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Abstract

Objective Acute pain sensitivity is reduced in clinical hypertension, but the precise relationship between pain perception and altered blood pressure control is not well-characterized. A negative correlation between resting blood pressure and pain sensitivity is observed throughout the normotensive range, suggesting links between basic mechanisms of blood pressure control and pain regulation. The opioid peptides are important endogenous analgesic mechanisms, but their role in the hypoalgesia of blood pressure elevations has not been well established. The current study sought to examine the effects of endogenous opioids on blood pressure associated hypoalgesia in young adults at risk for hypertension development.

Method The effects of the opioid receptor antagonist, naltrexone, on cold pressor pain sensitivity were assessed in young adult men and women with mildly elevated casual blood pressure.

Results Results indicate interactions between hypertension risk and the effects of opioid blockade on pain sensitivity.

Conclusions These findings suggest exaggerated opioid analgesia in persons at enhanced risk for hypertension, and point to important links between altered neuropeptide regulation of pain and altered blood pressure control mechanisms in the early stages of hypertension.

Keywords: opioids, pain, analgesia, blood pressure, hypertension risk

Acronyms: HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP= mean arterial pressure; HPA= hypothalamic pituitary adrenocortical; CRF= corticotropin releasing factor

Introduction

In recent years, it has become increasingly apparent that regulation of pain sensitivity is altered in clinical hypertension as well as in the early stages of hypertension development. Numerous studies have shown diminished pain sensitivity in hypertensive humans and animals (for reviews see 1, 2). Altered pain sensitivity in hypertension does not appear to be a simple pathophysiological consequence of prolonged clinical hypertension, but may, instead, indicate a basic regulatory mechanism that is altered in the early stages of hypertension. For example, reduced pain sensitivity precedes the development of frank hypertension, and is correlated with casual resting blood pressure throughout the normotensive range (3). Correlations between pain sensitivity and blood pressure have been seen in both normotensive men and women (4) and are observed during a variety of pain assessment procedures (1).

Mild blood pressure elevations in young adults are clearly linked to increased risk for hypertension development later in life (5), but the relationship of other hypertension risk factors to pain mechanisms is not clear. For example, there is evidence to suggest that positive family history of hypertension may predict altered pain sensitivity independent of blood pressure (6, 7), although there is some evidence that familial hypertension alone is not always associated with altered responses to pain (8). Regardless of the precise spectrum of hypertension risk factors, it is apparent that altered pain sensitivity in young adults has some association, albeit poorly characterized, with blood pressure control mechanisms. This alteration in pain sensitivity in mild hypertension may be involved, either directly or indirectly, in

dysregulated circulatory control and the developmental etiology of essential hypertension.

Opioid peptides are important in endogenous analgesia, and are also important in control of sympathoadrenomedullary, hypothalamic pituitary adrenocortical, and circulatory responses to stress (9). However, the role of opioid peptides in blood pressure associated hypoalgesia is not well established. There are indications that the reduced pain sensitivity associated with blood pressure elevations could reflect both opioid and nonopioid mechanisms (10, 11), but the relationship between opioid analgesia and hypertension development is not known. Therefore, systematic study of opioid hypoalgesia in young people at enhanced risk for hypertension is needed to clarify the possible pathogenic role of opioids and altered pain sensitivity in hypertension development. The present study was designed to examine the effects of the opioid antagonist, naltrexone, on cold pressor pain sensitivity in young men and women at enhanced risk for hypertension.

Method

Participants

Women and men between the ages of 18 and 30 were recruited during a blood pressure screening in which health history and 4 minute by minute sitting blood pressure measurements were obtained by a nurse. The screening procedures were similar to those previously used by us (9) and entailed a ten minute seated rest prior to blood pressure determination via a Critikon Dinamap Model 8100 Vital Signs Monitor (Johnson and Johnson, Tampa). Participants who were in the lower quartile (low-

normal blood pressure) and upper quartile (high-normal blood pressure) of the blood pressure distribution for their sex were asked to participate in placebo-controlled laboratory studies. Eligible participants were nonsmokers, nonobese, and free from current or past major medical disorders including chronic pain syndromes, cardiovascular disease, psychiatric disorders, and endocrine disorders. Also, participants had no history of significant trauma to either hand or arm. Participants did not consume more than 3 alcoholic beverages per week and were not currently taking any opioid or non-opioid pain medication. Because of a related interest in the effects of reproductive hormones on pain in naturally-cycling women, subjects who had taken oral contraceptives within the past 6 months were excluded. Subjects were also systematically screened and excluded from participation for history of opiate abuse, kidney disease and liver dysfunction.

Seventy-six women (40 low-normal blood pressure and 36 high-normal blood pressure) and 49 men (25 low-normal blood pressure and 24 high-normal blood pressure) completed the study. As part of a related investigation, most female participants were scheduled to complete the experiment in either the follicular (n=32) or luteal (n=31) phase of their menstrual cycles, determined by history. Blood sampling for reproductive hormones in selected women found 85% accuracy of menstrual cycle diary methodology. Table 1 shows characteristics of participants in the blood pressure subgroups.

Materials and Apparatus

The testing environment for each experimental session was a quiet, temperature controlled room. A Dinamap Model 8100 Vital Signs Monitor was used to measure heart

rate (HR) and oscillometrically-derived systolic (SBP), diastolic (DBP), and mean arterial blood pressure (MAP) from an appropriately-sized brachial cuff. The Dinamap has a high degree of reliability and accuracy, especially for repeated determinations. In a pilot study in our lab, a random sample of manually-derived auscultatory and Dinamap readings from 25 participants showed mean auscultatory SBP=122.2, sd=8.4, and mean Dinamap SBP=125.6, sd=12.6. Mean auscultatory DBP=77.7, sd=7.78, and mean Dinamap DBP=81, sd=6.7. In the present study, the research nurse routinely verified comparability of Dinamap and auscultatory values at the beginning of each experimental session.

Procedure

All procedures were approved in advance by the institutional review boards of Clemson University and Greenville Hospital System. Participants were scheduled for 2 laboratory sessions approximately one month apart. During one session, participants were administered 0.7 mg/kg naltrexone (ReVia, DuPont), a broad-spectrum oral opioid antagonist, one hour before stress testing. This dosage is consistent with our previous studies (12) and with product guidelines. During the other session, participants were administered a placebo. Order of drug administration was counterbalanced and participants were blind to condition. No untoward side effects of naltrexone were reported. As in our previous studies of opioid blockade, the protocol nurse (CG) was aware of drug conditions for each subject to maximize subject safety throughout the experiment. We attempted to minimize any effects of experimental demand by standardizing the instructions and by using automated and/or objective measures. The experimenters were blind to family history and details of the experimental hypotheses.

Upon arrival in the laboratory, participants granted informed consent. Following manual auscultatory blood pressure determination, they were fitted with a Dinamap blood pressure cuff on their non-dominant arm. They were then asked to rest quietly in an upright, seated position for a 10-min baseline HR and blood pressure measurement. Next, study medication was administered. Participants then rested for 50 minutes to allow for drug absorption. A second 10-min resting baseline was measured, and participants were given the cold pressor challenge. During the cold pressor, participants immersed their dominant hand in iced water at 4 degrees Celsius for 120 seconds. Participants were instructed that they could withdraw their hand at any time if it became too painful. HR and blood pressures were obtained throughout the cold pressor challenge. Immediately after removal of the hand from water, participants completed the short-form McGill Pain Questionnaire (13). Participants were asked to rate their overall pain experience during the task. Another 10-minute resting baseline occurred prior to conclusion of the experiment.

Data Analysis

First, resting blood pressure, height, weight and age were analyzed by sex, ethnicity and blood pressure grouping. Analyses were also done on responses to the McGill Pain Questionnaire to determine if order of administration of drugs or menstrual cycle phase had any effect on pain reports. Chi-square analyses were then used to determine if there were any group effects on tendency to discontinue the cold pressor task.

Responses to the McGill Pain Questionnaire were analyzed using mixed-factorial ANOVAs. Between-subjects factors were blood pressure group (low normal or high

normal) and sex. The within-subjects factor was drug (placebo or naltrexone). Correlations between pain ratings and resting blood pressure were also explored. Cardiovascular reactivity to the cold pressor was explored with mixed factorial ANOVAs. Between-subjects factors were blood pressure group (low normal or high normal), and sex. The within-subjects factor was drug (placebo or naltrexone). Dependent variables were change scores from the preceding baseline for SBP, MAP, DBP, and HR. Finally, analyses were repeated, adding family history of hypertension as an independent variable. Inclusion of ethnicity did not alter the results.

Results

Preliminary Analyses

Resting systolic blood pressure and mean arterial pressure were significantly higher in men than in women. Men were significantly taller and heavier than women. Laboratory resting systolic blood pressure, mean arterial pressure and diastolic blood pressure were significantly (p's $<.05$) higher in high-normal blood pressure participants (High BP) than low-normal blood pressure participants (Low BP). There were no effects of drug order on pain reports or resting blood pressure. In women, there were no differences in resting blood pressure or pain reports across menstrual cycle phase.

A mixed-factorial ANOVA was performed to explore blood pressure reactivity to the cold pressor. Within-subjects factors were drug (placebo versus naltrexone) and period (resting versus task). Between-subjects factors were sex and blood pressure grouping. For SBP, MAP, DBP and HR, there were main effects of drug, period, and group (p's $>.05$). This indicates that BPs and HR were higher during the cold pressor

than during rest, higher in high-normal blood pressure participants, and lower during naltrexone than during placebo.

Seventeen participants (10.6%) were unable to tolerate the cold pressor (withdrew their hand before 2 min) on the placebo day, and 20 (12.4%) were unable to tolerate it on the drug day. There were no significant differences in number of participants to discontinue the cold pressor according to sex or blood pressure grouping on either the naltrexone or placebo day.

Blood Pressure and Pain Sensitivity

Correlations between blood pressure and pain reports were conducted on the entire sample. On the placebo day, resting systolic blood pressure was negatively correlated with the sensory subscale of the McGill Pain Questionnaire ($r = -.21$, $p<.05$) and the total score ($r = -19$, $p<.05$). The sample was then split into high-normal and low-normal blood pressure groupings and the correlations were repeated. In the high-normal group, systolic blood pressure was negatively correlated with present pain intensity ($r = -.22$, $p<.05$), and pain severity ($r = -.23$, $p<.05$). In the low-normal group, resting systolic blood pressure was negatively correlated with the sensory subscale ($r=-.22$, $p<.05$), the affect subscale ($r=-.23$, $p<.05$) and the total score ($r=-.24$, $p<.05$). Correlations on the naltrexone day were similar.

There was a significant interaction between drug (placebo vs. naltrexone) and resting blood pressure group (low BP vs. high BP) for present pain intensity ($F[1,121]=6.17$, $p<.05$), indicating that the drug effect on pain intensity was significantly larger in the high-normal blood pressure group (see Figure 1). There was also a main effect of sex ($F[1,121]=8.74$, $p<.05$). For pain severity, there was a similar interaction

between drug and resting blood pressure ($F[1, 121]=4.01$, $p<.05$), and a main effect of sex ($F[1,121]=4.82$, $p<.05$). For the sensory subscale there was also a significant drug-by-group interaction ($F[1, 120]=4.06$, $p<.05$) and a main effect of sex ($F[1, 120]=7.58$, $p<.05$). For the total score, there was a main effect of sex ($F[1,119]=5.09$, $p<.05$). Together, these results indicate that participants with high-normal blood pressure have reduced sensitivity to the cold pressor which is reversed by opioid blockade. In addition, the main effect of sex indicates that women in general found the cold pressor to be more painful than men. The effect of naltrexone on resting blood pressures and the interaction with chronic blood pressure levels merits further study.

Family History of Hypertension and Pain Sensitivity

Participants were then divided into those with a positive family history of hypertension and those with a negative family history of hypertension, using self-report. Positive family history was defined as one or both parents with hypertension, and negative family history was defined as neither parent with hypertension. Questionnaires were mailed to the biological parents in about 90% of subjects. The offspring reports corresponded with parental reports in 80% of cases with return rates of 75% for fathers and 68% for mothers.

There was a three–way interaction between family history of hypertension, blood pressure group, and drug for present pain intensity ($F[1, 117]=7.77$, $p<.05$) and pain severity ($F[1, 117]=9.55$, $p<.05$). This indicates that reduced pain sensitivity is especially apparent in those participants with high-normal blood pressure and a positive family history of hypertension, and the risk associated analgesia is reversed by opioid

blockade. There were no interactions involving family history for SBP, MAP, DBP, or HR reactivity to the cold pressor.

Discussion

The negative correlation between resting blood pressure and pain sensitivity in both hypertensive and normotensive populations is a robust and pervasive finding. This association has been observed for different types of pain stimuli, including finger pressure (3), heat (11), cold (4) and dental pain (14), and has been seen in both women and men (4). The present study supports the negative correlation between blood pressure and pain sensitivity during placebo studies as well as following opioid blockade. Correlations between resting systolic blood pressure and the McGill Pain Questionnaire Total Score were observed, regardless of blood pressure grouping and drug. This supports the conclusions of McCubbin, Bruehl and colleagues (10, 11) that both opioid and nonopioid analgesic mechanisms are linked to chronic resting blood pressure.

Although correlations between pain and blood pressure are present throughout the sample, participants with high-normal blood pressure also have a naltrexone-reversible cold pressor analgesia. This indicates a greater degree of opioid analgesic tone in young persons at risk for hypertension, suggesting that endogenous opioid mechanisms could be involved in the link between altered pain sensitivity and dysregulated blood pressure control in the early stages of hypertension development. A recent study (15) found no naltrexone-sensitive opioid analgesia in normotensives, supporting the notion that opioid analgesic effects may uniquely associated with blood pressure dysregulation and/or elevated risk for hypertension. Moreover, analysis of

family history of hypertension in the present study suggests that opioid analgesia is further developed in persons with multiple hypertension risk factors. These data, taken together, indicate several mechanisms of endogenous analgesia associated with blood pressure control. Opioid-dependent analgesia is especially prevalent in persons at enhanced risk for hypertension, suggesting a possible pathogenic link between opioidergic control of pain sensitivity and mechanisms of blood pressure dysregulation.

The precise role of opioid analgesia in the developmental etiology of hypertension remains to be determined. There are three principle pathways by which analgesia and blood pressure elevations could interact. First, the elevations in blood pressure could cause analgesic responses. Second, changes in pain sensitivity could directly affect blood pressure control mechanisms. Third, a common factor could produce simultaneous changes in both blood pressure and pain sensitivity. These pathways are not mutually exclusive and transactional processes could allow multiple feedback exchanges.

Although the precise nature of this link is unknown at this time, there is some evidence to suggest that differences in pain sensitivity may have at least predictive utility, and perhaps direct pathogenic consequences, in the early stages of hypertension development. In a series of longitudinal studies, Campbell, Ditto and colleagues have linked pain sensitivity in adolescent boys to future blood pressure changes. For example, reduced pain sensitivity in 14 year-old boys independently predicted blood pressure increments upon five-year follow-up (16). At eight year follow-up, Campbell, Ditto, Seguin, Sinray and Tremblay (17) report that pain tolerance predicted ambulatory blood pressures and heart rate variability. This suggests that lower pain sensitivity in

young persons is linked to future blood pressure elevations and altered autonomic circulatory control mechanisms. In light of the current results, these overall findings indicate that opioidergic endogenous analgesic mechanisms are deranged in the early stages of hypertension and that these changes may have predictive and perhaps etiologic significance.

There are several views on how dysregulation of these two systems may interact. For example, Dworkin, Filewich, Miller, Craigmyle, and Pickering (18) described an operant view of the hypertension/analgesia relationship, suggesting that diminished pain sensitivity associated with mild BP elevations could engender further BP elevations via the reinforcing effects of diminished pain and/or discomfort. While this view has some empirical support (19), the complexity of long term BP regulatory mechanisms suggests that additional factors may also be pertinent. For example, several findings suggest common neuroendocrine pathways that could possibly affect both pain and blood pressure control mechanisms. McCubbin and colleagues (9) found a diminished opioid inhibition of both sympathoadrenomedullary and hypothalamic pituitary adrenocortical (HPA) axis responses to stress in persons at risk for hypertension. These findings have given rise to a central opioid hyposensitivity model of hypertension development (20). Briefly, this model states that young persons at risk for hypertension have reduced opioid inhibitory input to paraventricular hypothalamic corticotropin releasing factor (CRF) neurons controlling the anterior pituitary and sympathetic upper motor neurons. This opioid hyposensitivity, in turn, increases sympathoadrenomedullary and HPA axis responses to stress, contributing to circulatory dysregulation and hypertension development. France and colleagues (21, 2) expanded the McCubbin model to link

central opioid hyposensitivity to several endogenous analgesic mechanisms, including baroreflex arc stimulation, exaggerated opioid peptide release from pituitary and adrenal medullae during stress, and stimulation of descending pain modulatory mechanisms. Recent reviews (22) support the McCubbin/France composite model, but the precise role of altered opioid mechanisms in the developmental etiology of essential hypertension remains to be fully specified.

Interestingly, there is evidence in other chronic diseases for progressive, potentially pathogenic, alterations in the association between BP and pain sensitivity. For example, in patients with low back pain, long duration chronic pain distorts the BP/pain relationship, shifting it to an increasingly positive correlation with increasing chronicity (23, 11). Whether on not the BP/pain relationship in hypertension is distorted, or merely shifted along the normative regression line remains to be systematically explored. Regardless, the present study strongly suggests that opioidergic analgesic mechanisms are intimately linked with blood pressure control and risk for hypertension. These findings point to potentially pathogenic opioid mechanisms in the early stages of hypertension development. Additional research is necessary to fully characterize the links between altered opioidergic control of pain sensitivity and altered blood pressure control in hypertension development.

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Table 1. Participant Characteristics

Means with standard deviations in parentheses

		Women	Men
Low-Normal BP	Height (cm)	165 (4.6)	181 (5.9)
	Weight (kg)	61 (7.7)	80 (12.3)
	Age	19 (1.1)	20 (1.8)
	*SBP	102 (6.7)	114 (13.3)
	*DBP	59 (5.3)	59 (5.0)
	N	40	25
	% white	85%	88%
High-Normal BP	Height (cm)	167 (6.9)	180 (6.3)
	Weight (kg)	68 (16.7)	85 (15.8)
	Age	20 (2.5)	21 (3.3)
	*SBP	112 (7.6)	123 (12.0)
	*DBP	66 (5.9)	69 (7.5)
	N	36	24
	% white	72%	54%

*Baseline 1 resting blood pressures

Figure Captions:

Figure 1. Effect of opioid blockade with naltrexone and blood pressure groups on McGill Present Pain Intensity index ($F_{interaction}$ [1,121]=6.17, p<.05).

Figure 2. Effect of opioid blockade with naltrexone and blood pressure groups on McGill Pain Severity index ($F_{interaction}$ [1,121]=4.01, p<.05).

Figure 3. Effect of opioid blockade with naltrexone and blood pressure groups on McGill Sensory Subscale ($F_{interaction}$ [1,121]=4.06, p<.05).

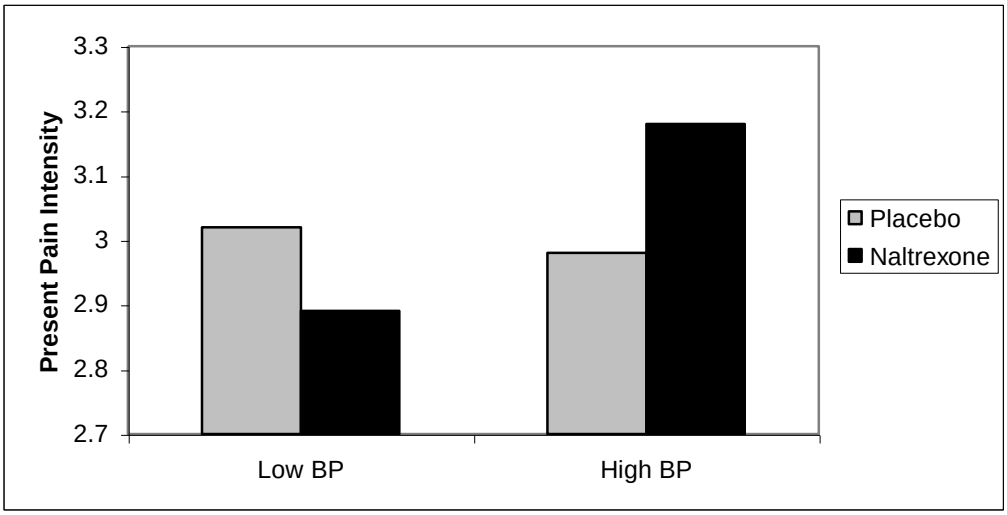
3.3
3.2
3.1
3
2.9
2.8
2.7
Present Pain Intensity
Low BP
High BP
Placebo
Naltrexone

Figure 1

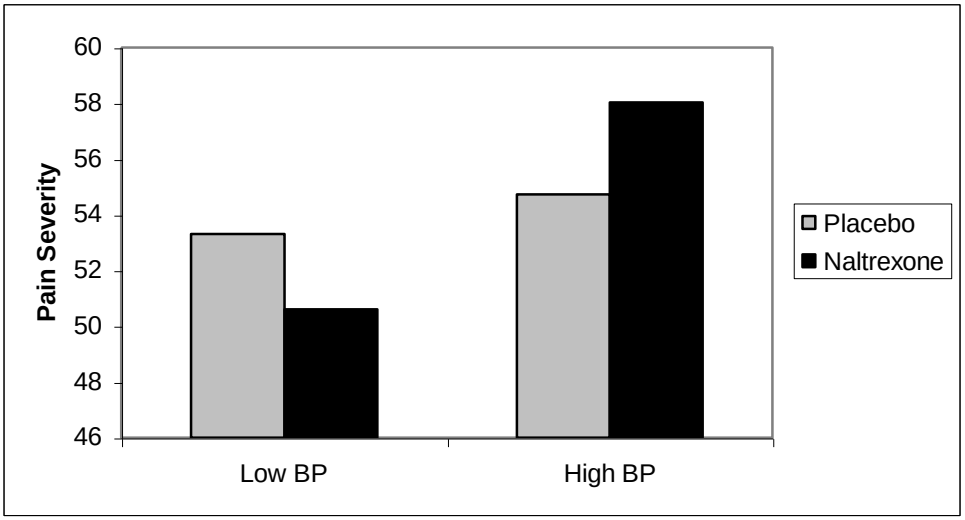
60
58
56
54
52
50
48
46
Pain Severity
Low BP
High BP
Placebo
Naltrexone

Figure 2

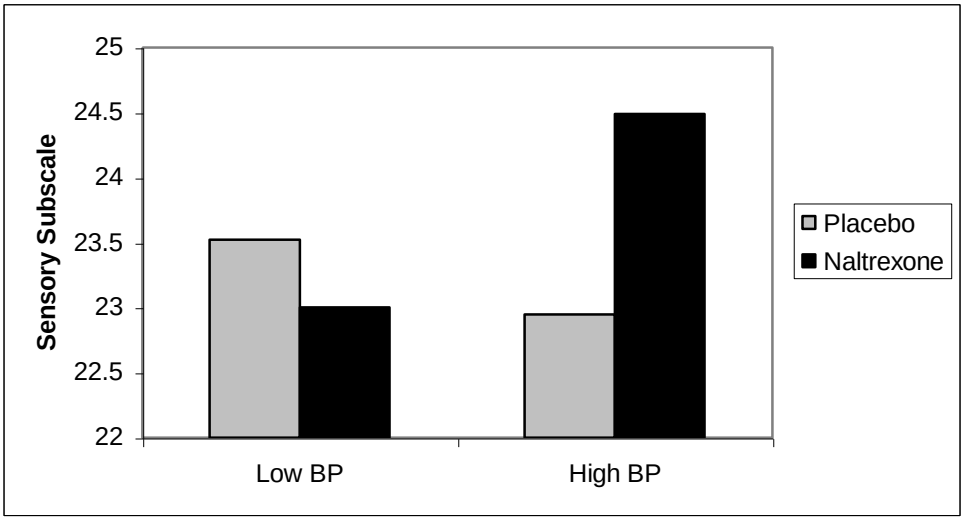
25
24.5
24
23.5
23
22.5
22
Sensory Subscale
Low BP
High BP
Placebo
Naltrexone

Figure 3