Effects of Short-Term Norepinephrine Infusion on Plasma Catecholamines, Renin, and Aldosterone in Normal and Hypertensive Man

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SUMMARY The acute responsiveness of plasma catecholamine, renin (PRA), and aldosterone levels to exogenous norepinephrine was studied under placebo conditions and following renin-angiotensin activation by diuretic pretreatment in 25 normal subjects and 34 patients with borderline-to-moderate essential hypertension. Norepinephrine infusion caused increases in plasma norepinephrine (PNE) that correlated with the infused norepinephrine dose (p < 0.001); this relationship was similar in normal and hypertensive subjects and unaltered by diuretic therapy. Plasma epinephrine and dopamine levels were unchanged during norepinephrine infusion. Norepinephrine infusion at pressor doses stimulated PRA (p < 0.01). The PRA responses correlated with the dose of infused norepinephrine (p < 0.0025), and norepinephrine-stimulated PRA correlated with basal PRA (p < 0.001). These norepinephrine-PRA relationships were unaltered by diuretic treatment and similar in normal and hypertensive subjects. In both groups, norepinephrine also caused a similar increase in plasma aldosterone (p < 0.05) under placebo conditions, but not following diuretic therapy. These findings demonstrate that an acute increase in the blood levels of the adrenergic neurotransmitter, norepinephrine, causes mild but distinct stimulation of plasma renin and aldosterone levels. Renin release in response to exogenous norepinephrine is not enhanced following renin-angiotensin activation by diuretic pretreatment. The responsiveness of the renin-angiotensin-aldosterone system to an acute norepinephrine input seems to be intact in essential hypertension. (Hypertension 2: 623–630, 1980)

KEY WORDS • norepinephrine infusion • plasma norepinephrine • plasma epinephrine • plasma dopamine • renin • aldosterone • essential hypertension

The adrenergic nervous system exerts a modulatory influence on the renin-angiotensin-aldosterone axis. Research in animals has shown that stimulation of the renal nerves or norepinephrine infusion increases renal renin secretion, and both norepinephrine and epinephrine augment renin release in vitro. In man, infusion of these catecholamines caused increases in plasma renin and aldosterone levels as well as aldosterone secretion rates.

It has been postulated that plasma renin levels in patients with essential hypertension are at least partly an index of adrenergic nervous activity. Although a close association between circulating catecholamines and renin has been reported by some investigators, others have found no such relationship. In hypertensive man, the dynamic regulatory links between catecholamines and the renin-angiotensin-aldosterone system have not been evaluated systematically. A previous study from this laboratory indicated that short-term adrenergic inhibition in patients with essential hypertension may cause an exaggerated reduction in plasma renin activity (PRA).

The present study was undertaken to investigate the effects of an acute increase in circulating norepinephrine on the blood levels of renin and aldosterone. Also, the relationship between norepinephrine infusion rates and plasma concentrations of norepinephrine (PNE), epinephrine, and dopamine was monitored. Since the activity of the renin-angiotensin-aldosterone axis and of the adrenergic nervous system may be influenced by age and sodium balance, normal and hypertensive study populations of similar age distribution and with comparable urinary sodium excretion rates were chosen. Finally, to extend the
observation range of basal activity of the renin-angiotensin-aldosterone system for this analysis, norepinephrine infusions were performed under placebo conditions as well as following renin stimulation by short-term diuretic treatment.

Subjects and Methods

Twenty-five normal subjects (20 males and five females, ranging in age from 20 to 63 years; mean, 41 ± 16 SD years) and 34 patients with borderline-to-moderate essential hypertension (25 males and nine females, ranging in age from 18 to 65 years; mean, 39 ± 16 years) were studied. The normal subjects were healthy volunteers with blood pressure (BP) values consistently below 140/90 mm Hg, and unfamiliar with laboratory environment or procedures. Fifteen patients had borderline hypertension as defined by intermittent BP values between 141/91 and 159/94 mm Hg and below. Nineteen patients had established essential hypertension as defined by an average BP greater than 160/95 mm Hg. Secondary hypertension was excluded by the usual tests. Hypertension was always benign, and no patient had congestive heart failure, ischemic coronary artery disease, arrhythmia, stroke, peripheral ischemic angiopathy, or relevant renal functional impairment (plasma creatinine > 1.3 mg/100 ml). All subjects were instructed to ingest a normal diet but without very salty foods or adding salt to their food. The present study was part of a larger protocol on BP regulation in normal or hypertensive subjects and on the effects of 6 weeks of diuretic treatment on BP-regulating factors. At first, both groups were given a placebo, one tablet every morning for 4 weeks.

The following procedures were carried out at the end of the placebo period. A 24-hour urine was collected for determination of sodium and potassium excretion rates. Following a 60-minute equilibration period with slow intravenous infusion of 5% glucose in water (6 ml/hr by constant infusion pump) in the supine subject, basal BP and heart rate were obtained. Blood samples were drawn through an indwelling intravenous cannula (placed 30 to 60 minutes previously) from the arm contralateral to the infusion, for determination of plasma sodium, potassium, PRA, aldosterone, PNE, epinephrine, and dopamine levels. These blood samples were collected between 8 and 10 a.m. The glucose infusion was then replaced by a solution of norepinephrine-bitartrate in 5% glucose. Utilizing various pump speeds and solutions with concentrations of norepinephrine base ranging from 16 to 30 μg/ml, the dose rate was titrated to reach two target levels of mean BP, namely, 10 to 15 (Step I) and 25 to 35 (Step II) mm Hg respectively, above the basal mean BP. Blood samples were obtained following 10 to 15 minutes of infusion at these two rates for determination of PRA, PNE, epinephrine, and dopamine levels; at the higher dose, plasma aldosterone was also measured.

Twenty-two normal subjects and 32 patients with hypertension were subsequently given a thiazide-like diuretic, acting on the cortical diluting segment of the distal renal tubule. Eleven normal subjects and 23 patients received chlorthalidone, one tablet (100 mg) every morning; 11 normal and nine hypertensive subjects received indapamide, one tablet (2.5 mg) every morning. All procedures performed under placebo conditions were repeated following 6 weeks of administration of the diuretics.

Blood pressure was recorded with the automatic recorder, Physiometric SR 2, and each record was the mean of at least five measurements. Mean BP was calculated as the sum of the diastolic and one-third of the pulse pressure. Sodium and potassium were measured by flame photometer; PRA and aldosterone by radioimmunoassay. Levels of PNE, epinephrine, and dopamine were determined by the radioenzymatic method of Da Prada and Zürcher; this highly sensitive procedure allows such low quantities of the catecholamines to be detected as 1 to 5 pg. Mean coefficients of intraassay variations for 110 unselected consecutive determinations in our laboratory were 9.8 ± 6.5% for PNE, 12.5 ± 9.4% for plasma epinephrine, and 12.2 ± 8.8% for plasma dopamine; the coefficient of interassay variation for control plasma was 2% for PNE, 2.5% for plasma epinephrine, and 5.2% for plasma dopamine. The counts of the blanks averaged 41 ± 25 cpm for PNE, 34 ± 18 cpm for plasma epinephrine, and 158 ± 64 cpm for plasma dopamine.

Since natural logarithm transformation rather than absolute values followed a gaussian distribution, the natural logarithm transformation of PRA, plasma aldosterone, catecholamines, or dose of infused norepinephrine was used for t test or regression analysis.

Results

Studies under Placebo Conditions

At the end of the 4-week placebo period, there was no significant difference between normal and hypertensive subjects in mean plasma potassium, PRA, aldosterone, PNE, and dopamine levels (table I); plasma sodium (137.5 ± 2.0 SD vs 137.8 ± 2.1 mEq/liter), and urinary sodium (134 ± 56 vs 138 ± 57 mEq/24 hr) and potassium (64 ± 23 vs 57 ± 25 mEq/24 hr) excretion rates were also comparable between the two groups. Mean plasma epinephrine concentration tended to be slightly higher in the hypertensive patients.

The norepinephrine dose rate required to elevate the mean BP to the two determined target levels (Step I and Step II, see Method section) tended to be slightly lower in the patients (table I). However, with the dosages used, increases in mean BP were comparable between the two groups at infusion Step I (+ 13 vs + 13 mm Hg) or Step II (+ 28 vs + 27 mm Hg).

Norepinephrine infusion caused very marked increases in PNE (table I). The PNE measured during
Norepinephrine infusion at the higher dose rate caused a significant increase in PRA in normal and hypertensive subjects. In both groups, percentile increases in PRA correlated significantly with norepinephrine dosage ($r = 0.47$ and $0.38$ respectively; $p < 0.0025$) or with the associated changes in PNE ($r = 0.57$, $p < 0.0025$; and $r = 0.33$, $p < 0.01$). Moreover, norepinephrine-stimulated PRA correlated ($p < 0.001$) even better with basal (preinfusion) PRA; this relationship was again comparable in normal and hypertensive subjects (fig. 2).

The infusion correlated significantly with the norepinephrine dose in both groups, and the slope of this relationship was similar in normal and hypertensive subjects (fig. 1). Plasma epinephrine was unchanged during norepinephrine infusion at medium and high pressor doses. Values obtained for plasma dopamine tended to be increased slightly following norepinephrine infusion, but this was probably due to a 0.8% cross-reactivity with norepinephrine. When corrected for this cross-reactivity, true plasma dopamine concentrations appeared to be unchanged during norepinephrine infusion (table 1).

### Table 1. Clinical and Biochemical Parameters Under Placebo Conditions and During Norepinephrine Infusion in Normal and Hypertensive Subjects (mean ± 80)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Preinfusion</th>
<th>Norepinephrine infusion</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Step I</td>
</tr>
<tr>
<td>Norepinephrine dose (ng/kg/min)</td>
<td>N</td>
<td>84 ± 43</td>
</tr>
<tr>
<td></td>
<td>H</td>
<td>66 ± 48</td>
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<tr>
<td>Body weight (kg)</td>
<td>N</td>
<td>68.7 ± 10.0</td>
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<tr>
<td></td>
<td>H</td>
<td>76.5 ± 11.5</td>
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<tr>
<td>Blood pressure (mm Hg)</td>
<td>N</td>
<td>119/73 ± 12.7</td>
</tr>
<tr>
<td></td>
<td>H</td>
<td>144/91 ± 25/12</td>
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<tr>
<td>Heart rate (beats/min)</td>
<td>N</td>
<td>66 ± 11</td>
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<tr>
<td></td>
<td>H</td>
<td>67 ± 10</td>
</tr>
<tr>
<td>Plasma potassium (mEq/liter)</td>
<td>N</td>
<td>4.1 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>H</td>
<td>3.9 ± 0.3</td>
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<tr>
<td>Plasma renin activity (ng/ml/hr)</td>
<td>N</td>
<td>1.78 ± 1.2</td>
</tr>
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<td></td>
<td>H</td>
<td>1.34 ± 0.92</td>
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<tr>
<td>Plasma aldosterone (ng/100 ml)</td>
<td>N</td>
<td>4.3 ± 2.6</td>
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<tr>
<td></td>
<td>H</td>
<td>4.7 ± 3.3</td>
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<tr>
<td>Plasma norepinephrine (ng/100 ml)</td>
<td>N</td>
<td>23.0 ± 8.6</td>
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<td></td>
<td>H</td>
<td>23.8 ± 11.5</td>
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<tr>
<td>Plasma epinephrine (ng/100 ml)</td>
<td>N</td>
<td>3.1 ± 2.1</td>
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<td></td>
<td>H</td>
<td>4.5 ± 2.8**</td>
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<tr>
<td>Plasma dopamine (ng/100 ml)</td>
<td>N*</td>
<td>5.2 ± 2.9</td>
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<tr>
<td></td>
<td>H†</td>
<td>7.3 ± 2.2</td>
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<tr>
<td></td>
<td>— measured</td>
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<tr>
<td></td>
<td>— corrected for cross-reactivity with norepinephrine</td>
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</tr>
</tbody>
</table>

*13 normal subjects.
†22 patients.
§Significant difference at $p < 0.05$ vs corresponding preinfusion value.
†Significant difference at $p < 0.01$ vs corresponding preinfusion value.
## Abbreviations: N = normal subjects; H = hypertensive patients.
Separate analysis of the patients with borderline or established hypertension revealed that PNE and PRA levels under basal conditions as well as during norepinephrine infusion were comparable between the two subgroups (table 2). Plasma epinephrine or dopamine values were also comparable.

Plasma aldosterone was increased significantly by norepinephrine infusion (table 1), and the mean increase was comparable in normal and hypertensive subjects (+87% vs +73%). The degree of aldosterone stimulation was not significantly correlated with norepinephrine dosage (r = 0.04 and 0.16 respectively), with associated changes in PNE (r = 0.09 and 0.26) or PRA (r = 0.20 and 0.08) in both normal or hypertensive subjects. Plasma aldosterone concentration at the end of the infusion was significantly correlated with preinfusion aldosterone levels in hypertensive patients (r = 0.75, p < 0.001), but not in normal subjects (r = 0.06).

Studies Following Administration of a Diuretic

Administration of either chlorthalidone or indapamide had similar clinical and biochemical effects; therefore, results were analyzed jointly. Compared to placebo conditions, basal PRA and aldosterone levels measured following 6 weeks of diuretic treatment were markedly increased (p < 0.005); BP was decreased (p < 0.01) in the hypertensive group, but not in normal subjects. Diuretic-treated normal and hypertensive subjects did not differ significantly in their mean PRA, plasma potassium (table 3), or sodium (137 ± 2 vs 137 ± 2 mEq/liter) levels, or urinary potassium (75 ± 24 vs 67 ± 20 mEq/24 hr) or sodium (158 ± 73 vs 166 ± 61 mEq/24 hr) excretion rates.

Mean PNE, epinephrine, and dopamine levels tended to be slightly higher (p < 0.0025) and plasma aldosterone slightly lower (p < 0.025) in the hypertensive patients (table 3). Mean norepinephrine doses required to elevate the mean BP to the two defined target levels (Step I and Step II) were comparable in both study groups. With the dosages used, increases in mean BP were equal in the two groups at infusion Step I (+13 mm Hg) or Step II (+27 mm Hg).

Norepinephrine infusion following diuretic treatment caused large increases in PNE. The PNE during norepinephrine infusion was significantly correlated with the norepinephrine infusion rate, and the slope of this relationship was again similar in normal and hypertensive subjects (fig. 1). Plasma epinephrine was unchanged during norepinephrine infusion at medium and high pressor doses in diuretic-treated normal and hypertensive subjects; plasma dopamine corrected for norepinephrine cross-reactivity was also unchanged (table 3).

Norepinephrine infusion following diuretic treatment caused a significant increase in PRA in both normal and hypertensive subjects. Percentile PRA stimulation correlated significantly with norepinephrine dose (r = 0.52 and 0.60 respectively; p < 0.0025) or with the associated changes in PNE (r = 0.29; p < 0.05; and r = 0.50; p < 0.001). Norepinephrine-stimulated PRA (measured at higher infusion rates) correlated also positively (p < 0.001) with basal (preinfusion) PRA. This relationship was again comparable in normal and hypertensive subjects (fig. 2).

Plasma aldosterone was not significantly changed during norepinephrine infusion at high pressor doses in diuretic-treated normal or hypertensive subjects.
TABLE 2. Biochemical Parameters Under Placebo Conditions and During Norepinephrine Infusion in Patients with Borderline or Established Essential Hypertension (mean ± SD)

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<th>Preinfusion</th>
<th>Norepinephrine infusion</th>
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<tbody>
<tr>
<td></td>
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<td>Step I</td>
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<tr>
<td>Norepinephrine dose</td>
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<tr>
<td>(ng/kg/min)</td>
<td>B</td>
<td>67 ± 34</td>
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<tr>
<td></td>
<td>E</td>
<td>52 ± 37</td>
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<tr>
<td>Plasma renin activity</td>
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<tr>
<td>(ng/ml/hr)</td>
<td>B</td>
<td>1.33 ± 0.85</td>
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<tr>
<td></td>
<td>E</td>
<td>1.36 ± 0.99</td>
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<tr>
<td>Plasma norepinephrine</td>
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<tr>
<td>(ng/100 ml)</td>
<td>B</td>
<td>22.7 ± 10.0</td>
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<tr>
<td></td>
<td>E</td>
<td>24.8 ± 12.8</td>
</tr>
</tbody>
</table>

*Significant difference at p < 0.02 vs corresponding preinfusion value.
†Significant difference at p < 0.002 vs corresponding preinfusion value.
Abbreviations: B = borderline hypertension; E = established hypertension.

TABLE 3. Clinical and Biochemical Parameters Before and During Norepinephrine Infusion in Normal and Hypertensive Subjects Studied Following Diuretic Pretreatment (mean ± SD)

<table>
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<th>Preinfusion</th>
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<tr>
<td></td>
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<td>Step I</td>
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<tr>
<td>Norepinephrine dose</td>
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<tr>
<td>(ng/kg/min)</td>
<td>N</td>
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<tr>
<td>Body weight (kg)</td>
<td>N</td>
<td>69.8 ± 9.9</td>
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<td></td>
<td>H</td>
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<tr>
<td>Blood pressure (mm Hg)</td>
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<td>119/73 ± 13/8</td>
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<td></td>
<td>H</td>
<td>128/81 ± 17/9</td>
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<td></td>
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<td>158/93 ± 19/10</td>
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<td>Heart rate (beats/min)</td>
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<td>65 = 9</td>
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<td>66 = 11</td>
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<tr>
<td></td>
<td></td>
<td>58 = 10§</td>
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<tr>
<td>Plasma potassium (mEq/liter)</td>
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<td></td>
<td>H</td>
<td>3.2 ± 0.4</td>
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<tr>
<td>Plasma renin activity</td>
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<tr>
<td>(ng/ml/hr)</td>
<td>N</td>
<td>4.44 ± 3.62</td>
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<td>H</td>
<td>4.90 ± 3.13</td>
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<td></td>
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<td>7.97 ± 7.02§</td>
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<td>Plasma aldosterone (ng/100 ml)</td>
<td>N</td>
<td>11.2 ± 6.4</td>
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<td></td>
<td>H</td>
<td>7.0 ± 3.7**</td>
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<td></td>
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<td>12.9 ± 8.4</td>
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<tr>
<td>Plasma norepinephrine</td>
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<tr>
<td>(ng/100 ml)</td>
<td>N</td>
<td>20.4 ± 10.2</td>
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<td></td>
<td>H</td>
<td>29.2 ± 11.5**</td>
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<td></td>
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<td>328 ± 208‡</td>
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<td>Plasma epinephrine (ng/100 ml)</td>
<td>N</td>
<td>2.3 ± 1.6</td>
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<tr>
<td></td>
<td>H</td>
<td>4.2 ± 2.6**</td>
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<td></td>
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<td>2.9 ± 1.9</td>
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<td>Plasma dopamine (ng/100 ml)</td>
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<tr>
<td></td>
<td>N†</td>
<td>8.8 ± 4.7**</td>
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<td></td>
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<td>7.0 ± 3.9</td>
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<tr>
<td></td>
<td>corrected for cross-reactivity with norepinephrine</td>
<td>5.5 ± 2.0</td>
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<tr>
<td></td>
<td>N†</td>
<td>8.8 ± 4.7**</td>
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<td></td>
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<td>6.8 ± 5.4</td>
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</table>

*Significant difference at p < 0.05 vs corresponding preinfusion value.
†Significant difference at p < 0.01 vs corresponding preinfusion value.
‡Significant difference at p < 0.005 vs corresponding preinfusion value.
**Significant difference at p < 0.01 vs preinfusion value in normal subjects.
Abbreviations: N = normal subjects; H = hypertensive patients.

*13 normal subjects.
†22 patients.
‡Significant difference at p < 0.05 vs corresponding preinfusion value.
§Significant difference at p < 0.01 vs corresponding preinfusion value.
¶Significant difference at p < 0.005 vs corresponding preinfusion value.
||Significant difference at p < 0.01 vs preinfusion value in normal subjects.
Abbreviations: N = normal subjects; H = hypertensive patients.
Discussion

Basal PNE concentrations obtained under placebo conditions were comparable between our normal subjects and patients with essential hypertension, who had also a comparable mean age and urinary sodium excretion. This is consistent with previous reports of normal age-adjusted PNE levels in essential hypertension, both in the supine and upright body positions. Moreover, infusion of 1-norepinephrine bitartrate caused a similar increase in PNE concentrations in our normal and hypertensive populations, and this relationship between PNE and infused dose was not altered following short-term administration of a diuretic agent. The kinetics and the metabolism of infused norepinephrine may differ from those of norepinephrine released at the nerve terminals. However, since isolated activation of the noradrenergic component of the sympathetic nervous system may be difficult to achieve under clinical conditions, the model of intravenous norepinephrine infusion was used to evaluate possible effects of the neurotransmitter. The observation of similar dose-related increases in PNE concentrations during norepinephrine infusion in our normal subjects and patients with either borderline or established hypertension provided the necessary basis to compare other effects of norepinephrine among these populations.

Plasma dopamine concentrations were not significantly altered during norepinephrine infusion. This and several previous observations support the concept that peripheral adrenergic nervous activity exerts no major acute influence on plasma or urinary dopamine levels. Thus, both PNE and dopamine are increased concomitantly in response to sodium depletion, but several other conditions such as upright posture, isometric or treadmill exercise, or exposure to cold are associated with elevated sympathetic activity while blood levels of dopamine remain unchanged. Moreover, the response of urinary dopamine excretion to orthostasis and changes in salt intake is discordant with that of plasma and urinary norepinephrine, suggesting an inverse relationship between the sympathetic nervous system and the dopaminergic axis at the renal level. Plasma epinephrine was unchanged during norepinephrine infusion in both study groups and under placebo conditions as well as following diuretic administration. This is consistent with the apparent independence of adrenomedullary epinephrine release during several physiological conditions with increased sympathetic activity.

Acute elevation of circulating norepinephrine from basal values of about 23 ng/100 ml to mean levels of 140 to 180 ng/100 ml had no effect on PRA. However, a further marked increase of PNE to mean concentrations of 325 to 424 ng/100 ml caused significant renin stimulation in both our normal subjects and patients with essential hypertension ($p < 0.01$ and $p < 0.005$ respectively). Moreover, the norepinephrine-induced increases in PRA were comparable in borderline and established hypertensive subjects. Activation of renin release by norepinephrine has been noted previously in experimental animals and in vitro. Adrenergic renin stimulation is thought to be mediated at least in part by beta-receptor activation. Alpha-receptors may also participate, but whether they transmit an inhibitory or a stimulatory signal on renin release is not entirely clear. Moreover, a norepinephrine-infusion in vivo could also influence renin release indirectly through an effect on renal circulation. Our studies in normal or hypertensive subjects do not allow us to specify the exact mechanism of norepinephrine-induced renin stimulation. Intravenous infusions of norepinephrine at pressor doses in a small group of patients with essential hypertension caused renin stimulation in subjects with normal basal PRA, but not in those with low renin hypertension. Our findings under placebo conditions and following diuretic administration suggest that, over a wide range of activity of the renin-angiotensin system, renin release in response to exogenous norepinephrine is closely related to the basal level of PRA and also related to the dose and corresponding plasma concentrations of norepinephrine.

The responsiveness of renin release to an acute increase in circulating norepinephrine appears to be generally intact in patients with either borderline or established essential hypertension. This conclusion is supported by the observation of similar relationships between norepinephrine-stimulated PRA and basal PRA, and between norepinephrine-induced changes in PRA and norepinephrine dose or PNE concentrations in our normal and hypertensive study groups. Since PRA responses to upright posture or chronic diuretic treatment as well as renin suppression by intravenously infused angiotensin II were also comparable between age-matched normal and hypertensive patients, regulation of renin secretion under several conditions appears to be intact in essential hypertension. Nevertheless, renin responsiveness to acute diuretic administration may be blunted in established essential hypertension.

Considering the massive increase in circulating PNE (14- to 18-fold) required to cause a significant increase in PRA, one could extrapolate that acute fluctuations of sympathetic nervous activity may exert only a weak modulating influence on renin control. The finding of normal PRA in patients with primarily norepinephrine producing pheochromocytoma is consistent with this conclusion. Moreover, elevation of basal activity of the renin-angiotensin system by pretreatment with a diuretic failed to enhance renin release in response to exogenous norepinephrine in our normal or hypertensive subjects. It may be speculated that the weak norepinephrine-renin interaction could be due in part to a limited affinity of the neurotransmitter to the renin-stimulating beta-receptor system. Nevertheless, our observations may underestimate somewhat the acute renin responsiveness to norepinephrine, since it must be assumed
that part of the intravenously infused catecholamine

did not reach the synaptic cleft, and the pressor
response to norepinephrine may have attenuated beta-
receptor-mediated renin stimulation by activating the
renal baroreceptors.31

It appears possible that renin-norepinephrine inter-
relationships in the chronic state may differ from
those under acute conditions. Certain reports of a
close positive correlation between plasma renin and
norepinephrine or total catecholamine levels in essen-
tial hypertension6,9 could not be confirmed by other
investigators.10,11 In fact, the existence of such a
relationship in unselected normal and hypertensive
populations would be surprising since PNE tends to
increase while renin levels decrease with the progres-
sive age of the subjects.12,34,35 However, a re-
cent study from our laboratory pointed to an altered
relationship between sympathetic nervous activity and
PRA in established hypertension; observations follow-
ing adrenergic inhibition suggested that PRA-depen-
dence on a given sympathetic input may be ex-
gaggerated in patients with essential hypertension as
compared to normal subjects.19

Plasma aldosterone concentrations measured under
placebo conditions were also increased significantly
following norepinephrine infusion, and the response of
the mineralocorticoid was again comparable in our
normal and hypertensive subjects. This differs from
previous experience, from which 24-hour aldosterone
secretion rates obtained by urine analysis with iso trope
dilution methodology were reported to be unchanged
or even decreased by norepinephrine infusion in some
normal and hypertensive men.39 Others noted in-
creases in blood levels or secretion rates of aldosterone
following the combined stimulus on norepinephrine
and epinephrine.44 Angiotensin II being the major
regulator of aldosterone secretion,6 it is probable that
aldosterone activation in our subjects was at least
partly due to the concomitant increase in PRA. Nev-
evertheless, the absence of a significant correlation be-
tween norepinephrine-induced increases in PRA and
those in plasma aldosterone suggest that addi-
tional factors may be involved. There is no evidence
for a direct action of the neurotransmitter
norepinephrine on aldosterone secretion.41 However,
variations in plasma potassium during norepinephrine
infusions42 could per se modulate aldosterone regula-
tion.49 Moreover, it is possible that the hypokalemia occurring following diuretic
may have interfered, at least in part, with
norepinephrine-renin-mediated aldosterone stimula-
tion under this condition.

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