DOPA in the presence of normal renal function. To explore the hypothesis that CRF has an effect additive to that of HBP in catecholamine sulfoconjugation and action, we compared age-matched control subjects with subjects having HBP of a comparable degree subgrouped into those with normal renal function and those with moderate CRF. The two groups and age-matched, normotensive control subjects were studied before and after an exogenous DOPA-induced increase of circulating DOPA. The parameters measured included metabolites of DOPA, such as 3-O-methyl DOPA and DOPA sulfate, and, of dopamine, such as dopamine sulfate, 3,4-dihydroxyphenylacetic acid (DOPAC), 3-methoxytyramine (3-MT), and homovanillic acid (HVA), in plasma and urine as well as the renal and vascular responses to dopamine generated from DOPA. In addition, we measured as an alternative regulator of natriuresis, probably acting as a permissive factor of dopamine action, the plasma N-terminal fragment of pro–atrial natriuretic factor (pro-ANF), which is cosecreted with ANF-(99-126) and reflects CRF more faithfully than ANF.

Methods

We investigated 10 stable HBP patients with moderate CRF (4 men and 6 women aged 54.2±4.5 years) matched with 12 stable HBP patients (9 men and 3 women aged 54.9±2.2 years with normal renal function) and 5 control subjects (3 men and 2 women aged 52.2±1.8 years); all were white, and both latter groups have been previously reported. All HBP patients were considered to be stable when their hypertension was consistently more than 160/95 mm Hg and their previously tested blood pressure did not decrease (when medication had been stopped) to normotensive values after 4 days of bed rest. Moderate CRF (defined by creatinine clearance between 35 and 80 mL/min) in 7 of 10 patients was related to the kidney being affected by the consequences of HBP. In 3 patients, HBP secondary to a renal disease (atrophic pyelonephritis in 2 patients and polycystic renal disease in 1) could not be eliminated, but any other cause, such as chronic glomerulonephritis, had been excluded. Proteinuria in all patients varied between negative and trace or 1+ amounts. There were no hematuria, casts, or immunologic abnormalities. All HBP

From the Laboratory of the Autonomic Nervous System, Clinical Research Institute of Montreal, and Hôtel-Dieu de Montréal, Université de Montréal (Canada).

Correspondence to Otto G. Kuchel, MD, Clinical Research Institute of Montreal, 110 Pine Ave W, Montreal (Quebec), Canada H2W 1R7.
patients with or without CRF had been treated with several categories of antihypertensive drugs for as long as 25 years. They stopped all medication for at least 10 days (or 3 to 5 weeks in the case of long-acting drugs) before examination and were admitted to the clinical research center. They received a diet containing between 100 and 150 mmol/d Na⁺, 100 mmol K⁺, and 90 g/d protein for 5 days and citrus fruits, cereals, and coffee excluded for 3 days before the test. None of the women had taken oral contraceptives at any time. On the day preceding the test, a 24-hour urine sample was collected with urinary Na⁺ excretion of 65.3±10, 60±9, and 50±9 mmol/min in the control, HBP, and HBP+CRF groups, respectively, suggesting a comparable basal sodium excretion. After an overnight fast, control subjects arrived at the clinical center and remained in a supine position until the study was completed. At 8 AM a heparin lock for blood collection was placed in the right antecubital vein, and baseline blood samples were taken at 8:30 AM (~30 minutes) and 9 AM (0 minutes). At 9 AM 500 mg (2.53 mmol) of DOPA (L-evodopa-Larodop, Roche Laboratories, Nutley, NJ) 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 and 10 AM, 250 mL of tap water was administered orally. Blood pressure and pulse rate were monitored every 30 minutes before and after DOPA treatment, and body weight was measured before and after the test. This study was approved by the Clinical Research Institute of Montreal Ethics Committee, and all subjects gave their informed consent. Blood samples collected in tubes were placed on ice and immediately centrifuged at 5000g for 15 minutes at 4°C. Plasma and urine were poured into cooled plastic vials containing 0.5 mg/mL sodium metaabisulfite as antioxidant and then frozen and stored at −80°C until assay. Free and sulfoconjugated catecholamines (norepinephrine, epinephrine, and dopamine) in plasma and urine were determined radioenzymatically using catechol-O-methyltransferase before and after sulfate hydrolysis, plasma and urinary 3-O-methyl-DOPA, DOPA, and DOPA sulfate by high-performance liquid chromatography with electrochemical detection, as well as DOPAC and HVA and 3-MT. Plasma N-terminal ANF was assessed by radioimmunoassay. Because DOPA is immediately metabolized to 3-O-methyl-DOPA and DOPA sulfate and the dopamine generated from DOPA is metabolized to either DOPAC or 3-MT and subsequently to HVA or dopamine sulfate, their plasma and urinary metabolites served as indexes of DOPA metabolism and dopamine generation and metabolism, respectively. Mean absolute values and their changes in all hypertensive patients were analyzed by multiple analysis of variance. DOPA-induced modifications of each parameter containing two factors (time and the value change) were analyzed by two-way analysis of variance with repeated measures on one factor. When the distribution of values was uneven or seven inacceptable values were present in both groups, nonparametric tests (Wilcoxon rank-sum and Kruskal-Wallis test) were used.

Results

Cardiovascular and Renal Responses to DOPA

Both HBP groups had comparably elevated basal blood pressures. DOPA induced a significantly greater decrease in systolic and diastolic blood pressures in HBP patients with normal renal function than in HBP patients with CRF or in control subjects (Fig 1). DOPA induced significant increases in urinary volume and urinary Na⁺ concentrations in all three groups. The increase in the Na⁺ excretion after DOPA (change in micromoles of Na⁺ per minute) was higher (60 to 120 minutes after DOPA) in HBP patients without CRF than in the other two groups. Creatinine clearance corrected for body surface was approximately 40% lower before and after DOPA administration in patients with CRF. After DOPA administration, it exhibited an approximately 40-mL/min increase in control subjects (60 to 120 minutes after DOPA) and HBP subjects without CRF (0 to 60 minutes after DOPA) compared with a negligible change in HBP patients with CRF.

Effect of DOPA on Plasma DOPA and Dopamine, Their Metabolites, and ANF

Under basal conditions, all three sulfates of DOPA, dopamine (Fig 2), and norepinephrine were elevated in HBP patients with CRF. Norepinephrine sulfate was 7.84±1.8 pmol/mL (2.15±0.5 ng/mL) in HBP+CRF compared with 1.96±0.3 (0.54±0.1) in control subjects and 2.36±0.3 (0.65±0.1) in HBP patients with normal renal function (P<.05). Plasma DOPA, 3-O-methyl-DOPA, free dopamine, dopamine sulfate, DOPAC, HVA, and 3-MT increased considerably after DOPA administration, but only plasma DOPA (60 minutes after DOPA) and DOPA (60 and 120 minutes after DOPA) elevations were significantly lower in the control subjects than in the two hypertensive groups. There also was a lower increase in the ratio of plasma DOPA to dopamine, an approximate index of DOPA decarboxylation to dopamine, in the control subjects compared with both hypertensive groups: from 25±6 to 139±20 in control subjects compared with 65±16 to 283±40 in HBP and 48±25 to 369±74 in HBP+CRF at 60 and 120 minutes after DOPA (P<.05). The most evident distinction between the HBP groups with and without CRF was that DOPA sulfate, in addition to elevated basal values, increased almost 20-fold after DOPA administration in HBP patients with CRF, whereas those without CRF and control subjects had very low mean values of basal plasma DOPA sulfate that remained undetectable after DOPA treatment. In contrast with this finding, a comparable rise of dopamine sulfate occurred after DOPA administration in all three groups without intergroup differences, despite an elevated basal dopamine sulfate concentration only in HBP patients with CRF. N-terminal ANF in plasma was clearly augmented in HBP patients with CRF at baseline and after DOPA administration.

Urinary Catecholamine Precursors and Metabolites Before and After DOPA

The glomerular DOPA load (calculated as plasma DOPA concentrations x creatinine clearance) was markedly increased after DOPA administration in all three groups. At 60 minutes, it was higher (P<.05) in HBP patients without CRF than in those with CRF and in the control subjects. The most consistent change in HBP patients with CRF was their baseline and DOPA administration–induced (almost 500-fold) increase in urinary DOPA sulfate (Fig 3); such elevations were absent in control subjects and considerably delayed in HBP patients without CRF. Urinary free dopamine, dopamine sulfate, DOPAC, and HVA excretions were markedly increased. Closest to a significant difference were lower urinary free dopamine excretions 60 minutes after DOPA in the HBP+CRF group: 31.6±5.2 μmol/h (4.84±0.8 mg/h) compared with 48.7±14 (7.47±2.2) in control subjects and 77±16 (11.8±2.5) in HBP patients (P<.06). One hundred twenty minutes after DOPA...
administration, urinary dopamine sulfate excretion was lower in HBP patients with CRF, whereas DOPAC and HVA excretions were higher in the HBP group without CRF than in the two remaining groups. There were no significant differences in basal urinary 3-O-methyl-DOPA excretion and in its augmentation after DOPA administration in the three groups. The ratio of urinary dopamine to the DOPA load, which reflects the rate of DOPA decarboxylation to dopamine in the kidney, approximately doubled in all three groups 60 minutes after DOPA administration; its basal and peak values were higher in HBP patients with or without CRF than in control subjects, with no statistical difference between both HBP groups. The only additional difference in CRF patients was lower (P<.05) urinary basal epinephrine excretion (3.44±0.5 nmol/h [0.63±0.1 μg/h]) compared with 16.9±6 [3.1±1.1] in control subjects and 16.9±3 [3.1±0.57] in HBP patients without CRF).

**Discussion**

The two hypertensive groups studied and their comparison with normotensive control subjects permitted an evaluation of the separate roles of hypertension and moderate renal insufficiency in abnormalities of catecholamine metabolism and the biologic implications of considerable dopamine generation from administered DOPA. Previously described5 DOPA-induced changes distinguishing HBP patients from control subjects (hypernatriuresis and more profound blood pressure decrease) were blunted in HBP patients with CRF despite comparable plasma and urinary free dopamine values in both hypertensive groups. HBP patients with CRF maintained their basal natriuresis by increased tubular Na+ rejection compensating for decreased creatinine clearance but did not exhibit the hypernatriuresis in response to DOPA seen in HBP with normal renal function; their response, however, was not different from that in the control subjects.

The absent systemic depressor effect, as well as the creatinine clearance unresponsive to dopamine generated from DOPA while its natriuretic response is conserved, indicates that even hypertensive patients share a previous observation in usually normotensive patients that there is, in CRF in response to exogenous dopamine, an impaired hemodynamic, particularly renal, response, but their natriuretic reaction is maintained.3 Either the maintenance of the natriuretic effect of dopamine in CRF is attributable to an upregulation of tubular dopaminergic receptors in HBP5 in the face of the failure to increase the glomerular filtration rate and glomerular Na+ load or natriuresis in HBP patients with CRF may be maintained by increased ANF, which with dopamine has mutual permissive actions.6 The second main feature distinguishing hypertensive patients with CRF from those without CRF involves their elevated basal plasma DOPA, dopamine, and
Dopamine in Renal Insufficiency and Hypertension

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Fig. 2. Bar graphs show plasma dihydroxyphenylalanine (DOPA), DOPA sulfate, dopamine (DA) sulfate, and atrial natriuretic factor (ANF)-N-terminal (N-TERM) concentrations in the control, stable hypertension (HBP), and HBP+ chronic renal failure (CRF) subjects before and 60, 120, and 180 minutes after L-DOPA administration (mean±SEM). *Statistical difference between study groups adjusted for multiple comparisons. The single point symbol indicates differences of the respective group compared with the other two groups.

Elevated conjugated dopamine levels have been observed in patients with severe renal insufficiency; with an increasing degree of CRF, a higher percentage of each catecholamine was excreted as conjugate, possibly because of an increased tubular secretion of sulfoconjugates compensatory to a decreased glomerular filtration rate. Decreased overall renal clearance of conjugated catecholamines is probably the cause of high plasma conjugates because they decrease considerably after hemodialysis. The striking increase in DOPA sulfate concentrations, even in moderate CRF and under basal conditions, is a new observation. DOPA is sulfoconjugated not only in the intestinal wall but also in other tissues, as suggested by its continuous sulfation when administered intravenously. The approximately 400-fold increase of urinary DOPA excretion after DOPA administration exceeds the approximately 20-fold increase in plasma DOPA concentration. Thus, in contrast to HBP patients and control subjects with normal renal function, ingested DOPA in patients with CRF appears to be avidly sulfoconjugated with secondary excessive DOPA tubular sulfoconjugation and urinary excretion. On the other hand, elevated plasma dopamine sulfate in HBP and CRF may in part reflect the decreased renal clearance of dopamine sulfate, as suggested by decreased urinary dopamine sulfate in CRF patients at the height of DOPA administration.

HBP patients with CRF share with patients without CRF another anomaly, ie, a defect in DOPA decarboxylation to dopamine, as reflected by a higher ratio of DOPA to dopamine as well as accelerated dopamine metabolism with higher plasma DOPAC (not urinary DOPAC and HVA) after DOPA administration. The lower urinary products of dopamine oxidation and methylation, DOPAC, and HVA in hypertension with CRF may be in part due to enhancement of an alternative pathway, dopamine sulfoconjugation. Despite a comparable elevation after DOPA administration of plasma DOPA in HBP patients without and with CRF, the blunted increase in glomerular filtration rate in CRF...
Supplement I  Hypertension  Vol 23, No 1  January 1994

Fig. 3. Bar graphs show urinary dihydroxyphenylalanine (DOPA) sulfate, dopamine (DA) sulfate, 3,4-dihydroxyphenylacetic acid (DOPAC), and homovanillic acid (HVA) excretions in control, stable hypertension (HBP), and HBP+chronic renal failure (CRF) subjects before and 60, 120, and 180 minutes after L-DOPA administration (mean±SEM). *Statistical difference between study groups adjusted for multiple comparisons. The single point symbol indicates differences of the respective group compared with the other two groups.

may cause lower urinary excretion of the dopamine metabolites DOPAC and HVA and of dopamine itself (at the limit of significance). The decreased renal excretion of epinephrine in patients with CRF indicates that even moderate renal failure may be sufficient to induce inhibition of the epinephrine-synthesizing enzyme phenol-O-methyltransferase, previously observed in the erythrocytes of uremic patients.17

Taken together, these data suggest that HBP patients with moderate CRF share with HBP patients with normal renal function a defect in DOPA decarboxylation to dopamine. There is, however, increased sulfoconjugation of dopamine. Dopamine sulfate is an endogenous inhibitor of dopamine actions18; as a consequence, one of the renal dopamine actions (a predominantly efferent glomerular vasodilatation)3 may be attenuated, contributing to intraglomerular hypertension, a hallmark of renal damage due to hypertension.19 It probably is no simple coincidence that dopamine deficiency is best known in subjects who are most susceptible to the unabatedly progressing renal complication of hypertension, ie, blacks,20 the elderly,21 and diabetics.22

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References


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