Cardiovascular Counterregulation During Sympathetic Inhibition in Normal Subjects and Patients with Mild Hypertension

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SUMMARY The influence of agents that inhibit sympathetic nerve activity on cardiovascular responsiveness as related to major pressor factors has been unclear. Therefore, these components were evaluated in 11 normal subjects and 13 patients with mild essential hypertension before and after 4 weeks of sympathetic neuron blockade with the agent debrisoquine. In these normal and mildly hypertensive subjects, sympathetic neuron blockade caused approximately similar decreases in urinary and supine or upright plasma norepinephrine (NE) levels (average changes in the two groups, −41% and −45%, respectively; p < 0.05 to < 0.005), the chronotropic dose of isoproterenol (−45% and −38%), and the NE pressor dose (−47% and −51%, p < 0.01), while the relationship between NE-induced changes in blood pressure and concomitant plasma NE concentrations was displaced to the left (p < 0.01). Supine heart rate was also lowered (−10% and −8%, p < 0.05). Compared to the orthostatic variations during placebo conditions, mild postural decreases in blood pressure were apparent in both the normal and hypertensive groups (−8% and −7.5%). However, supine blood pressure was unchanged following debrisoquine treatment. Other parameters were also not consistently changed, such as total blood volume, exchangeable body sodium, urinary electrolytes, plasma epinephrine, renin, and angiotensin II (All) levels, the pressor dose of infused All, and the relationship between All-induced changes in blood pressure and plasma All measured before and during All infusion. These findings demonstrate that the reduction in sympathetic outflow during sympathetic neuron blockade may elicit a hyperresponsiveness of alpha- and beta-adrenergic receptors that is equal in normal subjects and patients with mild essential hypertension.

(Hypertension 5: 873-880, 1983)

Key Words. • sympathetic nervous system • sympathetic inhibition • blood pressure regulation • norepinephrine • renin • angiotensin II • cardiovascular pressor responsiveness • cardiac beta-receptor response

The arterial blood pressure is determined both by the absolute quantities of pressor factors and by cardiovascular responsiveness. In normal humans, the pressor effects of norepinephrine (NE) and angiotensin II (All) correlate inversely with their preexisting blood levels, 1-3 and this may contribute to blood pressure homeostasis. However, cardiovascular NE responsiveness tends to be exaggerated relative to plasma NE concentrations in normotensive offspring of hypertensive families4 and patients with borderline5 or established2,3,6 essential hypertension. Moreover, diuretic treatment had no influence on this relationship in normal subjects, but reduced the abnormal NE responsiveness, without causing an equivalent increase in circulating NE, in essential hypertension.7,8

The various sympatholytic drugs that also are widely used for antihypertensive pharmacotherapy are well defined with regard to their primary effect, which is either a reduced sympathetic outflow or blockade of postsynaptic adrenergic receptors. However, their influence on the plasma NE concentration-responsiveness relationship has not been evaluated. Studies limited to either one of the components are difficult to interpret. In considering agents that may inhibit adrenergic activity, the sympathetic neuron inhibitor, guanethidine, and methyldopa were found to increase the vascular NE reactivity in the experimental animal9,10 or in human essential hypertension.11 The effect of guanethidine could be due in part to receptor denervation.12 Debrisoquine, another sympathetic neuron in-
hibitor, is devoid of such a neurotoxic influence. Therefore, short-term treatment with debrisoquine was chosen as a model to assess the relationship between some important pressor factors and cardiovascular responsiveness before and during a state with reduced sympathetic outflow in normal subjects and patients with mild essential hypertension.

**Subjects and Methods**

We studied 11 normal subjects (five women and six men, aged 24 to 62 years; mean age, 39 ± 15 years) and 13 with mild essential hypertension (three women and 10 men, aged 21 to 65 years; mean age, 44 ± 16 years). The normal subjects were healthy volunteers with a blood pressure consistently below 140/90 mm Hg. The presence of mild hypertension was defined by repeated blood pressure measurements between 140/90 and 170/105 mm Hg under outpatient conditions. Secondary forms of hypertension were excluded by the usual tests; no patient had malignant phase hypertension (hypertensive retinopathy Stage III-IV), edema, or heart failure. Where given previously, antihypertensive drugs and potassium supplements were discontinued for at least 4 weeks before study. No woman was on hormonal contraceptives.

The subjects, who had given their informed consent to the study, were instructed to eat a normal diet, avoiding very high or low sodium intakes. Initially, a placebo, two tablets daily, was given for 2 weeks. The placebo was then replaced by active debrisoquine, given in two daily doses during 4 weeks at weekly increasing doses; during the last treatment week, mean doses were 45 ± 5 mg/day in the normal and 52 ± 15 mg/day in the hypertensive subjects. These doses were previously found to reduce plasma NE by about 50%.

At the end of the placebo and debrisoquine treatment phases, the following measurements were made. After the collection of a 24-hour urine sample for determination of sodium, potassium, creatinine, NE, and epinephrine excretion rates, blood pressure, heart rate, exchangeable sodium, blood volume, plasma sodium, potassium, creatinine, renin activity. NE and epinephrine levels were determined in the morning after an overnight fast and after 1 hour of recumbency, according to our standard procedure. Blood pressure, heart rate, plasma renin activity, NE and epinephrine levels were measured again after 1 hour of walking. Thereafter, the patients emptied their bladder and rested in the supine position. A 5% dextrose solution was infused during 20 minutes, and an isoproterenol sensitivity test was performed with bolus injections of 0.2, 0.4, 0.8, 1.6 μg, and when the increase in heart rate did not reach 25 bpm, bolus injections of 3.2 and 6.4 μg isoproterenol hydrochloride, as described previously. One to 3 days later, NE and All were infused intravenously as described previously from this laboratory. After overnight fasting and an equilibration period with slow intravenous infusion of 5% dextrose in the supine position (6 ml/hr), basal blood pressure and heart rate were measured. Blood samples were drawn from the arm contralateral to the infusion through an indwelling intravenous cannula (inserted 30 to 60 minutes previously) for determination of plasma renin activity, NE, and epinephrine levels. These basal samples were collected between 0830 and 0930 hours. The dextrose solution was then replaced by an infusion of 1-NE bitartrate in 5% dextrose, which was infused at stepwise increasing dose rates of approximately 20, 40, and 100 ng/kg body weight/min and, when the NE-induced increase in mean blood pressure did not reach 20 mm Hg, at a rate of 200 ng/kg/min, during 20 minutes each. During the last 10 minutes of each infusion step, blood pressure and heart rate were recorded every minute. At the end of each infusion step, blood was drawn from the arm contralateral to the infusion for determination of plasma norepinephrine.

The NE solution was then replaced by 5% dextrose, which was infused during 45 to 50 minutes at a constant rate. At the end of this second equilibration period, basal blood pressure and heart rate were measured, and blood was drawn for determination of plasma renin and All levels. The dextrose infusion was then replaced by a solution of All (Hypertensin) in 5% dextrose, which was infused at increasing dose rates of approximately 2, 4, and 10 ng/kg/min and, when the All-induced increase in diastolic blood pressure did not reach 20 mm Hg, at a rate of 20 ng/kg/min, during 20 minutes each. Blood pressure and heart rate were monitored as described above; at the end of each All infusion step, blood was collected for determination of plasma All levels.

Blood pressure was measured with standard cuff and sphygmomanometer; the mean of three readings was used for analysis. During the infusion studies, blood pressure was monitored with the automatic recorder, Physiometrics SR 2; the mean of eight to 10 measurements was used for analysis. Mean arterial pressure was calculated as the sum of the diastolic and one-third of the pulse pressure. During the isoproterenol sensitivity test, heart rate was monitored by electrocardiography; the resting (preinfusion) heart rate was calculated as the mean resting rate from 10 R-R intervals. The heart rate after isoproterenol injection was calculated from the three shortest R-R intervals after injection. Plasma and urinary sodium and potassium concentrations were measured by flame photometer, creatinine by autoanalyzer, plasma renin and All by radioimmunoassay, and plasma and urinary NE and epinephrine concentrations by a radioenzymatic method. Cardiovascular responsiveness was analyzed as follows. Increases in mean blood pressure (NE infusion) or diastolic blood pressure (All infusion) were related to blood levels of NE or All respectively, obtained before and during the infusions. Pressor doses of infused NE or All were calculated from dose-response curves relating mean (NE infusion) or diastolic (All infusion) blood pressure to infused dose rates. The chronotropic isoproterenol dose was derived from the dose response curve relating heart rate to the isoproterenol dose; it was defined as the dose causing an increase in heart rate of 25 bpm.
Since natural logarithmic transformation rather than absolute values followed a Gaussian distribution, for statistical analysis we used the natural logarithmic transformation of plasma renin activity, AIr, and NE levels, doses of infused NE, AIr or isoproterenol, pressor doses of NE or AIr, and chronotropic doses of isoproterenol. Statistical analysis included paired and unpaired (two-tailed) Student t test, regression analysis, and analysis of variance and covariance.

**Results**

**Blood Pressure, Heart Rate, and Some Biochemical and Pressor Factors Before and After Debrisoquine Treatment**

Under placebo conditions, the measured parameters did not differ significantly between the normal and mildly hypertensive groups, except for the higher blood pressure in the latter. After treatment with debrisoquine, supine blood pressure was not consistently altered in both groups (table 1). The upright blood pressure was decreased significantly in the patients, and this tendency was also noted in the normal subjects. Moreover, compared to orthostatic variations in blood pressure under placebo conditions, the percentage of postural decreases in the normal and hypertensive groups were of similar magnitude (-8% and -7.5%, respectively). Supine heart rate was decreased significantly, and a similar tendency was noted for upright heart rate. Plasma and urinary NE levels also were reduced significantly and similarly in the two groups; epinephrine values were not consistently altered. Supine plasma renin activity was not significantly changed during debrisoquine treatment, but the postural rise tended to be slightly enhanced. Body weight, exchangeable sodium, blood volume, plasma and urinary sodium and potassium, and plasma creatinine levels were not significantly changed in the debrisoquine-treated normal or mildly hypertensive subjects.

**Isoproterenol Testing**

Under placebo conditions, the response of heart rate to isoproterenol bolus injections was similar in the normal and mildly hypertensive groups, as judged by the mean chronotropic dose (heart rate + 25 bpm, table 2) and the slope of the dose-response curves relating the isoproterenol-induced changes in heart rate to isoproterenol dose (10 ± 4 and 9 ± 3, respectively). During debrisoquine treatment, the mean chronotropic dose was significantly reduced in both groups, and the slope of the dose-response curves was also significantly altered.

**Table 1. Blood Pressure and Pressor Factors after Placebo or Debrisoquine in Normal and Mildly Hypertensive Subjects (means ± sd)**

<table>
<thead>
<tr>
<th>Normal subjects</th>
<th>Debrisoquine</th>
<th>Placebo</th>
<th>Debrisoquine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine (mm Hg)</td>
<td>110/79 ±11/9</td>
<td>116/74 ±10/11</td>
<td>120/79 ±11/9</td>
</tr>
<tr>
<td>Upright (mm Hg)</td>
<td>110/80 ±13/9</td>
<td>104/79 ±7/10</td>
<td>135/100 ±11/8</td>
</tr>
<tr>
<td>Heart rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine (bpm)</td>
<td>61 ± 9</td>
<td>55 ± 7†</td>
<td>68 ± 7</td>
</tr>
<tr>
<td>Upright (bpm)</td>
<td>85 ± 10</td>
<td>80 ± 15</td>
<td>87 ± 14</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>70.7 ± 9.9</td>
<td>70.7 ± 9.9</td>
<td>77.4 ± 15.1</td>
</tr>
<tr>
<td>Plasma concentrations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.9 ± 0.1</td>
<td>0.9 ± 0.1</td>
<td>1.0 ± 0.1</td>
</tr>
<tr>
<td>Sodium (mmol/liter)</td>
<td>140 ± 2</td>
<td>140 ± 2</td>
<td>130 ± 3</td>
</tr>
<tr>
<td>Potassium (mmol/liter)</td>
<td>4.4 ± 0.5</td>
<td>4.3 ± 0.3</td>
<td>4.2 ± 0.3</td>
</tr>
<tr>
<td>Renin activity supine (ng/ml/hr)</td>
<td>0.8 ± 0.6</td>
<td>0.7 ± 0.5</td>
<td>0.8 ± 0.5</td>
</tr>
<tr>
<td>Renin activity upright (ng/ml/hr)</td>
<td>2.1 ± 1.3</td>
<td>3.8 ± 3.1†</td>
<td>2.0 ± 1.7</td>
</tr>
<tr>
<td>Norepinephrine supine (ng/dl)</td>
<td>24.9 ± 12.4</td>
<td>12.7 ± 4.8‡</td>
<td>23.2 ± 6.4</td>
</tr>
<tr>
<td>Norepinephrine upright (ng/dl)</td>
<td>54.8 ± 17.2</td>
<td>31.3 ± 10.1‡</td>
<td>30.4 ± 17.7</td>
</tr>
<tr>
<td>Epinephrine supine (ng/dl)</td>
<td>2.5 ± 3.1</td>
<td>3.5 ± 3.6</td>
<td>3.4 ± 2.0</td>
</tr>
<tr>
<td>Epinephrine upright (ng/dl)</td>
<td>5.7 ± 3.8</td>
<td>4.9 ± 2.0</td>
<td>9.3 ± 6.2</td>
</tr>
<tr>
<td>Blood volume (ml)</td>
<td>4483 ± 1121</td>
<td>4519 ± 1083</td>
<td>4475 ± 822</td>
</tr>
<tr>
<td>Exchangeable sodium (mmol)</td>
<td>2804 ± 422</td>
<td>2955 ± 448</td>
<td>3011 ± 598</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min/1.73 m²)</td>
<td>97 ± 23</td>
<td>82 ± 18</td>
<td>77 ± 14</td>
</tr>
<tr>
<td>Urinary excretion rates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium (mmol/24 hr)</td>
<td>164 ± 58</td>
<td>153 ± 66</td>
<td>177 ± 58</td>
</tr>
<tr>
<td>Potassium (mmol/24 hr)</td>
<td>84 ± 25</td>
<td>77 ± 29</td>
<td>77 ± 17</td>
</tr>
<tr>
<td>Norepinephrine (ng/24 hr)</td>
<td>3390 ± 1484</td>
<td>2436 ± 1687*</td>
<td>5230 ± 3662</td>
</tr>
<tr>
<td>Epinephrine (ng/24 hr)</td>
<td>1326 ± 922</td>
<td>1287 ± 1369</td>
<td>1327 ± 814</td>
</tr>
</tbody>
</table>

* p < 0.05 vs corresponding value under placebo conditions.
† p < 0.01 vs corresponding value under placebo conditions.
‡ p < 0.005 vs corresponding value under placebo conditions.
TABLE 2. Infusion Studies after Placebo or Debrisoquine in Normal and Mildly Hypertensive Subjects (means ± SD)

<table>
<thead>
<tr>
<th>Infusion</th>
<th>Normal subjects</th>
<th></th>
<th>Mild hypertension</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Debrisoquine</td>
<td>Placebo</td>
<td>Debrisoquine</td>
</tr>
<tr>
<td>Isoprenaline</td>
<td>2.11 ± 2.05</td>
<td>1.17 ± 0.53</td>
<td>2.43 ± 2.47</td>
<td>1.52 ± 1.3</td>
</tr>
<tr>
<td>Chronotropic dose (μg)</td>
<td>22.1 ± 10.0</td>
<td>13.1 ± 7.2*</td>
<td>23.9 ± 13.4</td>
<td>11.5 ± 8.6*</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>129 ± 68</td>
<td>55 ± 20*</td>
<td>102 ± 65</td>
<td>50 ± 49*</td>
</tr>
<tr>
<td>Preinfusion plasma norepinephrine (ng/dl)</td>
<td>12 ± 3</td>
<td>10 ± 2</td>
<td>16 ± 7</td>
<td>14 ± 5</td>
</tr>
<tr>
<td>Pressor dose (ng/kg/min)</td>
<td>7.4 ± 5.4</td>
<td>8.1 ± 4.9</td>
<td>8.3 ± 3.1</td>
<td>5.7 ± 3.0</td>
</tr>
<tr>
<td>Angiotensin II</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preinfusion plasma angiotensin II (pg/ml)</td>
<td>12 ± 3</td>
<td>10 ± 2</td>
<td>16 ± 7</td>
<td>14 ± 5</td>
</tr>
<tr>
<td>Pressor dose (ng/kg/min)</td>
<td>7.4 ± 5.4</td>
<td>8.1 ± 4.9</td>
<td>8.3 ± 3.1</td>
<td>5.7 ± 3.0</td>
</tr>
</tbody>
</table>

*p < 0.01 vs corresponding value under placebo conditions.

The slope of the dose-response curve was unaltered.

Norepinephrine Infusion

Under placebo conditions, basal (pre-NE infusion) plasma NE levels (table 2), and the slope of the NE infusion rate-pressor response curve (12 ± 4 in normal and 15 ± 8 in hypertensive subjects) did not differ between the two groups. The NE pressor dose tended to be lower in the mildly hypertensive group, but with the number of subjects studied this difference did not reach statistical significance. The maximal increase in blood pressure during NE infusion was accompanied by a comparable decrease in heart rate in the normal subjects (mean pressure, +23 ± 7 mm Hg; heart rate, -8 ± 6 bpm = -13%), and hypertensive patients (mean pressure +24 ± 4 mm Hg; heart rate -12 ± 7 bpm = -17%).

Following debrisoquine treatment, preinfusion plasma NE and the pressor dose of NE were decreased significantly and by an approximately similar extent in the two groups (-40% to 50%, table 2). The relationship between NE-induced changes in mean blood press-

![Figure 1](http://hyper.ahajournals.org/)

**Figure 1.** Relationship between norepinephrine-induced changes in mean blood pressure and plasma norepinephrine concentrations before and during norepinephrine infusion in normal and mildly hypertensive subjects under placebo conditions and following sympathetic neuron blockade with debrisoquine. In both groups, the displacement to the left during debrisoquine treatment is statistically significant (p < 0.01).
sure and concomitant plasma NE concentrations was significantly displaced to the left in both the normal subjects ($F = 9.33; p < 0.01$) and mildly hypertensive patients ($F = 10.03; p < 0.01$) (fig. 1). The response of heart rate to the increase in blood pressure induced by the highest NE infusion rate did not differ between the normal subjects (mean pressure $+28 \pm 9$ mm Hg; heart rate $-8 \pm 5$ bpm $= -15\%$) and hypertensive patients (mean pressure $+28 \pm 11$ mm Hg; heart rate $-7 \pm 9$ bpm $= -12\%$).

Plasma NE concentrations measured at the end of each NE infusion step correlated closely with the corresponding infusion rates; these relationships were comparable in normal and hypertensive subjects under placebo conditions and were unchanged following debrisoquine treatment (fig. 2). No significant correlation was found between the debrisoquine-induced changes in NE pressor dose and those in supine preinfusion blood pressure.

### Angiotensin II Infusion

Under placebo conditions, basal (preinfusion) plasma All concentrations, the All pressor doses (table 2), the slope of the All infusion rate-pressor response curve ($12 \pm 4$ in normal and $10 \pm 3$ in hypertensive subjects), and the correlation between All-induced changes in diastolic blood pressure and concomitant plasma All levels (fig. 3) did not differ significantly between the normal and mildly hypertensive groups. Moreover, these parameters were all unchanged following debrisoquine treatment (table 2, fig. 3). Plasma All levels measured at the end of each All-infusion step correlated closely with the corresponding infusion rates; these correlations did not differ between normal and hypertensive subjects under placebo conditions or following debrisoquine treatment ($r = 0.72$ to $0.83$).

### Discussion

Postganglionic blockade with debrisoquine depletes the peripheral NE stores and also inhibits the enzyme monoamino oxidase in sympathetic nerve endings;

13, 16-24 no influence on the adrenomedullary portion of the sympathetic system has been found. The observation of markedly decreased plasma and urinary NE levels and unchanged epinephrine values in the present and previous studies,14, 16 and an increased ratio between the urinary excretion rates of normetanephrine and NE16 in humans treated with debrisoquine are consistent with this concept. Moreover, this agent is devoid of a neurotoxic potential, 13 has no known direct effects on other nonadrenergic blood-pressure-regulating mechanisms and, in particular, does not per se modify the sensitivity of blood vessels to NE or All. 13, 25 A daily debrisoquine dose of 40 mg has been found to exert maximal sympathetic inhibition. 16

![Figure 2](http://hyper.ahajournals.org/)

**Figure 2.** Relationship between norepinephrine infusion rates and concomitant plasma norepinephrine concentrations in normal and mildly hypertensive subjects under placebo conditions and following sympathetic neuron blockade with debrisoquine.
Based on these considerations, treatment of our 11 normal subjects and 13 patients with mild essential hypertension with debrisoquine in final fourth week doses of 45 ± 5 and 52 ± 15 mg/day, respectively, provided an appropriate model with which to study the impact of selective NE inhibition on cardiovascular regulation. The efficacy of the pharmacological intervention is evident from the distinct and significant reductions (p < 0.05 to < 0.005) in supine and upright plasma NE concentrations and urinary NE excretion rates. Moreover, average decreases in the four different NE measurements (three in plasma, one in urine) were similar in the normal and mildly hypertensive patients (−41% and −45%, respectively).

In both groups, the reduction in NE outflow during sympathetic neuron blockade was accompanied by a marked increase in cardiovascular responsiveness to NE. This is evidenced by a: 1) decrease in the NE pressor dose (−47% and −51% in the normal and hypertensive groups; p < 0.01); 2) distinct shift in the relationship between pressor responses and plasma NE concentrations before and during NE infusion, and 3) mild reduction in the chronotropic dose of isoproterenol, averaging about 40%. Therefore, a modest decrease of NE levels during sympatholytic therapy in humans may be accompanied by supersensitivity of both alpha and beta receptors.

Apart from a reduced sympathetic outflow, some other mechanisms could theoretically also contribute to enhanced NE pressor responsiveness during post-ganglionic neuron blockade with debrisoquine. These include a decreased plasma clearance of the infused NE, a lowered sensitivity of the baroreflex, or body sodium-fluid volume retention that tends to develop during chronic sympathetic blockade. However, the unchanged relationships between NE infusion rates and concomitant plasma NE concentrations in both groups point to stable plasma NE clearances during debrisoquine treatment. The baroreflex sensitivity, as judged from the responses of heart rate to the NE-induced increases in blood pressure, also appeared to be unaltered. Mean body weight, urinary sodium excretion rate as an index of dietary intake, and plasma sodium and potassium concentrations were stable, and mean blood volume and exchangeable sodium tended to be increased only minimally and not significantly during the 4-week observation period. Therefore, these factors could have played at most a minor role in the adaptation of cardiovascular NE responsiveness to sympathetic inhibition.

Any increase in the sensitivity of adrenergic receptors would be expected to blunt the potential impact of sympatholytic therapy on cardiovascular function. Mean supine heart rate was lowered slightly but significantly during debrisoquine treatment in our normal and mildly hypertensive subjects (−10% and −8%, p < 0.05 to < 0.01), and a similar tendency was noted for heart rate in the upright position. This suggests that the accompanying increase in cardiac beta-receptor responsiveness was probably insufficient to fully compensate for the sympathetic hypoactivity. Supine blood pressure was on the average unchanged during

**Figure 3.** Relationship between angiotensin II (AII)-induced changes in blood pressure and plasma AII concentrations before and during angiotensin AII infusion in normal and mildly hypertensive subjects under placebo conditions and following sympathetic neuron blockade with debrisoquine.
adrenergic inhibition. However, a tendency for orthostatic decreases in blood pressure occurred both in the normal subjects (−8% as compared to change under placebo condition) and the mildly hypertensive group (−7.5%). The mechanism underlying this blood pressure constellation is difficult to judge. In considering postural activation of the sympathetic system during the debrisoquine treatment, percentage increases in plasma NE were unaltered. However, enhanced venous pooling of blood during sympathetic neuron blockade may favor orthostatic decreases in blood pressure. On the other hand, the lack of a statistically significant correlation between debrisoquine-induced changes in supine blood pressure and those in responsiveness to NE or isoproterenol could indicate that a factor other than receptor supersensitivity also played an important homeostatic role in the recumbent position.

The mechanism whereby noradrenergic depletion affects blood pressure control may also involve the angiotensinergic regulation. Renal renin secretion is partly influenced by the adrenergic system, while all may possibly activate the sympathetic system centrally and by facilitation of NE release or inhibition of NE uptake at the nerve endings. In the present or previously studied groups of normal subjects or patients with mild essential hypertension, effective sympatholytic intervention with debrisoquine or methyldopa failed to decrease plasma renin and All levels. In fact, postural rises in circulating renin tended to be even slightly enhanced in our debrisoquine-treated normal or mildly hypertensive subjects, perhaps as a response to mild orthostatic decreases in blood pressure. Information on the responsiveness of renin-regulating beta-receptors during conditions of reduced sympathetic outflow is not available. However, in view of the tendency for increased heart rate responses to isoproterenol, a similar adaptation of beta-receptor-mediated renin release is equally possible. An end organ adjustment of this kind could maintain stable plasma renin and All levels despite sympathetic hypertension in normal or mildly hypertensive subjects. A different trend may occur in patients with established moderate essential hypertension in whom similar doses of debrisoquine or methyldopa caused distinct renin suppression not explained by fluid volume retention.

Cardiovascular pressor responsiveness to All was not affected by short-term sympathetic neuron blockade with debrisoquine. This conclusion is supported by the stable All pressure doses and the unaltered relationships between All-induced changes in blood pressure and concomitant plasma All concentrations or between the latter parameter and All infusion rates in both study groups. Thus, there is no evidence for an important role of the angiotensinergic control mechanism in the cardiovascular adjustment to reduced NE outflow in normal or mildly hypertensive subjects.

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