Reversal by naloxone of the antihypertensive action of clonidine: involvement of the sympathetic nervous system

Csaba Farsang, M.D., C. Sc., Judit Kapocsi, M.D., Lidia Vajda, Ph.D., Karoly Varga, M.D., Zita Malisak, M.D, Marton Fekete, M.D., C. Sc., and George Kunos, M.D., Ph.D.

ABSTRACT The effects of clonidine, naloxone, and their combination on arterial blood pressure (BP), heart rate (HR), and hemodynamic and biochemical parameters were examined in 29 patients with essential hypertension. Treatment for 3 days with 0.3 mg/day clonidine reduced BP and HR, and these effects were quickly reversed by a single injection of 0.4 mg iv naloxone in 17 of the patients (responders), but not in the remaining 12 (nonresponders). Responders had higher control values for cardiac output, stroke index, plasma renin activity (PRA), and plasma epinephrine levels than did nonresponders. Basal BP was similar in the two groups, but clonidine decreased BP, PRA, and plasma epinephrine more in responders than in nonresponders. Naloxone given during placebo treatment had no significant effects. During clonidine treatment naloxone increased BP, HR, total peripheral resistance, PRA, and plasma epinephrine and norepinephrine, and decreased stroke volume in responders, whereas in nonresponders its only effect was a small increase in HR. It is concluded that in a subset of hyperadrenergic, hypertensive patients the antihypertensive effect of clonidine involves a naloxone-reversible inhibition of central sympathetic outflow, probably mediated by the release of an endogenous opioid.


THE ANTIHYPERTENSIVE AGENTS clonidine and \( \alpha \)-methylldopa are believed to produce their cardiovascular effects through a central mechanism. They stimulate \( \alpha \)-adrenergic receptors in the pontomedullary region, which results in a reduction of sympathetic and increase in parasympathetic tone. Recent reports have demonstrated that in hypertensive rats the antihypertensive action of these drugs is inhibited by the opiate antagonists naloxone and naltrexone, or by central administration of an antiserum to \( \beta \)-endorphin. Furthermore, clonidine and \( \alpha \)-methylnorepinephrine increase the release of immunoreactive \( \beta \)-endorphin from the superfused brain stem of spontaneously hypertensive rats in vitro. These findings have been interpreted to indicate that the antihypertensive effect of central \( \alpha \)-adrenergic stimulation involves the release of a \( \beta \)-endorphin–like material from the brain. A similar adrenergic-opioid interaction is present in certain forms of human hypertension. In patients with moderate essential hypertension the blood pressure– and heart rate–lowering effects of clonidine were quickly reversed by a single intravenous injection of 0.4 mg of naloxone in about one-half of the patients studied, whereas in the remaining patients naloxone was ineffective even when a larger dose was given. In an attempt to analyze the difference between naloxone “responders” and “nonresponders,” and to clarify the mechanism of the adrenergic-opioid interaction in the former group, we have examined hemodynamic and biochemical changes produced by clonidine, naloxone, and their combination in patients with uncomplicated essential hypertension.

Methods

Study population. A crossover, single-blind study was done with 29 hospitalized patients from 26 to 55 years old who had moderate essential hypertension. Patients with signs of cardiac, renal, cerebral, or peripheral vascular complications as well as those with secondary forms of hypertension were excluded from the study. The absence of such factors was verified with appro-
prie physical, electrocardiographic, x-ray, and laboratory examinations, as before. Volunteer participation was based on informed consent. All patients had normal weight for height, and were screened for possible narcotic drug abuse. Patients were off all medications for at least 8 days before the trial (11.2 ± 2.3 days). Each entered the trial when his or her blood pressure had been stable for 4 consecutive days and its level (systolic/diastolic) was 145 to 210/90 to 120 mm Hg. Previously prescribed antihypertensive medications included oxprenolol, dihydrochlo-rothiazide, prazosin, or dihydralazine (but not clonidine, α-methyl dopa, guanfacine, or guanethidine). Patients in whom blood pressure exceeded 210/120 mm Hg during the drug-free period were given their usual medication and were excluded from the study. All patients were on a no salt-added diet throughout the trial.

Protocol. During the drug-free control period blood pressure was measured four times a day by sphygmomanometry after 15 min of recumbent rest; the disappearance of Korotkoff sounds was used to measure diastolic pressure. Heart rate was measured from the radial pulse. The patients were given 75 μg clonidine or placebo four times a day for 3 days. Blood pressure and heart rate were measured four times a day, 1 hr after each dose of medication. On the third day, 1 hr after the second daily dose, each patient was transferred to the isotope laboratory where an intravenous line was inserted into an antecubital vein for removal of blood samples and injection of naloxone and the radioactive tracer. After 15 min of recumbent rest, blood samples were drawn for determination of plasma renin activity (PRA) and plasma levels of norepinephrine (NE) and epinephrine (E). This was followed by determination of the cardiac output (CO) as detailed below, after which a single intravenous injection of 0.4 mg of naloxone was given. Blood pressure and heart rate were measured 1, 2, 3, 5, 7, and 10 min after the injection. Immediately after the 10 min measurements a second blood sample was taken for determination of PRA and plasma catecholamines, and CO was determined again. This protocol was repeated on the third day of the second treatment period with crossover for clonidine and placebo. The sequence of treatment was determined by random allocation. To avoid interference by circadian variations in plasma levels of catecholamines, all tests were done at around 2 P.M. Because of this, basal values are somewhat higher than in studies in which samples are taken early in the morning after patients have had a night of bed rest. Plasma samples were stored at −70°C before being assayed.

**Hemodynamic parameters.** CO was determined by a radio-circulographic method with some modifications. In this study indium-113m was used as the radiotracer because of its short half-life (90 min). After a bolus intravenous injection of 10,000 cps in a volume of 0.5 ml, radioactivity was monitored precordially. The recordings were stored on magnetic tape and were played back into a compensograph operated at a paper speed of 10 mm/sec. CO was calculated from the area below the precordial radioactivity–time curve (A) with the equation

$$\text{CO} = \frac{\text{Blood volume} \times 51 \times \text{average isotope conc.}}{A}$$

where 51 is a constant and blood volume is computed from the dilution of radioactivity in the plasma as measured 20 min after the injection of the isotope. For the second measurement of CO correction was made for the existing background radioactivity. We found that in the absence of interventions the second measurement differed from the first by only 8.3 ± 6.0%. Stroke volume and stroke index were derived from the values for CO, heart rate, and body surface area, which was estimated from height and weight with a nomogram. Total peripheral resistance (TPR) was calculated from the CO (ml/sec) and the mean arterial blood pressure (P_a, mm Hg) with the equation

$$\text{TPR} = \frac{P_a \times 1332}{\text{CO}}$$

**Biochemical parameters.** Blood samples for determination of PRA and plasma catecholamines were taken through an intravenous catheter after subjects had had 15 min of recumbent rest. PRA was determined by radioimmunoassay of angiotensin I generated in vitro under optimal generating conditions (Angiotensin I 125I radioimmunoassay kit, New England Nuclear Co.). Plasma NE and E were quantified by a radioenzymatic assay that was modified to increase sensitivity (Upjohn Diagnostics, Cat-A-Kit). Levels of E and NE were determined after thin-layer chromatographic separation of 3H-labeled, O-methylated products.

**Statistical analyses.** Data were analyzed with the Mann-Whitney U test, Scheffe’s multiple-range test, and linear regression analysis, as appropriate.

**Results**

In agreement with our previous findings clonidine significantly reduced blood pressure and heart rate in all patients, and naloxone reversed these effects in some patients but not in others. According to their blood pressure response to naloxone during clonidine treatment, patients could be divided into naloxone responder (Δ mean blood pressure ≥ 10 mm Hg, n = 17) and nonresponder groups (Δ mean blood pressure ≤ 10 mm Hg, n = 12). This division was justified by our recent finding that in a total of 80 patients studied so far, the blood pressure response to naloxone during clonidine treatment displayed a nonuniform, bimodal distribution.* The pretreatment blood pressure and heart rate values were not significantly different in the two groups (table 1). There was also no difference in mean ages of the groups (responders, 36.3 ± 2.4 years; nonresponders, 37.1 ± 2.0 years), in body weights, or in number of men and women in each group, but responders had a significantly shorter history of hypertension (5.6 ± 0.7 years) than nonresponders (9.3 ± 1.3 years, p ≤ .05). Clonidine caused a significantly greater reduction in both systolic and diastolic blood pressures in the responders than in the nonresponders (table 1, figure 1). Naloxone did not influence blood pressure when the patients of either group were on placebo. When given during clonidine treatment, naloxone caused an abrupt rise in blood pressure to preclonidine levels in the responders, but it was ineffective in the nonresponders. Our earlier observations have indicated that naloxone remains ineffective in nonresponders even when given at three times the dose given here.7

The selectivity of the clonidine-naloxone interaction

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was examined by testing the effects of naloxone on blood pressure and heart rate after dihydrochlorothiazide treatment. Four of the responders were treated with 25 mg dihydrochlorothiazide twice daily and were given an intravenous dose of 0.4 mg naloxone on the third day 1 hr after their second daily dose of dihydrochlorothiazide. The data in table 2 indicate that, in sharp contrast to the findings in the same patients after clonidine treatment, naloxone had no effect on either blood pressure or heart rate, although dihydrochlorothiazide was as effective as clonidine in reducing blood pressure; dihydrochlorothiazide did not reduce heart rate.

Clonidine decreased heart rate to the same extent in responders and nonresponders (table 1), and naloxone did not influence heart rate during the placebo period (figure 1, bottom). During clonidine treatment heart rate was increased by naloxone in both groups, but the increase was significantly greater in responders than in nonresponders (figure 1).

CO was significantly higher in responders than in nonresponders (table 1), and clonidine decreased CO in both groups (table 1, figure 2, top). Naloxone did not influence CO either during placebo or during clonidine treatment in either group of patients. TPR was slightly but not significantly lower in responders than in nonresponders, and was not influenced by clonidine in either group (figure 2, middle). Naloxone did not affect TPR during placebo treatment, but increased TPR significantly when it was given during clonidine treatment. Except for a decrease caused by naloxone when given to responders during clonidine treatment, stroke volume (figure 2, bottom) was unaffected by the drugs.

PRA was significantly higher in responders than in nonresponders (table 1). The effects of clonidine and naloxone on PRA are illustrated in figure 3, top. Clonidine decreased PRA in both groups, and the decrease was significantly greater in responders than in nonresponders. Naloxone was ineffective during the placebo period, but caused a marked increase in PRA in responders during clonidine treatment.

Mean levels of plasma catecholamines during various treatments are shown in figure 3, bottom. NE (middle panels) levels during the placebo period were not different in the two groups (see also table 1), and were not influenced by the administration of naloxone. Clonidine caused a similar reduction in plasma NE in the two groups, and naloxone, when given during clonidine treatment, caused a sharp rise in NE in the responders but was ineffective in nonresponders. In contrast to plasma NE, plasma E was more than twice as high in responders as in nonresponders (table 1). The clonidine-induced reduction in plasma E was much greater in the former than in the latter group. Naloxone, when given during clonidine treatment, was ineffective in nonresponders but increased plasma E in responders.

The data in table 3 summarize the results of analyses of correlations between basal levels and drug-induced changes in mean blood pressure on the one hand, and biochemical parameters on the other. Since the bio-

### TABLE 1

<table>
<thead>
<tr>
<th>Systolic BP (mm Hg)</th>
<th>Diastolic BP (mm Hg)</th>
<th>HR (beat/min)</th>
<th>CO (l/min)</th>
<th>CI (l/min/m²)</th>
<th>SV (ml)</th>
<th>SI (ml/m²)</th>
<th>TPR (dynes·sec·cm⁻²)</th>
<th>PRA (ng/ml/min)</th>
<th>NE (pg/ml)</th>
<th>E (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Responders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Basal level</td>
<td>167.2</td>
<td>101.3</td>
<td>86.7</td>
<td>8.13</td>
<td>4.58</td>
<td>93.3</td>
<td>52.5</td>
<td>1305</td>
<td>4.98</td>
<td>614</td>
</tr>
<tr>
<td>±4.2</td>
<td>±2.1</td>
<td>±2.8</td>
<td>±0.63</td>
<td>±0.39</td>
<td>±5.4</td>
<td>±3.4</td>
<td>±90</td>
<td>±0.78</td>
<td>±33</td>
<td>±47</td>
</tr>
<tr>
<td>Change by clonidine</td>
<td>−37.4</td>
<td>−20.6</td>
<td>−15.9</td>
<td>−1.59</td>
<td>−0.84</td>
<td>−0.9</td>
<td>−0.1</td>
<td>−38</td>
<td>−4.06</td>
<td>−190</td>
</tr>
<tr>
<td>±2.7</td>
<td>±1.7</td>
<td>±2.1</td>
<td>±0.53</td>
<td>±0.28</td>
<td>±5.6</td>
<td>±3.1</td>
<td>±74</td>
<td>±0.79</td>
<td>±66</td>
<td>±27</td>
</tr>
<tr>
<td><strong>Nonresponders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal level</td>
<td>163.7</td>
<td>102.5</td>
<td>80.2</td>
<td>6.54^</td>
<td>3.44^</td>
<td>75.2</td>
<td>43.0^</td>
<td>1569</td>
<td>1.71^</td>
<td>492</td>
</tr>
<tr>
<td>±5.2</td>
<td>±1.2</td>
<td>±2.0</td>
<td>±0.44</td>
<td>±0.22</td>
<td>±7.5</td>
<td>±2.0</td>
<td>±103</td>
<td>±0.49</td>
<td>±42</td>
<td>±7</td>
</tr>
<tr>
<td>Change by clonidine</td>
<td>−21.7^</td>
<td>−12.9^</td>
<td>−11.0</td>
<td>−0.70</td>
<td>−0.39</td>
<td>−2.9</td>
<td>−1.3</td>
<td>−12</td>
<td>−1.09^</td>
<td>−125</td>
</tr>
<tr>
<td>±1.3</td>
<td>±2.4</td>
<td>±2.1</td>
<td>±0.30</td>
<td>±0.16</td>
<td>±3.8</td>
<td>±2.5</td>
<td>±93</td>
<td>±0.36</td>
<td>±27</td>
<td>±5</td>
</tr>
</tbody>
</table>

Values are means and SEs. Number of patients was 17 in the responder and 12 in the nonresponder groups, except for the last three parameters, for which measurements in responders and nonresponders were done only in nine and eight (PRA) and five and four cases (NE and E). Significant differences from corresponding values in responders: ^p ≤ .05; ^p ≤ .005.
The effects of naloxone during placebo or clonidine treatment on mean blood pressure and heart rate in patients with essential hypertension. A, Nonresponders (n = 12); B, responders (n = 17). Means and SEs are shown. Asterisks indicate significant differences from control value during placebo period (★) or from control value during clonidine treatment (☆). Dashed lines indicate the effect of clonidine treatment. C = control; N = naloxone. For detailed protocol, see text.

The effects of naloxone on blood pressure (BP) and heart rate in hypertensive responders to naloxone pretreated with clonidine or dihydrochlorothiazide

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Systolic BP (mm Hg)</th>
<th>Diastolic BP (mm Hg)</th>
<th>Heart rate (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>167.5 ± 4.8</td>
<td>97.5 ± 2.5</td>
<td>81.0 ± 3.4</td>
</tr>
<tr>
<td>Clonidine</td>
<td>127.5 ± 7.5</td>
<td>78.8 ± 5.2</td>
<td>69.0 ± 4.1</td>
</tr>
<tr>
<td>Clonidine + naloxone</td>
<td>165.0 ± 5.4</td>
<td>102.5 ± 3.2</td>
<td>77.0 ± 2.5</td>
</tr>
<tr>
<td>Dihydrochlorothiazide</td>
<td>132.5 ± 8.1</td>
<td>84.8 ± 3.3</td>
<td>80.3 ± 5.7</td>
</tr>
<tr>
<td>Clonidine + naloxone</td>
<td>132.0 ± 7.8</td>
<td>83.5 ± 4.2</td>
<td>81.0 ± 6.1</td>
</tr>
</tbody>
</table>

Values are means and SEs from measurements in four responders. The values after naloxone represent the highest values measured over a 60 min period following the intravenous injection of 0.4 mg of naloxone. Clonidine treatment was with 0.075 mg, four times a day for 3 days. Dihydrochlorothiazide, 25 mg, was given twice daily for 3 days.

A significant difference from corresponding value during placebo treatment. *Significant difference from value obtained with clonidine alone.

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FIGURE 2. The effects of naloxone during placebo or clonidine treatment on CO, TPR, and stroke volume. A, Responders (n = 17); B, nonresponders (n = 12). Symbols as in figure 1.

chemical parameters were not measured in every patient, these analyses only included blood pressure measurements from those patients in whom the given biochemical parameter was also determined. There was a significant linear correlation between mean blood pressure and plasma NE and E, but not between blood pressure and PRA. The clonidine-induced decrease in mean blood pressure correlated with the reduction in plasma E, but not with that in NE or PRA, and the change in mean blood pressure caused by naloxone during clonidine treatment correlated with the change in PRA and NE but not with that in E.

Discussion

Earlier studies in which hypertensive animals were used, as well as observations in patients with essential hypertension, have documented a naloxone-reversible component in the antihypertensive action of clonidine and α-methyldopa. This effect was attributed to an endorphin-like opioid released by stimulation of α2-adrenergic receptors in the central nervous system. It has also been proposed that this mechanism is activated by the hypertensive process, since no such interactions are found in normotensive animals or human subjects.
hypertension, whereas in others it has no such effects. In addition, the present findings extend these observations in three important respects by suggesting that (1) the naloxone responders represent a subset of patients with hyperadrenergic hypertension and signs of hyperkinetic cardiac function, (2) the antihypertensive action of clonidine is related to a central reduction in sympathoadrenal activity, which is greater in responders than in nonresponders, and (3) the reversal of the effects of clonidine by naloxone in responders is due to a centrally mediated increase in sympathetic tone.

When hypertensive patients are divided into naloxone responder and nonresponder groups, a number of differences become apparent (table 1). Some of these differences are present in the absence of drug treatment and include higher levels of CO, stroke index, PRA, and plasma E in the responders. Basal blood pressure is similar in the two groups, since the effect of the higher CO is offset by a lower TPR in the responders, although the latter difference is not statistically significant. In addition, clonidine lowers blood pressure, PRA, and plasma E levels more in responders than in nonresponders. These findings suggest that the responders to naloxone represent a subset of hyperadrenergic patients with hyperdynamic cardiac function in whom the increased effectiveness of clonidine is probably related to a higher resting sympathetic tone. The significantly shorter history of hypertension in responders than in nonresponders may suggest but does not prove that the two groups represent sequential stages rather than independent subsets of hypertension. A hyperadrenergic subgroup of hypertensive patients has also been identified in a number of previous studies.19-20 Recently Bolli et al.21 have reported higher PRA and E levels, but similar NE levels, in a subset of hypertensive patients with increased hypotensive response to propranolol treatment. These authors have also suggested that a selective increase in plasma E rather than NE reflects sympathetic overactivity in patients with essential hypertension.22 The selective increase in plasma E in the naloxone responders in our study is in agreement with such a possibility. The increased CO type of hypertension of the responders is also more consistent with the hemodynamic effects of E than of NE.23 As the major source of plasma E is the adrenal medulla, the hyperadrenergic state of the responders may represent a preferential increase in adrenomedullary as compared with peripheral sympathetic neuronal activity. Such differential changes are not unexpected, as the central neurogenic control of the adrenal medulla is partially distinct from that of peripheral sympathetic neurons.24

**FIGURE 3.** The effects of naloxone during placebo or clonidine treatment on PRA and plasma NE and E levels. A, Responders (n = 9 for PRA, n = 5 for NE and E); B, nonresponders (n = 8 for PRA, n = 4 for NE and E). Symbols as in figure 1.

We have confirmed our earlier observation that naloxone quickly reverses the hypotensive and bradycardiac actions of clonidine in some patients with essential hypertension, but in others it has no such effects. In addition, the present findings extend these observations in three important respects by suggesting that (1) the naloxone responders represent a subset of patients with hyperadrenergic hypertension and signs of hyperkinetic cardiac function, (2) the antihypertensive action of clonidine is related to a central reduction in sympathoadrenal activity, which is greater in responders than in nonresponders, and (3) the reversal of the effects of clonidine by naloxone in responders is due to a centrally mediated increase in sympathetic tone.

**TABLE 3**
Correlation coefficients (r) for relationships between basal values or drug-induced changes in mean blood pressure and PRA, plasma NE, and E

<table>
<thead>
<tr>
<th></th>
<th>Mean blood pressure</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>PRA</td>
<td>NE</td>
</tr>
<tr>
<td>Placebo</td>
<td>.37</td>
<td>.74a</td>
</tr>
<tr>
<td>Δ Mean blood pressure</td>
<td>Δ PRA</td>
<td>Δ NE</td>
</tr>
<tr>
<td>Clonidine</td>
<td>.49</td>
<td>.10</td>
</tr>
<tr>
<td>Naloxone after clonidine</td>
<td>.71b</td>
<td>.83b</td>
</tr>
</tbody>
</table>

Values from responders and nonresponders were treated as a single group and the numbers of patients were 17 (PRA) and nine (NE and E). *p ≤ .05, **p ≤ .01.
A recent report of the failure of naloxone to inhibit the hypotensive response to clonidine in six hypertensive patients may be related to a preponderance of nonrespondents in that small group. Also, differences in the way drugs were administered (continuous infusion of 6 μg/kg/hr naloxone followed by a single large dose of clonidine) may influence their possible interaction. We found that the rise in plasma β-endorphin in hypertensive patients treated with clonidine for 3 days is much smaller when tested after a single dose of clonidine.

In agreement with earlier findings by others, in supine patients with essential hypertension the blood pressure–lowering effect of clonidine is associated with a reduction in CO, while TPR remains unchanged. The unchanged vascular resistance reflects, however, a reduction in vasomotor tone, since resistance would be expected to rise in response to the reduction in CO. The decrease in CO is probably related to the bradycardic effect of clonidine. This, in turn, could result from a decrease in central sympathetic or an increase in parasympathetic outflow to the heart, although stimulation of cardiac presynaptic α-receptors, resulting in decreased neurotransmitter release, may also contribute to the bradycardia. The marked reductions in plasma catecholamines and PRA induced by clonidine (figure 3) are consistent with a central reduction of sympathetic tone, which is further supported by the significant correlation between the clonidine-induced decrease in blood pressure and plasma E (table 3).

In the absence of drug treatment, naloxone did not significantly influence blood pressure and heart rate, which could suggest the absence or the inactivity of a physiologic regulatory system involving endogenous opioids. Alternatively, naloxone may simultaneously inhibit tonically active, opposing pressor (enkephalinergic) and depressor (endorphinergic) systems, the effects of which would cancel each other out. Indeed, both the depressor and the pressor opioid effects are potentiated in experimental hypertension.

Our observations also indicate that the reversal of the effects of clonidine by naloxone in a subgroup of the patients studied is related to an increase in central sympathetic outflow that is probably due to the reversal of the sympathoinhibitory effect of the opioid released by clonidine. The specificity of this effect is indicated by the absence of a similar reversal of the hypotensive action of dihydrochlorothiazide (table 2). A similar selective reversal of the effects of clonidine,

but not hydralazine, by naloxone has been observed in rats. The short-term pressor effects of naloxone in the responders were accompanied by significant elevations in PRA and plasma catecholamines, while no such changes were noted in the nonresponders. Unlike clonidine, which reduced plasma E more than plasma NE, naloxone induced a more marked increase in NE than in E, and only the former correlated with the increase in blood pressure. This suggests that the effects of naloxone are more closely related to an increase in sympathetic neuronal activity than to increased adrenomedullary discharge.

That the pressor effect of naloxone during clonidine treatment is not simply a reversal of the effects of clonidine is also indicated by the effects of naloxone on hemodynamic parameters. While clonidine reduced CO and did not alter TPR, naloxone increased TPR. CO remained unchanged since the effect of increased heart rate was offset by a reduction in stroke volume that probably resulted from an increase in afterload. These changes are also more consistent with a sympathetic neuronal as opposed to adrenomedullary activation, since the released NE is a potent α-adrenergic vasconstrictor and does not have the β2-adrenergic vasodilator activity of E.

Previous experiments in hypertensive rats have provided evidence that the adrenergic-opiate interaction is mediated by an endorphin-like opioid, the release and action of which occurs in the central nervous system, within the anatomic region of the brainstem. Our findings in hypertensive patients are consistent with such a possibility. Alternatively, clonidine could increase plasma levels of β-endorphin, which can reach and act on brainstem structures, or could activate peripheral opiate receptors in the cardiovascular system. Further work is necessary to determine which of these is the case.

References

7. Farsang C, Kaposi J, Juhasz I, Kunos G: Possible involvement of

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 PATHOPHYSIOLOGY AND NATURAL HISTORY—HYPERTENSION


Erratum

Figures 3 and 4 were transposed in the above article and appear with the incorrect legends (i.e., correct legend to figure 3 appears with figure 4). In addition, the blood pressure scale in the lower half of figure 4 (printed as figure 3) should be identical to that in figure 2.
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C Farsang, J Kapocsi, L Vajda, K Varga, Z Malisak, M Fekete and G Kunos

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