Cardiovascular and Renal Profile of Acute Peripheral Dopamine$_1$-Receptor Agonism with Fenoldopam

Zeev Glück, Leander Jossen, Peter Weidmann, Markus P. Gnädinger, and Edgar Peheim

SUMMARY Whether the dopaminergic system may be involved in essential hypertension is of pathogenetic as well as therapeutic interest. Therefore, we investigated in eight hypertensive and 12 normal subjects cardiovascular, endocrine, and renal responses to fenoldopam, which has been characterized experimentally as an agonist of peripheral postsynaptic dopamine$_1$ receptors. A single oral dose of fenoldopam, 100 mg, changed blood pressure (BP) in hypertensive subjects (from 163/103 to 147/76 mm Hg; $p<0.01$ for systolic and $p<0.001$ for diastolic BP) and normal subjects (from 121/81 to 123/65 mm Hg; $p<0.001$ for diastolic BP); percentage decreases in diastolic BP averaged $-20 \pm 6$ and $-16 \pm 7\%$, respectively. Fenoldopam-induced effects on other variables were similar in the two groups. Heart rate rose ($p<0.001$) on average from 69 to 92 beats/min in hypertensive and from 64 to 84 beats/min in normal subjects. Effective renal plasma flow increased (from 552 to 765 and 634 to 937 ml/min/1.73 m$^2$; $p<0.01$), while glomerular filtration rate tended to decrease (from 121 to 99 ml/min/1.73 m$^2$ in the hypertensive and from 119 to 97 ml/min/1.73 m$^2$; $p<0.001$ in the normal group). Fractional sodium clearance was elevated (from 2.8 to 5.2 and 1.7 to 3.8%; $p<0.01$), as was free water clearance (from $-1.7$ to 0.6 and $-1.7$ to 0.1 ml/min/1.73 m$^2$; $p<0.01$). Potassium clearance was largely unchanged. Plasma renin activity increased about twofold ($p<0.01$ in normal subjects), and plasma aldosterone by 40% (NS). Plasma norepinephrine levels increased twofold to 2.5-fold ($p<0.001$), and urinary norepinephrine excretion fivefold to 10-fold ($p<0.01$). Fenoldopam-induced changes were not significantly modified by intravenous and/or oral pretreatment with the dopamine-receptor antagonist metoclopramide or the cyclooxygenase inhibitor indomethacin. These findings suggest that in humans, fenoldopam may acutely override the dopaminergic antagonism of metoclopramide given in clinical dosage and that its cardiovascular and renal effects are not prostaglandin-mediated. Although acute sympathetic stimulation may be partially antagonistic, the concomitant BP-lowering, renal vasodilating, and natriuretic actions of fenoldopam represent a desirable profile of a potential antihypertensive agent. (Hypertension 10: 43-54, 1987)

KEY WORDS • dopamine$_1$-receptor agonist • essential hypertension • renal function • renin-aldosterone system • catecholamines

Dopamine-related mechanisms may modulate cardiovascular, endocrine, and renal functions. Dopamine (DA) produces, through stimulation of postsynaptic DA$_1$ receptors, splanchnic, renal, and, to a lesser extent, peripheral vasodilation.$^{1-4}$ Its renal actions include an increased natriuresis.$^5$ Through activation of presynaptic DA$_2$ receptors, DA inhibits the secretion of prolactin from the pituitary gland and may reduce the release of norepinephrine (NE) from sympathetic nerve endings.$^5,7$ Furthermore, DA can attenuate angiotensin II-mediated aldosterone secretion,$^5$ promote renal renin release,$^8,10$ and by nonspecific or, following conversion to NE and epinephrine, direct activation of $\alpha$-adrenergic and $\beta$-adrenergic receptors,$^2$ modify additional cardiovascular and renal control factors.

The relative contribution of DA-dependent mechanisms to the regulation of blood pressure (BP) and kidney function in normal humans and in pathological states, such as essential hypertension, is not entirely clear. Major abnormalities incriminated in the pathogenesis of essential hypertension, such as peripheral and, particularly, renal vasoconstriction,$^{11-13}$ reduced
renal capacity to excrete sodium, inappropriately high plasma aldosterone levels, and enhanced sympathetic outflow, could potentially be facilitated by impaired dopaminergic control or treated with selective DA-receptor agonists.

Fenoldopam, a new benzazepine derivative, has been characterized as a specific DA agonist. Compared with DA, fenoldopam is about 3.5 times more potent as a renal vasodilator in dogs, is devoid of α-adrenergic and β-adrenergic receptor-stimulating activity, and does not inhibit NE release. Moreover, fenoldopam does not cross the blood-brain barrier and is well absorbed when given orally. The few published observations on its actions in humans suggest that fenoldopam may lower BP in normotensive and particularly in hypertensive subjects, acutely increase natriuresis, and regardless of the presence or absence of essential hypertension, augment renal blood flow and plasma renin levels. Reported effects of fenoldopam on heart rate (HR) have been conflicting, and its influence on levels of the different catecholamines is unclear. The present study was undertaken 1) to further evaluate the hemodynamic, endocrine, and renal profile of fenoldopam in humans, and 2) to assess whether and to what extent the response of BP, HR, plasma and urinary catecholamines, the renin-angiotensin-aldosterone system, renal hemodynamics, and excretory function to selective DA-receptor activation may be modified in essential hypertensive as compared with normal subjects. In an attempt to further elucidate mechanisms of action, studies were repeated after oral pretreatment with the cyclooxygenase inhibitor indomethacin and after oral as well as intravenous pretreatment with the DA-receptor antagonist metoclopramide.

Subjects and Methods

Study 1

The Study 1 group was composed of 12 normal subjects (7 women and 5 men), aged 39.7 ± 10.7 (SD) years, and eight subjects with essential hypertension (3 men and 5 women), aged 46.7 ± 10 years. The normal group consisted of healthy volunteers with BP consistently below 140/90 mm Hg. None of the hypertensive subjects had complications such as stroke, transient ischemic attacks, clinical or electrocardiographic evidence of ischemic heart disease, cardiac or renal failure (serum creatinine > 1.3 mg/dl), hypertensive retinopathy Keith-Wagener-Barker Grades 3 or 4, peripheral ischemic microangiopathy, or other systemic or organ disease. Secondary forms of hypertension were excluded by the usual tests. Written informed consent was obtained from all subjects. Antihypertensive and other drugs were withdrawn at least 3 weeks before the study, and the subjects were instructed to eat a normal diet avoiding very low or high salt intakes for at least 1 week before the study. Alcohol abusers were excluded, and subjects were advised to avoid alcohol or caffeine-containing drinks for 24 hours and smoking for 12 hours before the morning of the study.

A placebo (matched with fenoldopam), one capsule 4 times daily, was given during 3 weeks before the first study and during the interval between the different study days. During the washout period, BP and other relevant clinical parameters were monitored at weekly intervals. Hypertensive subjects were included in the study if their supine diastolic BP (mean of 3 readings) recorded on two consecutive occasions averaged 95 to 120 mm Hg or mean BP averaged 116 mm Hg or more. Subjects with diastolic BP exceeding 120 mm Hg or systolic BP exceeding 180 mm Hg were excluded.

The 12 normal and eight hypertensive subjects were randomly divided into two equal subgroups, each containing six normotensive (mean age, 39.8 ± 13 and 39.5 ± 9 years, respectively) and four hypertensive subjects (aged 44.5 ± 2 and 49 ± 15 years, respectively). All subjects were studied on 2 separate days at least 1 week apart. In one subgroup, effects of fenoldopam alone were compared with its effects after oral pretreatment with metoclopramide. In the other subgroup, effects of fenoldopam alone were compared with those after oral pretreatment with indomethacin, according to an open, randomized, crossover design. Pretreatment schedules were: metoclopramide, 10 mg four times daily for 2 days before the study day and 20 mg 1 hour before fenoldopam dosing, or indomethacin, 50 mg 3 times daily for 2 days and 50 mg 1 hour before fenoldopam administration.

On each study day, subjects were allowed to have a light breakfast with 500 ml of lime blossom tea not later than 0600. They attended the renal clearance laboratory at 0700. At 0730, a bladder catheter was placed and a plastic cannula was inserted in each arm into an antecubital vein; the subjects then remained supine until completion of the test. Glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were determined by a constant infusion clearance technique using 51Cr-EDTA and p-aminohippuric acid (PAH), respectively. At 0800, an intravenous priming dose of 25 μg 51Cr-EDTA, 0.5 ml) and 6 ml of a 20% solution of sodium PAH was given, followed by a constant infusion of 0.3 ml of 51Cr-EDTA and 4 ml of 20% Na PAH made up in 200 ml of 0.9% NaCl delivered by a calibrated pump (Infusomat Type 5094; sterile catgut; Gesellschaft, Neuhausen, Switzerland) at a rate of 3 ml/min.

For blood sampling, the venous access on the contralateral arm was used and blood was allowed to drip freely whenever possible. Urine sampling was obtained by catheter and rinsing with air as well as distilled water, 20 ml twice per urine collection. After a 30-minute equilibration period, starting at 0830, nine urine collection periods of 20 minutes each, with midline blood sampling for 51Cr-EDTA, PAH, hematocrit, sodium, potassium, chloride, and osmolality, were performed and urinary concentrations of these variables were determined in each period for calculation of their clearances. The first three periods served as the control phase. After the third period, a single oral dose of 100 mg fenoldopam (SKF 82526) was given. Body weight was recorded before and at completion of the test. BP and HR were recorded at the end of each
clearance period. Plasma renin activity (PRA) and aldosterone (PA) as well as plasma and urinary epinephrine and NE levels were determined at the beginning and end of the control phase and 1 and 2 hours after fenoldopam administration.

Study 2
In four subjects (mean age, 46 ± 8 years) previously studied with fenoldopam alone and following pretreatment with oral metoclopramide, the effects of fenoldopam were also studied on a third occasion (studies were at least 4 weeks apart) following combined oral and intravenous metoclopramide pretreatment (10 mg p.o. 4 times daily for 2 days before the study day, and 10 mg i.v. given over 2 minutes immediately before oral fenoldopam dosing, followed by continuous metoclopramide infusion at a constant rate of 5 mg/hr over the next 2 hours). Fenoldopam-induced changes were compared with those seen after oral or combined oral and i.v. metoclopramide pretreatment.

Analytical Methods
BP was measured using a mercury sphygmomanometer and cuff with diastolic BP recorded as Korotkoff Phase V; recorded values represented the mean of three consecutive measurements. Plasma and urinary 51 Cr activity was measured in a γ-counter (Tri-Carb Scintillation Spectrometer, Packard, Downers Grove, IL, USA), PAH by standard photometric method, hematocrit by the microcrit method, sodium and potassium by flame photometer, chloride by Greiner autoanalyzer (Langenthal, Switzerland), osmolality by freezing-point depression using a cryoscope with Peltier's element, PRA and PA levels by radioimmunoassay, and plasma and urinary NE and epinephrine by a radioenzymatic assay, as reported previously by this laboratory.

The filtration fraction (FF) was calculated as the ratio between GFR and ERPF, fractional clearance rates as the ratio clearance of excreted parameter/GFR, free water clearance as the difference between urinary volume and clearance of osmolality per minute. Statistical analysis was performed with the help of the software package SAS (Statistical Analysis System, Version OS 82.3; Cary, NC, USA). Methods included analysis of variance and Student-Newman-Keuls test corrected by covariables (i.e., the individual control values), for analysis of the time course, independent t test for comparison of basal values or maximal drug-induced changes between the hypertensive and normotensive groups, and dependent t test for analysis of maximal or 2-hour postfenoldopam values as compared with basal values. Assessments of correlation were performed using linear regression analysis.

Results

Study 1
Blood Pressure and Heart Rate
Oral administration of fenoldopam, 100 mg, significantly lowered diastolic and mean BP (p<0.001) but not systolic BP in the normal subjects and decreased all three BP values (p<0.001) in the hypertensive group (Table 1, Figure 1). The maximum BP-lowering effect of fenoldopam was seen at 40 to 60 minutes. Systolic BP in the hypertensive (p<0.05) and diastolic BP in both groups analyzed together (p<0.02) were still slightly below control values 2 hours after oral dosing. Fenoldopam-induced maximal changes in diastolic, mean, or systolic BP correlated with their control val-

Table 1. Effect of Fenoldopam on BP and Heart Rate

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotension (n = 12)</th>
<th>Essential hypertension (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basal</td>
<td>Maximal change</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>64 ± 7</td>
<td>84 ± 11*</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>121 ± 10</td>
<td>123 ± 11</td>
</tr>
<tr>
<td>Diastolic</td>
<td>81 ± 7</td>
<td>65 ± 6*</td>
</tr>
<tr>
<td>Mean</td>
<td>94 ± 7</td>
<td>84 ± 6*</td>
</tr>
</tbody>
</table>

|                           | Basal                 | Maximal change                | 2 hr                        |
|                           | 69 ± 6                | 92 ± 13*                      | 74 ± 6                      |

Values are means ± SD.
*p<0.001, †p<0.05, ‡p<0.01, compared with basal values.
FIGURE 2. Effects on BP and heart rate of fenoldopam alone or combined with orally administered metoclopramide pretreatment. Values are means ± SEM.

ues \((n = 20), r = -0.22, r = -0.39, r = -0.64, p < 0.05, p < 0.001, p < 0.001\), respectively, for percentage changes; \(r = -0.59, r = -0.60, r = -0.58\) and \(p < 0.001\) for absolute changes).

HR was significantly \((p < 0.001)\) increased following fenoldopam ingestion in the normal and hypertensive groups (see Table 1, Figure 1). Although the effect was maximal at 40 to 60 minutes, values still tended to be elevated 2 hours after fenoldopam dosing \((p < 0.05\) in the normotensive group). Fenoldopam-induced percentage changes in HR correlated positively with those in plasma NE \((n = 40, r = 0.52, p < 0.001)\) and inversely with changes in diastolic BP \((n = 120, r = -0.67, p < 0.001)\), but not with variations in plasma epinephrine or PRA levels. Fenoldopam-induced changes in BP or HR were not significantly modified by oral pretreatment with either metoclopramide or indomethacin in the normal or hypertensive subjects (Figures 2 and 3).

**Endocrine Findings**

Basal values of plasma NE, epinephrine, PRA, and PA levels did not differ significantly between the normal and hypertensive groups (Table 2). One hour after fenoldopam dosing, marked increases in plasma NE concentrations \((p < 0.001)\) and urinary NE excretion rate \((p < 0.01)\) occurred in both groups (Figure 4). Plasma epinephrine and PRA also tended to increase \((p < 0.05\) and \(p < 0.01\), respectively in the normotensive group), while a similar tendency for PA and urinary epinephrine excretion rate did not achieve statistical significance (see Figure 4). Plasma NE and epinephrine were still above control values 2 hours after ingestion of fenoldopam \((p < 0.001\) and \(p < 0.01\), respectively, for the normotensive subjects), whereas PRA and PA levels had largely returned to control levels.

Fenoldopam-induced percentage variations in plasma or urinary NE or epinephrine levels did not correlate significantly with concomitant percentage changes in PRA, while percentage changes in PA correlated significantly with those in PRA only for both groups analyzed together \((n = 40, p < 0.05)\).

Oral pretreatment with metoclopramide or indomethacin did not significantly modify the basal PRA, PA, and catecholamine values, except for slightly

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**Table 2. Endocrine Parameters Before Administration of Fenoldopam Under Basal Conditions or Pretreatment**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Basal value before fenoldopam alone</th>
<th>Metoclopramide study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normotension</td>
<td>Essential hypertension</td>
</tr>
<tr>
<td>No. of subjects</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Plasma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renin activity (ng ANG I/ml/hr)</td>
<td>1.6±0.4</td>
<td>2.2±1.1</td>
</tr>
<tr>
<td>Aldosterone (ng/dl)</td>
<td>5.8±3.4</td>
<td>7.8±4.3</td>
</tr>
<tr>
<td>Epinephrine (ng/dl)</td>
<td>2.0±1.6</td>
<td>1.7±1.1</td>
</tr>
<tr>
<td>Norepinephrine (ng/dl)</td>
<td>34±13</td>
<td>31±10</td>
</tr>
<tr>
<td>Urinary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epinephrine (ng/min)</td>
<td>12±6</td>
<td>9±4</td>
</tr>
<tr>
<td>Norepinephrine (ng/min)</td>
<td>30±24</td>
<td>25±8</td>
</tr>
</tbody>
</table>

Values are means ± SD. ANG I = angiotensin I.

*p < 0.02, compared with basal values.
higher plasma epinephrine following metoclopramide (see Table 2). Fenoldopam-induced changes in the various endocrine parameters were not influenced by oral pretreatment with either metoclopramide or indomethacin in either study group (Figure 5).

Renal Function
Fenoldopam produced a marked increase ($p<0.05$) in ERPF in the normal and hypertensive groups (Table 3, Figure 6). ERPF was modified maximally at about 60 to 80 minutes and was restored toward control values 2 hours after drug administration. GFR tended to decrease ($p<0.01$ in the normotensive group) transiently at 40 minutes and had already returned to control values 80 minutes after fenoldopam dosing. Filtration fraction was lowered distinctly by fenoldopam ($p<0.05$ to $p<0.01$). Fenoldopam caused significant increases in absolute and fractional clearances of sodium ($p<0.01$ to $p<0.001$), chloride ($p<0.01$ to $p<0.001$), and osmoles ($p<0.01$), which reached their maximum 100 to 120 minutes after dosing. A transient rise in free water clearance 40 minutes after dosing ($p<0.01$ to $p<0.001$; Figure 7, see Table 3) mirrored a concomitant tendency for decreased urinary osmolality. Absolute or fractional clearances of potassium were not significantly changed.

Fenoldopam-induced changes in renal function did not differ significantly between the normal and hypertensive subjects (see Table 3, Figures 6 and 7) and were not significantly modified by pretreatment with metoclopramide or indomethacin in either group (Figure 8). Nevertheless, the effects of fenoldopam on diuresis and natriuresis tended to be blunted following indomethacin pretreatment in the hypertensive group.

Correlations with Renal Function Parameters
Percentage changes in GFR correlated significantly with those in mean BP ($n=120$, $r=0.29$, $p<0.001$), diastolic BP ($r=0.39$, $p<0.001$), ERPF ($r=0.38$, $p<0.001$), the product of mean BP x ERPF ($r=0.46$, $p<0.001$), or clearances of sodium or chloride ($r=0.39$ and 0.41, respectively, $p<0.001$). No correlations were found between changes in ERPF and those in diastolic, systolic, or mean BP or in plasma NE, epinephrine, or PRA levels.

Table 2. (continued)

<table>
<thead>
<tr>
<th>Metoclopramide study</th>
<th>Indomethacin study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Essential hypertension</td>
<td>Normotension</td>
</tr>
<tr>
<td><strong>Basal</strong></td>
<td><strong>Metoclopramide</strong></td>
</tr>
<tr>
<td>4</td>
<td>1.4 ± 0.4</td>
</tr>
<tr>
<td>7.5 ± 2.9</td>
<td>7.6 ± 2.6</td>
</tr>
<tr>
<td>1.3 ± 0.7</td>
<td>1.6 ± 1.7</td>
</tr>
<tr>
<td>3 ± 0.7</td>
<td>4 ± 1.3</td>
</tr>
<tr>
<td>8 ± 2</td>
<td>6 ± 1</td>
</tr>
<tr>
<td>24 ± 10</td>
<td>20 ± 12</td>
</tr>
</tbody>
</table>
Study 2

Control values of BP, HR, kidney function, and endocrine variables did not differ significantly between the three studies using fenoldopam alone, oral pretreatment with metoclopramide followed by fenoldopam, or oral as well as i.v. pretreatment with metoclopramide followed by oral fenoldopam combined with sustained metoclopramide infusion. Moreover, i.v. metoclopramide administration did not distinctly modify the variations in cardiovascular, renal, and endocrine parameters observed following fenoldopam alone or combined with oral metoclopramide administration (Table 4).

Side Effects

Following administration of fenoldopam facial flushing was noted objectively in all 20 subjects and subjectively felt as a warm face by 17 of them. The flushing appeared 20 to 40 minutes after fenoldopam dosing and was not modified notably by pretreatment with metoclopramide or indomethacin.

Discussion

The findings of the present study indicate that fenoldopam, a new compound characterized in various animals23-25 as an agonist of peripheral DA receptors, produces a potent BP reduction, renal vasodilation, and natriuresis in humans. An oral dose of 100 mg acutely and significantly reduced diastolic BP in both normal subjects and subjects with essential hypertension but reduced systolic BP only in hypertensive subjects. The BP-lowering action was associated with a marked rise in renal blood flow as well as increases in HR, plasma and urinary NE, and PRA levels, which were all quite similar in normal and hypertensive subjects.

Whether and to what extent fenoldopam modifies the activity of the sympathetic nervous system has been largely unknown. The constellation of cardiac

![Figure 4](https://hyper.ahajournals.org/content/10/1/48.full)

**Figure 4.** Effects of fenoldopam on PRA, plasma aldosterone, and catecholamines. Values are means ± SEM.

![Figure 5](https://hyper.ahajournals.org/content/10/1/48.full)

**Figure 5.** Variations in catecholamines after fenoldopam alone or combined with either metoclopramide pretreatment (A) or indomethacin pretreatment (B). Values are means ± SEM.
PERIPHERAL POSTSYNAPTIC RECEPTOR AGONISM/Glück et al.

**TABLE 3. Effect of Fenoldopam on Renal Function**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotension (n = 12)</th>
<th>Essential Hypertension (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR (ml/min/1.73 m²)</td>
<td>119 ± 20</td>
<td>121 ± 16</td>
</tr>
<tr>
<td>ERPF (ml/min/1.73 m²)</td>
<td>634 ± 161</td>
<td>552 ± 133</td>
</tr>
<tr>
<td>FF</td>
<td>0.19 ± 0.26</td>
<td>0.23 ± 0.43</td>
</tr>
<tr>
<td>Urine flow (ml/min)</td>
<td>2.0 ± 0.9</td>
<td>3.3 ± 1.2§</td>
</tr>
<tr>
<td>Clearance (ml/min/1.73 m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osmolar</td>
<td>3.9 ± 0.9</td>
<td>5.1 ± 1.1</td>
</tr>
<tr>
<td>Na⁺</td>
<td>2.1 ± 0.7</td>
<td>3.2 ± 1.1§</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>2.7 ± 1.2</td>
<td>4.2 ± 1.5§</td>
</tr>
<tr>
<td>K⁺</td>
<td>25.4 ± 13.4</td>
<td>29.0 ± 6.7</td>
</tr>
<tr>
<td>Free water</td>
<td>−1.7 ± 0.9</td>
<td>−1.7 ± 0.4</td>
</tr>
<tr>
<td>Fractional Na⁺ clearance</td>
<td>1.7 ± 4.8</td>
<td>2.8 ± 1.0</td>
</tr>
<tr>
<td>Urinary osmolality (mosm/L)</td>
<td>618 ± 266</td>
<td>446 ± 91</td>
</tr>
</tbody>
</table>

Values are means ± SD. GFR = glomerular filtration rate; ERPF = effective renal plasma flow; FF = filtration fraction.

* p < 0.001, † p < 0.01, § p < 0.02, ‡ p < 0.05, compared with basal values.

Acceleration with raised NE and, less distinctly, epinephrine levels probably reflects at least in part baroreceptor reflex activation of the efferent sympathetic system secondary to decreases in BP. In fact, fenoldopam-induced changes in diastolic BP correlated inversely with those in HR and plasma NE levels, and fenoldopam-induced changes in diastolic BP correlated inversely with those in HR and plasma NE levels, and the latter tended to be decreased, the seemingly preferential rise in urinary NE following fenoldopam administration may reflect an increased sympathetic neuronal discharge to the kidney, mediated by a baroreceptor reflex mechanism. Furthermore, the fenoldopam-induced increase in NE levels supports its lack of D₁-receptor agonistic activity in humans, since stimulation of such receptors should have promoted suppression rather than activation of NE release.

Among the factors known to control renal renin release, the fall in mean arterial BP, acute sympathetic activation, and perhaps, a specific dopaminergic mechanism, may have promoted the modest hyperreninemia following fenoldopam dosing in our normal and hypertensive subjects and those studied by others. Sympathetic stimulation may be particularly important, since β-adrenergic receptor blockade with propranolol greatly blunted fenoldopam-induced rises in PRA. Infusion of DA into the renal artery enhanced renin release in experimental animals. Nevertheless, others postulated an inhibitory dopaminergic influence on renin secretion.

PA tended to increase following administration of fenoldopam, but this rise was not proportional to that of PRA, and plasma potassium levels were only minimally decreased. Aldosterone production is regulated mainly by angiotensin II, potassium, and, to some extent, adrenocorticotrophic hormone, but dopamine may play a modulating role by promoting aldosterone...
inhibition. Therefore, the tendency for slight aldosterone-renin dissociation following administration of fenoldopam may in part reflect a dopaminergic inhibitory influence on aldosterone secretion in both our normal and hypertensive subjects.

Renal hemodynamic effects of fenoldopam in our normal or hypertensive subjects were characterized by a significant rise in ERPF (on average +30%), an unchanged or, 40 minutes after fenoldopam-dosing, even slightly decreased GFR, and a distinct reduction in the FF (on average −20%). Others also noted an augmented renal blood flow, while GFR was reported to be unchanged27, 29, 30 or even slightly increased26; in the latter study, the use of prolonged urine collection
periods precludes a fractional analysis of the time course of GFR. When BP is lowered acutely, GFR depends largely on changes in systemic BP and ERPF. Following administration of fenoldopam, a negative influence of the rapid fall in BP on GFR may be compensated largely by the potent renal vasodilation. In the present study, the dependence of GFR on these two physical factors is corroborated by significant correlations between changes in GFR and those in heart rate, blood pressure, and other influences on renal blood flow, thus suggesting a more potent vasodilating action of fenoldopam at the efferent glomerular arterioles. Since the observed renal vasodilation alone could hardly explain the observed decrease in BP, other vascular beds, although not directly assessed in this study, must also be dilated by fenoldopam. The facial flushing experienced by our study subjects indicates a cutaneous vasodilation and represents a specific stimulation of DA receptors in the skin.

The urinary excretion rates of sodium and chloride rose slowly but significantly following short-term administration of fenoldopam. Since the filtered loads of these electrolytes were unchanged or even decreased, modifications in renal blood flow or other influences on tubular transport may underlie the natriuretic action of fenoldopam. The combination of increased renal blood flow and reduced FF augments the volume load to the proximal peritubular capillaries; the resulting increase in hydrostatic and decrease in oncotic peritubular pressure counterproximal tubular sodium reabsorption, thus resulting in a greater sodium/volume load to more distal tubular sites. However, an increased delivery of sodium to the distal tubules does not necessarily result in elevated sodium excretion. DA has been noted to redistribute the renal blood flow from outer to inner cortical regions. Although the effect of fenoldopam on renal regional hemodynamics has not yet been clarified, the possibility of a similar redistribution from outer to inner areas deserves consideration. A resultant washout of urea from the papilla could lead to a disruption of the countercurrent gradients, with reduction of sodium reabsorption in the thick ascending limb of the deep nephrons. Nevertheless, urinary osmolality tended to be decreased only during the first hour following fenoldopam dosing, suggesting that the further rise in sodium excretion up to 2 hours after fenoldopam probably was due to other mechanisms. A direct dopaminergic inhibition of tubular sodium reabsorption might also contribute. DA receptors have been identified in glomeruli and cortical and medullary tubules of the rat. Moreover, DA can produce natriuresis without concomitant changes in renal perfusion pressure, blood flow, GFR or even with reduced renal blood flow, thus suggesting a direct dopaminergic interaction with sodium reabsorption.

Free water clearance was increased transiently 40 minutes after fenoldopam dosing in both the normal and hypertensive subjects. Nevertheless, it is difficult to interpret changes in free water clearance in non-water-loaded subjects. Therefore, a theoretical contribution of medullary washout, antidiuretic hormone, or a direct inhibition of osmotic water flow in the distal nephron to the observed dissociation between water and sodium excretion following fenoldopam deserves clarification.

Based on previous observations, the administration of a substance with postsynaptic DA,-receptor agonism should reduce BP and produce a renal vasodilation alone could hardly explain the observed decrease in BP, other vascular beds, although not directly assessed in this study, must also be dilated by fenoldopam. The facial flushing experienced by our study subjects indicates a cutaneous vasodilation and represents a specific stimulation of DA receptors in the skin.

The urinary excretion rates of sodium and chloride rose slowly but significantly following short-term administration of fenoldopam. Since the filtered loads of these electrolytes were unchanged or even decreased, modifications in renal blood flow or other influences on tubular transport may underlie the natriuretic action of fenoldopam. The combination of increased renal blood flow and reduced FF augments the volume load to the proximal peritubular capillaries; the resulting increase in hydrostatic and decrease in oncotic peritubular pressure counterproximal tubular sodium reabsorption, thus resulting in a greater sodium/volume load to more distal tubular sites. However, an increased delivery of sodium to the distal tubules does not necessarily result in elevated sodium excretion. DA has been noted to redistribute the renal blood flow from outer to inner cortical regions. Although the effect of fenoldopam on renal regional hemodynamics has not yet been clarified, the possibility of a similar redistribution from outer to inner areas deserves consideration. A resultant washout of urea from the papilla could lead to a disruption of the countercurrent gradients, with reduction of sodium reabsorption in the thick ascending limb of the deep nephrons. Nevertheless, urinary osmolality tended to be decreased only during the first hour following fenoldopam dosing, suggesting that the further rise in sodium excretion up to 2 hours after fenoldopam probably was due to other mechanisms. A direct dopaminergic inhibition of tubular sodium reabsorption might also contribute. DA receptors have been identified in glomeruli and cortical and medullary tubules of the rat. Moreover, DA can produce natriuresis without concomitant changes in renal perfusion pressure, blood flow, GFR or even with reduced renal blood flow, thus suggesting a direct dopaminergic interaction with sodium reabsorption.

Free water clearance was increased transiently 40 minutes after fenoldopam dosing in both the normal and hypertensive subjects. Nevertheless, it is difficult to interpret changes in free water clearance in non-water-loaded subjects. Therefore, a theoretical contribution of medullary washout, antidiuretic hormone, or a direct inhibition of osmotic water flow in the distal nephron to the observed dissociation between water and sodium excretion following fenoldopam deserves clarification.

Based on previous observations, the administration of a substance with postsynaptic DA,-receptor agonism should reduce BP and produce a renal vasodilation and natriuresis. The present findings demonstrate that fenoldopam meets these characteristics in
generally accepted that the BP-lowering efficacy of fenoldopam in 10 hypertensive but not in five normotensive subjects complements previous data from animals.24 To investigate a possible prostaglandin-mediated action of fenoldopam, the present study also included observations after pretreatment with the cyclooxygenase inhibitor indomethacin in doses known to reduce renal prostaglandin synthesis in humans.25 The failure of this maneuver to blunt fenoldopam’s hypotensive, renal vasodilator, and natriuretic effects in our normal or hypertensive subjects complements previous data from animals,26 indicating that these actions are mediated by a prostaglandin-independent mechanism. In fact, DA and prostaglandin A1 can decrease renal vascular resistance through distinct pharmacological pathways.26

Whether and to what extent the dopaminergic system may be involved in essential hypertension is of pathogenic as well as therapeutic interest. Based on the report of a BP-lowering and tachycardic effect of fenoldopam in 10 hypertensive but not in five normotensive subjects, others postulated that essential hypertension is of pathogenic as well as therapeutic interest. Based on the report of a BP-lowering and tachycardic effect of fenoldopam in 10 hypertensive but not in five normotensive subjects, others postulated that essential hypertension is of

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