Possible Involvement of an Endogenous Opioid in the Antihypertensive Effect of Clonidine in Patients with Essential Hypertension

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SUMMARY  The effect of naloxone on the hypotensive and bradycardiac action of clonidine was studied in 27 hospitalized patients with uncomplicated mild-to-moderate essential hypertension. In a double-blind, crossover study, clonidine, 0.3 mg/day orally for 3 days, significantly reduced systolic and diastolic blood pressure and heart rate, whereas placebo was ineffective. Naloxone, 0.4 mg given intravenously on the third day of clonidine treatment, caused a rapid increase in blood pressure and heart rate in 14 patients (reacting group), but was ineffective in the remaining 13 patients (nonreacting group). Naloxone given during the placebo period was ineffective in all patients. Both the clonidine-induced hypotension and the rebound increase in blood pressure after cessation of clonidine were significantly greater in the reacting than in the nonreacting group. These observations suggest that release of an endogenous opioid contributes to the antihypertensive action of clonidine; this mechanism may also be involved in the discontinuation syndrome after cessation of clonidine.

ENDOGENOUS opioids of the brain have well-documented effects on pain sensation,1 behavior2 and the endocrine system,3 and have been implicated in the control of cardiovascular functions. The hypotension associated with various forms of shock,4-7 inhalation anesthesia8 and surgical trauma9 has been reversed by naloxone, which was interpreted to indicate that these hypotensive states were associated with the release of an endogenous opioid. We recently reported that in spontaneously hypertensive rats (SHRs), the hypotensive action of clonidine and α methyldopa could be prevented or reversed by opiate antagonists.10,11 Because clonidine and naloxone did not interact with the same receptor site in the brain,10 we suggested that the antihypertensive effect of central α-adrenergic receptor stimulation in SHRs involves the release of an endogenous opioid. Direct evidence for this was provided by the demonstration that in an in vitro brainstem preparation from SHRs, clonidine and L-α-methyladrenaline increased the release of a β-endorphin-immunoreactive material.12 Because β endorphin has potent hypotensive effects of its own,13,14 these findings strongly suggest that release of an endorphin-like substance from the brain is involved in the antihypertensive action of central α-receptor agonists in SHRs.

Hypertension in SHRs is different in some respects from essential hypertension in man,15 and it is not certain that the adrenergic-opioid interaction in SHRs also exists in hypertensive humans. We tested this possibility by studying the interaction of clonidine and naloxone on arterial blood pressure and heart rate in 27 patients with mild-to-moderate hypertension.

Methods

Patients

A double-blind, crossover study was done on 27 hospitalized patients, ages 26–55 years, with mild-to-moderate essential hypertension. Volunteer participation was based on informed consent and absence of cardiac, cerebral, renal or peripheral vascular disease by history, physical examination, ECG and creatinine clearance. Other forms of hypertension were excluded by appropriate clinical and laboratory examinations (urinalysis, intravenous urography, serum electrolytes, plasma cortisol levels at midnight and in the morning, 24-hour urine vanillyl mandelic acid, phenolamine or glucagon test, chest radiograph and renal scintigraphy). All patients had normal weight for height and were carefully screened for possible narcotic drug abuse. Blood pressure in the absence of medication was 148–210/90–120 mm Hg.

Trial Design

The patients had not taken medication for at least 7 days before the trial. Their previous antihypertensive medication included α methyldopa, oxprenolol, dihydrochlorothiazide or dihydralazine. Patients whose diastolic blood pressure exceeded 120 mm Hg during the drug-free period were excluded from the study. Blood pressure was measured by sphygmomanometry after 15 minutes of recumbent rest in a quiet environment; the disappearance of Korotkoff sounds was used to measure diastolic pressure. Heart rate was measured from the radial pulse. The patients entered the double-blind, crossover study after their blood pressure and heart rate measurements had stabilized and remained constant for 3 consecutive days. The patients were then given clonidine (Catapres, Boehringer Ingelheim), 0.1 mg orally three times a day, or placebo, for 3 days. The sequence of placebo or active drug was determined by random allocation. Blood pressure and heart rate were
measured 3 times a day, 1 hour after each dose of medication. On the third day and 1 hour after the second daily dose, an i.v. infusion of physiologic saline (1 ml/min) was started through an indwelling catheter in an antecubital vein. The ECG was monitored continuously and blood pressure and heart rate were determined frequently over a 15-minute period. Without knowledge of its timing by the patient, 0.4 mg of naloxone (Endo Laboratories) or physiologic saline was injected as a 2-ml bolus into the i.v. line. Blood pressure and heart rate were measured 1, 2, 3, 5, 7, 10, 20, 40 and 60 minutes after the i.v. injection. Then, the second injection (saline or naloxone) was given and blood pressure and heart rate were measured as before. In five of the patients whose blood pressure and heart rate were not influenced by naloxone (nonreacting group), the test was repeated with 1.2 mg of naloxone.

After this session, the second 3-day treatment period was started with crossover for clonidine-placebo. The following effects on blood pressure and heart rate were recorded: saline during placebo, naloxone during placebo, saline during clonidine, and naloxone during clonidine.

Rebound hypertension and tachycardia after cessation of clonidine therapy were analyzed retrospectively in patients who received clonidine first. Rebound was characterized by the highest blood pressure and heart rate readings during the subsequent 3-day placebo period.

**Statistical Analysis**

Differences in blood pressure and heart rate responses to clonidine in reacting and nonreacting patients were analyzed by the Mann-Whitney U test. Changes in blood pressure and heart rate caused by clonidine, naloxone, or by withdrawal of clonidine within the same patients were evaluated by two-way analysis of variance followed by Duncan’s multiple-range test. The correlation between the naloxone-induced maximal increase in blood pressure and the maximal increase in blood pressure observed during withdrawal of clonidine in the same patients was assessed by linear regression analysis. The possibility of nonuniform distribution of patients according to their mean blood pressure response to naloxone was tested by the Kolmogorov-Smirnov test for goodness of fit for normal distribution. A p value less than 0.05 was considered significant.

**Results**

The mean systolic and diastolic blood pressures at the end of the drug-free period (± SEM in 27 patients) were 167.3 ± 3.1 and 103.1 ± 1.6 mm Hg, respectively. The mean heart rate was 77.3 ± 1.2 beats/min. By the third treatment day, clonidine significantly reduced blood pressure to 139.3 ± 3.1/88.5 ± 1.8 mm Hg (p < 0.001) and heart rate to 64.2 ± 1.2 beats/min (p < 0.001). When 0.4 mg of naloxone was given during clonidine treatment, 14 of the 27 patients had a rapid and marked increase in blood pressure and heart rate to or above the preclonidine levels (fig. 1A). The increase in blood pressure and heart rate peaked within 3–10 minutes and returned to prenaloxone levels within 1 hour. The maximal increases in systolic and diastolic pressures ranged from 16 to 105 and 6 to 40 mm Hg, respectively, and heart rate increased by 7–24 beats/min. In the remaining 13 patients, naloxone caused no change, a slight decrease or an increase of less than 10 mm Hg in mean blood pressure, and caused no significant change in heart rate (nonreacting group, fig. 1A). In five of the latter patients, naloxone was tested at three times the original dose (1.2 mg). The mean blood pressure declined from 112.7 ± 4.2 to 108.8 ± 3.8 mm Hg and heart rate remained unchanged. Because these effects were the same as the effect of 0.4 mg of naloxone in the same patients, the remaining nonreacting patients were not tested with the higher dose. Naloxone given during the placebo

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**Figure 1.** The effect of intravenous naloxone on blood pressure and heart rate during clonidine (A) or placebo treatment (B). Points and vertical bars represent means and standard errors from 14 reacting patients (●—●) and 13 nonreacting patients (○—○). The higher blood pressure values are systolic and the lower ones are diastolic. Naloxone (N, 0.4 mg) was injected intravenously at 0 time.
period did not significantly change blood pressure and heart rate in the reacting or the nonreacting group (fig. 1B).

Although the distribution of the mean blood pressure response to naloxone looks bimodal (fig. 2), goodness-of-fit testing for a normal distribution in this relatively small sample (27 patients) could not reject the possibility that the data were drawn from a normally distributed population. Thus, the terms “reacting” and “nonreacting” are used only to describe quantitatively different responses to naloxone with a cutoff of a 10-mm Hg increase in mean blood pressure.

Blood pressure and heart rate during the drug-free control period were not significantly different in the two groups; nor was there a difference in average age, duration of hypertension or in the type of previous antihypertensive medication. However, an analysis of the effects of clonidine indicated that the decrease in mean blood pressure was significantly greater in the reacting than in the nonreacting patients, whereas the reduction in heart rate was not significantly different in the two groups (fig. 3). Another difference between reacting and nonreacting patients was in the degree of rebound hypertension and tachycardia after clonidine treatment was stopped. Rebound was analyzed retrospectively in eight reacting and six nonreacting patients who received clonidine first, followed by placebo. The measure of rebound was the highest reading of blood pressure and heart rate during the placebo period. The peak values were always detected on the first day, and by the third day of the placebo period blood pressure and heart rate were not different from the highest control values during the drug-free period. Figure 4 shows the peak mean blood pressure and heart rate values in these patients during the drug-free control period and values obtained on the third day of clonidine treatment. Peak “withdrawal” effects observed during the placebo period, as well as the peak effects during the naloxone test on the last day of clonidine treatment, are also shown. In the eight reacting patients, naloxone significantly increased the mean blood pressure and heart rate, and a similar or greater increase in these variables occurred during the first day of the placebo period. These rebound values were also significantly higher than the preclonidine control values. The six nonreacting patients showed no significant rebound, and naloxone did not significantly alter blood pressure and heart rate. The highest values registered during placebo did not exceed the preclonidine control values. When the increase in mean blood pressure caused by naloxone was plotted against the increase in mean pressure during withdrawal in the above 14 patients, a significant linear correlation was found ($r = 0.72, p < 0.005$).

Discussion

Naloxone, a potent opiate-receptor antagonist, is remarkably free of pharmacologic actions of its own. Therefore, naloxone has been used to unmask the actions of exogenous opiates or to suggest the involvement of endogenous opioids in various physiologic processes. Our findings indicate that in patients with

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**Figure 2.** Distribution of patients according to mean blood pressure response to naloxone during clonidine treatment. Twenty-seven patients were classified according to peak change in mean blood pressure.

**Figure 3.** The effect of clonidine on mean blood pressure and heart rate in reacting and nonreacting patients. Open columns indicate reacting patients ($n = 14$); hatched columns, nonreacting patients ($n = 13$). Columns and vertical bars represent means and standard errors. $^{*}p < 0.05$ vs corresponding value in reacting group.
mild-to-moderate essential hypertension, clonidine-induced hypotension and bradycardia can be acutely reversed by naloxone. Clonidine and naloxone do not interact with each other’s specific binding sites. Therefore, we propose that the action of clonidine in these patients involves the release of an endogenous opioid. The antihypertensive action of clonidine is believed to involve stimulation of sympathoinhibitory \( \alpha \)-adrenergic receptors in the central nervous system. Release of an endogenous opioid could occur distal to this site, and the released opioid could then stimulate opioid receptors that inhibit sympathetic tone. This sequence of events is supported by evidence obtained in SHRs, in which a similar interaction between clonidine and naloxone has been reported. In these rats, the hypotensive action of clonidine could be inhibited by naloxone or by the \( \alpha \)-receptor antagonist yohimbine, whereas the hypotensive action of morphine was only inhibited by naloxone and not by yohimbine, which suggests that \( \alpha_2 \) receptors are activated before opiate receptors during the action of clonidine. The nature of the opioid involved in humans is also not known, although an endorphin-like substance may be suspected on the basis of findings in SHRs.

The involvement of an endogenous opioid appears to be contributory rather than indispensable for the antihypertensive action of clonidine. Naloxone did not reverse the effect of clonidine in half of the hypertensive patients studied (nonreacting group), nor was there an interaction between the two drugs in normotensive rats or in normotensive human volunteers. Hypotensive and bradycardiac actions of clonidine can be elicited from various sites in the pontomedullary region and the pathways in which an endogenous opioid may be released could become more important in certain forms of hypertension. It has been reported that destruction of the nucleus of the solitary tract eliminates the hypotensive effect of clonidine in SHRs but does not influence it in normotensive rats. It is therefore tempting to speculate that endogenous opioid peptides in the human brain may contribute to the central control of sympathetic tone and blood pressure, and that this mechanism is normally inactive but becomes functional in certain forms of hypertension. Naloxone did not increase blood pressure and heart rate in any of the patients during placebo treatment (fig. 1B). Therefore the resting tone of the “opioidergic” neurons may be low, although they may be activated by sympathoinhibitory stimuli, such as central \( \alpha \)-receptor activation.

A statistically significant bimodality in the distribution of patients according to their blood-pressure response to naloxone could not be demonstrated in this relatively small group of patients. However, reacting patients responded to clonidine by a greater reduction in blood pressure than did the nonreacting patients. Because clonidine acts by reducing sympathetic outflow from the brain, basal sympathetic tone may be increased in the subset of reacting patients. Other studies also indicate that essential hypertension is not a homogenous entity. For example, Kuchel et al. could distinguish patients with labile essential hypertension as “normoadrenergic” or “hyperadrenergic”; the latter showed signs of excessive sympathetic reactivity. De Champlain et al. found that about 50% of patients with either labile or stable essential hypertension were hyperadrenergic, characterized by enhanced catecholamine and heart rate increases in response to change from the supine to the upright position. These hyperadrenergic patients also showed a greater hypotensive response to chronic propranolol treatment than did the normoadrenergic patients. Further studies are needed to determine whether patients in whom naloxone can reverse the antihypertensive action of clonidine correspond to the hyperadrenergic patients identified in either of the above studies. Alternatively, it is possible that reacting patients are more prone to endogenous opioid release than nonreacting patients, which may have etiologic relevance in certain forms of hypertension.

Finally, the possible involvement of an endogenous opioid in the effects of clonidine may also be relevant to the mechanism of the so-called clonidine discontin-
uation syndrome. Signs of sympathetic overreactivity with rebound or overshoot hypertension have been noted after cessation of clonidine therapy, but the incidence and severity of this syndrome vary widely in different reports.22 Our observations on rebound are affected by the relatively few patients studied and by the retrospective nature of the analysis. Nevertheless, overshoot hypertension and tachycardia were present only in the reacting patients; in the six nonreacting patients (fig. 4), blood pressure and heart rate returned to, but did not exceed, pretreatment levels. Furthermore, there was a significant linear correlation between the ability of naloxone to reverse the hypertensive response to clonidine and the degree of rebound hypertension after cessation of clonidine treatment. These observations suggest that temporary deficiency in a sympathoinhibitory endogenous opioid may contribute to the rebound after clonidine treatment is stopped.

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References
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