Endogenous Opiate Peptides, Stress Reactivity, and Risk for Hypertension

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SUMMARY  Endogenous opiate peptides can regulate neuroendocrine and circulatory responses to behavioral stress and may be important in the pathogenic effects of sympathoadrenal reactivity. We tested this hypothesis by examining the effect of the opiate antagonist naloxone on blood pressure responses to behavioral stress in young adults with high, medium, or low casual blood pressures. Naloxone increased mean arterial pressure responses to stress in subjects with low casual pressure, but had no significant effect on responses in subjects with high casual pressure. These results suggest opioidergic inhibition of sympathetic nervous system responses may be deficient in persons at risk for essential hypertension. (Hypertension 7: 808-811, 1985)

KEY WORDS  • naloxone • sympathoadrenal reactivity • blood pressure • behavioral stress • young adults • hypertension • opioid peptides

YOU NG people with hypertension or at-risk populations show pharmacological and biochemical manifestations of sympathetic hyperreactivity,1,2 possibly accounting for their exaggerated blood pressure responses to behavioral stress.3-5 The mechanism underlying sympathoadrenal hyperreactivity is unknown despite the potential importance of this issue to the etiology of essential hypertension. Opiate peptide systems have a close anatomical relationship to circulatory reflex pathways, and their role in blood pressure regulation has only recently been appreciated. For example, opioid cell bodies or receptors have been found in nucleus tractus solitarius, locus coeruleus, nucleus intermediolateralis, and other nuclei involved in central control of blood pressure.6,7 Additionally, these peptides are present in anterior and intermediate lobes of pituitary as well as adrenal medullae and other sympathetic ganglia.8-10 This rich anatomical substrate is important for neuroendocrine and cardiovascular response systems. Administration of opiate antagonists alters basal levels and response characteristics of important stress hormones including adrenocorticotropic hormone, cortisol, growth hormone, and luteinizing hormone.11 Furthermore, the opiate antagonist naloxone reverses circulatory shock induced by endotoxin,12 hypovolemia,13 and spinal transection.14 There is also evidence that opioid systems are altered in some forms of hypertension. For example, naloxone antagonizes the blood pressure lowering effects of clonidine in spontaneously hypertensive rats but not in Wistar-Kyoto controls nor in normotensive humans.15,16 Additionally, baroreflexes are altered by systemic and central administration of enkephalin in spontaneously hypertensive rats.17

There have been few direct inquiries into opiate peptide control of sympathoadrenal reactivity, specifically its role in the developmental pathophysiology of essential hypertension. Since chronic hypertension could produce opiate abnormalities, prospective studies of prehypertensive populations are necessary to establish the etiological importance of peptidergic mechanisms in this disease. The present study was designed to determine the role of opiate peptides in the sympathoadrenal expression of risk for hypertension by examining the effect of naloxone on blood pressure responses to behavioral stress in young adults with high, medium, or low casual blood pressure.
Materials and Methods

One hundred Duke University undergraduate men between 18 and 24 years of age participated in a blood pressure screening at the student activity center on campus. Subjects reported no major medical problems, and none were taking prescribed medication at the time of testing. Volunteers completed a brief family medical history and were then accompanied to a quiet, semidarkened room where they rested for blood pressure measurement. After a 5-minute rest period, four automatic blood pressure determinations were made at 1-minute intervals. The distribution of mean arterial pressures was examined, and subjects were ranked order by their fourth pressure reading and divided into quintiles before recruitment. Twelve participants (4 per group) with values falling in the upper (high blood pressure), middle (medium blood pressure), and lower (low blood pressure) quintile were recruited for counterbalanced, placebo-controlled, in-laboratory stress tests.

Systolic, diastolic, and mean blood pressures were determined both on campus, and in laboratory by oscillometric techniques using a Dinamap Vital Signs monitor (Critikon, Inc., Tampa, FL, USA). Before any laboratory tests, subjects visited the laboratory for orientation. At that time all subjects were instructed in the nature of the task and given a 3-minute practice session. The purpose of this practice session was twofold. First, it ensured that all subjects understood the instructions and were capable of performing the task. Second, it provided preexposure to the laboratory and testing envirion, thereby reducing novelty effects and minimizing further habituation over repeated testing. In-laboratory stress testing entailed entry to the clinical research unit for insertion of an indwelling intravenous cannula for later drug infusion. Subjects were escorted to the laboratory, where they were seated in a darkened, soundproof chamber (Industrial Acoustics Company, New York, NY, USA) and told to relax until the experimental task began. Blood pressure determinations were made at 1-minute intervals throughout the experiment. Thirty minutes was allowed for recovery from venipuncture and adaptation to measurement. Following a preinfusion rest, 8 mg of naloxone HCl (Narcan) or saline placebo was slowly infused over 10 minutes. A 10-minute prestress rest period followed infusion. The behavioral stressor was a 10-minute performance on a self-paced, mental arithmetic task, which entailed serial additions of three-digit numbers for speed and accuracy. Following task performance, a final 10-minute rest allowed response parameters to return to baseline. Participants returned for a similar stress test 1 week later. All subjects received naloxone on one visit and saline on the other visit with the order counterbalanced within blood pressure subgroups. Subjects were single-blinded to the infusion and reported being unaware of the order of administration. All of the procedures were supervised by a physician (R.B.W., Jr).

Data were scored as the average of 3-minute blocks for the first 9 minutes of each experimental period.

Blood pressure reactivity data were derived for each subject by subtraction prestress scores from values obtained during stress. Naloxone effects were defined as the difference in reactivity scores for drug and placebo sessions for each subject. Naloxone effects were averaged and tested with analysis of variance by casual blood pressure subgroups with least-squares correction for order.

Results

The casual mean arterial pressure averages (± se) of recruited subjects from the upper, middle, and lower blood pressure quintiles were 93.8 ± 1.6 mm Hg, 82.3 ± 0.48 mm Hg, and 72.3 ± 1.1 mm Hg respectively. Blood pressure subgrouping was significantly related to incidence of cardiovascular disease in reported family histories. There was a significant relation between blood pressure subgroups and reported frequency of coronary heart disease (chi square = 8.85, df = 2, p < 0.02) in recruited subjects. Furthermore, these casual blood pressure subgroups produced differential diastolic and mean arterial pressure reactivity during the first 3 minutes of arithmetic performance after saline infusion. For example, despite higher initial arterial pressure levels, average diastolic pressure response at task onset for the high blood pressure subgroup was 11 ± 2.7 mm Hg versus 4.3 ± 2.2 mm Hg in low blood pressure subjects (p < 0.05).

Infusion of naloxone produced no significant effect on resting blood pressure in the three groups. In contrast, opiate blockade during stress resulted in a significant group by drug interaction for mean pressure reactivity (F[2,7] = 9.06, p < 0.05) at task onset, as seen in Figure 1. Naloxone produced no noticeable effect for high and medium blood pressure groups, but it produced a significant increase in the magnitude of response for the low blood pressure group. This drug effect eliminated group reactivity differences that were observed with intact opioidergic innervation (i.e., after saline infusion).

![Figure 1. Effects of casual blood pressure (BP) levels and opiate antagonism with naloxone on mean arterial blood pressure response to behavioral stress. Data are expressed as response magnitude on drug and placebo days. Naloxone pre-treatment significantly increased mean arterial pressure reactivity in the low blood pressure quintile (p < 0.05) only. ANOVA = analysis of variance.](http://hyper.ahajournals.org/Downloadedfrom)
Casual blood pressure subgroups showed differences in average mental arithmetic performance during saline infusion. Low blood pressure subjects produced 9.8 ± 1.35 responses per minute compared with 6.9 ± 1.16 in high blood pressure subjects during saline infusion. The high rate of total responses resulted in more problems solved correctly by low blood pressure subjects (9.1 ± 1.44 correct responses/min in low blood pressure subjects; 6.1 ± 1.15 correct responses/minute in high blood pressure subjects), but did not affect percentage of correct responses. The subgroup differences in task performance were affected by opiate blockade, as shown in Figure 2. Naloxone increased total responses and total correct responses in high and medium blood pressure subgroups, but it decreased both response parameters in the low blood pressure subgroup. Reflecting group differences in naloxone effects on performance, group by drug interactions approached significance for total responses per minute (F[2, 6] = 4.73, p < 0.06) and for correct responses per minute (F[2, 6] = 3.81, p < 0.10).

**Discussion**

These results warrant two basic conclusions regarding casual blood pressure in young adults: 1) high casual blood pressure is associated with increased blood pressure response and decreased speed of performance during an in-laboratory mental arithmetic challenge. 2) Opiate antagonism with naloxone reduces casual blood pressure subgroup differences in cardiovascular and behavioral response to stress (e.g., naloxone increased blood pressure response and decreased speed of performance in the low blood pressure subgroup only).

Subgrouping by casual blood pressure has predictive utility for later hypertension. Longitudinal studies indicate that the level of blood pressure in young adults predicts both level of pressure and incidence of hypertension in later life. In the present study, high and low blood pressure subgroups differed by about 20 mm Hg in casual mean arterial pressure. Furthermore, reported familial incidence of coronary heart disease was significantly greater in the high blood pressure subgroup than in the other subgroups.

Concurrent validity of casual blood pressure subgrouping was demonstrated by differential arterial pressure response to the laboratory stressor during saline infusion. Subjects with high blood pressure had significantly larger blood pressure responses and slower task performance than those with low blood pressure. This exaggerated blood pressure response to stress in subjects with high pressure is also a characteristic of offspring of hypertensive parents. Although this differential responsiveness was short lived (observed only during the first 3 min of task performance), the magnitude and duration of effect compares favorably with those reported in previous studies. The sympathoadrenal mechanism of subgroup response differences is suggested by reports of corresponding changes in plasma catecholamine concentration as well as by blockade with propranolol.

A differential effect of opiate antagonist suggests different levels of opioid tone in the casual blood pressure subgroups. Since blockade of opiate receptors with naloxone reduced subgroup response differences, it can be argued that some individual differences in blood pressure response to stress reflected the integrity of opioid peptide systems. The effect of opiate antagonism on sympathoadrenal responses remains to be determined, but the present data suggest that intact opiate systems may have either direct or indirect inhibitory action on the sympathetic nervous system. This hypothesis is consistent with recent demonstrations that naloxone increases heart rate responses to painful stimuli in horses and humans. The protective importance of this peptidergic neuromodulation is suggested by naloxone effects on digitalis-induced cardiotoxicity during stress. In the present study, absence of a pressor response to naloxone in the high blood pressure subgroup suggests that these persons may be characterized by a preexisting state of functional opiate blockade. This condition could result from a defect in opiate biosynthesis, a deficiency in number or sensitivity of opiate receptors, or an overproduction of an endogenous opiate antagonist.

The relation between behavioral and cardiovascular drug effects warrants further investigation. Interestingly, intact high blood pressure subjects show reaction time slowing that resembles the performance deficit associated with malignant hypertension. Opiate blockade reduced these subgroup response differences by slowing reaction time of low blood pressure subjects. The correlation between naloxone effects on blood pressure responses and math performance suggests a common opioid mechanism regulating both behavioral and cardiovascular reactions to stress. Further research is needed to evaluate the impact of these peptide systems on cognitive appraisal.
and motivational importance of naturally occurring stressors in humans. These peptides may be involved in the biobehavioral expression of risk for cardiovascular disease such as type A behavior patterns and other forms of stress hyperreactivity. Regardless of precise mechanism, the present findings suggest inadequate opioidergic modulation of cardiovascular responses to acute stress in persons at risk for development of essential hypertension.

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