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Hypoalgesia associated with elevated resting blood pressure: evidence for endogenous opioid involvement

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Abstract

This study used a placebo-controlled, between-subjects opioid blockade design to evaluate endogenous opioid involvement in the hypoalgesia associated with elevated resting blood pressure (BP) in 163 healthy individuals. Participants were randomly assigned to Drug condition (placebo, naltrexone) and Task Order (computerized maze task with harassment followed by an ischemic pain

task or vice versa). Resting BP was assessed, followed by drug administration, and then the pain and maze tasks. A significant Drug $\times$ Systolic BP (SBP) interaction was observed on McGill Pain Questionnaire-Affective pain ratings ($P < .01$), indicating that BP-related hypoalgesia observed under placebo was absent under opioid blockade. A significant Gender $\times$ Drug $\times$ SBP $\times$ Task Order interaction was observed for VAS pain intensity ($P < .02$). Examination of simple effects comprising this interaction suggested that BP-related hypoalgesia occurred only in male participants who experienced the pain task in the absence of emotional arousal, and indicated that this hypoalgesia occurred under placebo but not under opioid-blockade. Results suggest that under some circumstance, BP-related hypoalgesia may have an endogenous opioid-mediated component in healthy individuals, particularly men.

Keywords

Blood pressure; Acute pain; Endogenous opioid; Opioid blockade; Gender; Emotional arousal

Introduction

Elevated resting blood pressure (BP) is consistently associated with hypoalgesia (reduced acute pain responsiveness) in healthy normotensive individuals (Bruehl et al. 1992; McCubbin and Bruehl 1994; Fillingim and Maixner 1996; Page and France 1997; Ditto et al. 1998; al'Absi et al. 2000; Edwards and Fillingim 2001; Edwards et al. 2001, 2003; Lewkowski et al. 2008). Neurohumoral mechanisms contributing to this association are not well understood. Limited prior work suggests a possible role for alpha-2 adrenergic mechanisms, at least in the baroreflex-mediated component of BP-related hypoalgesia (Chung et al. 2008). Animal studies also clearly indicate a role for endogenous opioids (Zamir et al. 1980; Maixner et al. 1982; Sitsen and DeJong 1983, 1984). Consistent with animal work, one human study reported enhanced endogenous opioid analgesia in normotensives at increased risk for hypertension (McCubbin et al. 2006). More recent work indicated that opioid blockade can eliminate hypoalgesia related to elevated BP on cold pressor pain responses (Lewkowski et al. 2008; Frew and Drummond 2009). However, other human research suggests that hypoalgesia related to elevated normotensive BP levels (McCubbin and Bruehl 1994; Bruehl et al. 2002), increased parental hypertension risk (France et al. 2005; al'Absi et al. 2006), and presence of clinical hypertension (Ring et al. 2008) can occur even when opioid systems are pharmacologically blocked. Thus, the role of endogenous opioids in human BP-related hypoalgesia remains uncertain. One aim of the current study was to further explore this issue.

Some evidence suggests that gender might moderate any opioid influences on BP-related hypoalgesia. Previous reports indicate that BP-related hypoalgesia may be somewhat weaker in women (e.g., Fillingim and Maixner 1996; Girdler et al. 1998; al'Absi et al. 1999). This might in part be due to hormonally related variability in pain responses among women across the menstrual cycle (Fillingim and Ness 2000), and endogenous opioids may contribute to this menstrual cycle-related variability in pain sensitivity (Straneva et al. 2002; Smith et al. 2006). Other work also suggests possible gender differences in endogenous opioid analgesic systems, although the direction of these findings is mixed. Results of several studies using opioid blockade designs suggested that women display greater opioid-mediated analgesia (al'Absi et al. 2004, 2006; France et al. 2005; Frew and Drummond 2008). In contrast, brain imaging studies using PET scan techniques indicate significantly greater pain-induced endogenous opioid analgesia in men (Zubieta et al. 1999). Although the nature and determinants of gender differences in endogenous opioid analgesia are not fully understood, the findings above suggest that gender moderation of opioid mechanisms that may contribute to BP-related hypoalgesia should be further investigated. Given the large and gender-balanced

nature of the current study sample, another aim was to explore whether gender might moderate any role that endogenous opioids play in BP-related hypoalgesia.

Available studies of hypoalgesia associated with resting BP have used designs examining pain responses in the absence of specific emotional arousal. The influence of such arousal on BP-related hypoalgesia has not been well-studied, but might be anticipated given that arousal of negative emotions may increase endogenous opioid analgesia (Bandura et al. 1988; Frew and Drummond 2007, 2008). That is, to the extent that individuals with higher resting BP are hypoalgesic due to more effective endogenous opioid analgesia, experiencing pain after negative emotions have been evoked may exaggerate these opioid-mediated hypoalgesic effects.

In summary, the current study sought to clarify inconsistent past findings regarding opioid involvement in BP-related hypoalgesia by using a large, gender-balanced sample to test main and interactive effects of gender, and by systematically manipulating emotional arousal to address whether absence of emotional arousal in past studies may have contributed to negative findings. The study had three key aims: (1) to test for involvement of endogenous opioids in BP-related hypoalgesia in healthy individuals, (2) to examine possible gender moderation of these effects, and (3) to explore the effects of acute arousal of negative emotions on BP-related hypoalgesia. The primary hypothesis was that if BP-related hypoalgesia were opioid-mediated, significant inverse associations between resting BP and acute pain sensitivity observed in participants receiving placebo blockade would be absent in individuals whose endogenous opioids were blocked pharmacologically by oral naltrexone.

Method

Participants

Participants were 168 healthy normal volunteers recruited through posted flyers, media advertisements, and e-mail announcements. Five participants withdrew from the study prior to engaging in the ischemic pain task (three of whom had received naltrexone and were experiencing apparent side effects), leaving a final sample of 163 participants with useable data. Volunteers were paid \$75 for their participation. Exclusion criteria were: (a) history of cardiovascular disorder; (b) history of renal or hepatic disease; (c) current use of medications that affect cardiovascular function (e.g., beta blockers); (d) current or past history of chronic pain (e.g., low back pain, frequent headaches); (e) current alcohol or substance abuse problems; (f) a history of psychotic or bipolar disorders, or posttraumatic stress disorder; (g) a current diagnosis of major depression; and (h) pregnancy (as determined by pregnancy test conducted on all female potential participants). Other than pregnancy, all study exclusion criteria were evaluated based on self-reported presence or absence of each during an initial screening interview by study staff. Sample characteristics are described in Table 1. The majority of the sample was white and non-Hispanic, with approximately equal numbers of male and female participants. Due to chance differences in random assignment, the Placebo group had significantly more Hispanic participants than the Naltrexone group (8 and 1, respectively), with the former group also displaying a moderately but significantly higher body mass index (although resting blood pressure levels did not differ).

Design overview

Data presented in this study were obtained as part of a project examining opioid mechanisms underlying analgesia related to anger arousal (see Burns et al. 2009 for details). A double-blind, placebo-controlled, between-subjects opioid blockade design was used. A between-subjects design rather than a within-subjects design was used due to the necessity of debriefing participants immediately following the experimental session regarding the deception involved

in the anger induction procedure (see below). This debriefing would render the anger manipulation invalid on repetition in a within-subjects design. Participants were randomly assigned to one of two Drug conditions (placebo or naltrexone) in a double-blinded manner (48.5% of participants received placebo). Participants were also randomly assigned to one of two Task Orders of: (1) a computer maze task with harassment (to arouse negative emotions, especially anger), and (2) a forearm ischemia task (pain-induction). They performed either the computer maze task first and then underwent the forearm ischemia (Maze/Pain), or underwent the forearm ischemia first and then performed the computer maze task (Pain/Maze). The latter condition permitted evaluation of pain responses in the absence of specific emotional arousal, and the former permitted evaluation of pain responses in the context of arousal of negative emotions. Assignment to Drug condition did not differ significantly across Task Orders [Chi Square (1) = 1.54, $P > .10$].

Study drug

Naltrexone hydrochloride (Mallinckrodt Pharmaceuticals, Inc.) was given in the standard oral therapeutic dose (50 mg) which achieves peak blood concentrations within 60 min (Product Information, Mallinckrodt Pharmaceuticals, Inc.). Naltrexone is a nonselective opioid receptor antagonist that temporarily blocks endogenous opioid activity at all three major classes of opioid receptors. The mean elimination half-life for naltrexone and its major active metabolite (6-beta-naltrexol) are 4 and 13 h, respectively, and the standard dose has been shown to block the effects of intravenously administered heroin for up to 24 h (Product Information, Mallinckrodt Pharmaceuticals, Inc.). To maintain blinding, both naltrexone and the placebo were placed in identical capsules prepared by the Vanderbilt University Investigational Pharmacy. Given the half-life of naltrexone, it is unlikely that significant escape from opioid blockade occurred during the study tasks. Although participants were not asked specifically what drug they believed they had received, they did provide numeric (anchored with 0 = "None at All" and 10 = "The Most Possible") ratings to indicate how much they were experiencing ten possible naltrexone side effects post-drug. Compared to the placebo group, participants receiving naltrexone reported significantly more headache [0.4 ± 0.12 vs. 0.1 ± 0.05 ; $t(159) = 2.53$, $P < .05$] and drowsiness [1.8 ± 0.23 vs. 1.2 ± 0.22 ; $t(159) = 2.06$, $P < .05$], although absolute differences were small. Placebo and naltrexone groups did not differ significantly in nausea, vomiting, diarrhea, restlessness, tremors, rapid heartbeat, sweating, or weakness ($P > .10$).

Anger induction task

Arousal of negative emotions (primarily anger) was achieved with a procedure in which participants were required to take instruction from an antagonistic confederate during performance of an ostensible computerized maze task (5 min in duration). The task was portrayed as a collaborative task for two people (the participant and a trained study confederate presented as another study participant). Instructions were presented describing the object of the task as being for the participant to use a computer mouse to move a computer icon as quickly as possible and with as few errors as possible from the entry to the exit of a "complex computer-generated maze." The participant operating the mouse was unable to see the maze on the screen and had to perform the task based solely on guidance provided by the other study participant (i.e., the confederate) who was able to view the computer screen.

The confederate assumed an unfriendly attitude from the outset. He or she followed a semi-standardized script that included instructions to move the cursor in certain directions, exclamations about errors, derogatory comments about the participants' ability, and comments indicating that the confederate blamed the participant for all mistakes. Trained university students served as confederates. To avoid confounds involving participant-confederate gender matches, approximately equal numbers of same sex, male participant-female confederate, and

female participant-male confederate matches were used. This task and the harassment manipulation were adopted from Engebretson et al. (1989).

Pain-induction

Pain was induced with an ischemic pain procedure based on that described by Maurset et al. (1992). Participants engaged in 2 min of dominant forearm muscle exercise using a hand dynamometer at 50% of his or her maximal grip strength (as determined prior to beginning the laboratory procedures). Immediately following this, a blood pressure cuff was inflated on the participant's dominant bicep to 200 mmHg. The cuff remained inflated until participants indicated that their maximal pain tolerance had been reached (up to a maximum of 5 min due to requirements of IRB approval). Because nearly 50% of participants reached this 5 min limit, a skewed distribution owing to ceiling effects prevented valid analysis of pain tolerance data for testing primary hypotheses. Tolerance values did not differ significantly between task orders ($P > .10$), with a comparable tolerance range for the Pain/Maze (30–300 s) and Maze/Pain orders (25–300 s).

Procedure

Participants were screened for exclusion criteria and asked not to consume caffeine for 3 h prior to their appointments, nor use analgesics or medications potentially affecting blood pressure (e.g., pseudoephedrine) for 12 h prior to their appointments. Written informed consent was obtained prior to beginning study procedures. When participants arrived at the laboratory, the equipment, procedures, and function (and risks) of naltrexone were explained, and maximum grip strength was determined. Participants were seated in a comfortable chair in an upright position throughout all experimental procedures. A 10-min resting adaptation period commenced, after which three resting blood pressure (BP) readings were obtained at 1-min intervals using an automated oscillometric cuff (Dinamap Compact T, Johnson & Johnson, Inc.). After BP determinations, participants were asked to complete numeric ratings scales to describe their current levels of anger and anxiety (0 = "None at All" and 100 = "The Most Possible"). Participants then received the appropriate randomized drug (placebo or naltrexone), and rested quietly for 60-min to allow peak opioid blockade activity to be achieved.

Next, for participants in the Maze/Pain task order condition, the confederate entered the room and sat approximately two meters from the participant on the opposite side of the computer table. They were told not to speak. The instructions for both tasks were given, but the instructions for the maze task were emphasized and directed to both the confederate and participant. The maze task then began, and BP was repeatedly assessed at 1-min intervals during this task. Immediately after termination of the maze task, anger and anxiety ratings were again obtained to be used as a manipulation check for the anger-induction manipulation. Instructions for the ischemic task were then briefly reiterated and it began approximately 90 s after the computer maze was completed. Immediately after the ischemic task, participants provided pain ratings using the McGill Pain Questionnaire-Short Form (MPQ; Melzack 1987), which includes separate subscales assessing sensory (MPQ-Sensory) and affective (MPQ-Affective) pain qualities. The MPQ also includes a 100 mm visual analog scale of overall pain intensity (VAS Intensity).

For participants in the Pain/Maze task order, after the 60-min drug absorption period, instructions for both tasks were given, but the instructions for the ischemic task were emphasized. The ischemic pain task was then conducted, and immediately following this, participants completed the MPQ. The confederate then entered the room, and instructions for the maze task were given and directed to both the confederate and participant. The maze task then was conducted, with repeated BP determinations at 1-min intervals during this task.

Immediately upon cessation of the maze task, participants again provided ratings of anger and anxiety as a manipulation check.

After completion of both tasks, participants were thoroughly debriefed (especially with regard to the harassment manipulation), asked whether they had believed the “other participant” was part of the study, and were provided with information regarding possible side effects of naltrexone. Participants were kept under observation until 3 h following drug administration to monitor for side effects, and were discharged after this time unless side effects required further monitoring.

Statistical analysis

All analyses were conducted using the SPSS for Windows Version 15 statistical package (SPSS, Inc., Chicago, IL). Preliminary manipulation check analyses were conducted to determine whether the anger induction manipulation had produced the desired effects on emotional arousal. These analyses used paired-sample *t*-tests to examine changes in systolic (SBP) and diastolic (DBP) blood pressure, and ratings of anger and anxiety from baseline to the maze task. Primary hypotheses were tested using a series of three univariate General Linear Model (GLM) analyses to examine the main and interactive effects of resting BP on responses to the ischemic pain task. All GLM analyses used Type III sums of squares, so results reflected the unique influence of each effect described. Because BP-related hypoalgesia is typically observed for SBP rather than DBP (Bruehl and Chung 2004), analyses were restricted to SBP to reduce the risks of inflated type I error. Each analysis specified a full factorial model including the main and interactive effects of resting SBP, Drug condition (placebo or naltrexone), Task Order (Pain/Maze or Maze/Pain), and Gender (male or female). Ischemic pain ratings were the dependent measure. The SBP variable used in analyses was the mean resting pre-drug baseline value. Significant interactions in primary analyses were dissected via relevant simple effects tests, and within-cell correlations are presented as an index of effect size. All probability values reported are two-tailed with a $P < .05$ criterion for statistical significance.

Results

Anger induction manipulation check

Paired-sample *t*-tests indicated that the anger induction manipulation produced significant increases in both anger [$t(160) = 9.39, P < .001$] and anxiety [$t(160) = 2.25, P < .05$]. Changes in anger ($d = 0.91$) were notably larger in magnitude than changes observed for anxiety ($d = 0.18$), indicating that the harassment manipulation aroused primarily anger as intended. Harassment-related increases in both SBP [$t(160) = 6.73, P < .001$] and DBP [$t(160) = 9.43, P < .001$] were also significant, although effect sizes were relatively modest in magnitude ($d = 0.37$ and $d = 0.54$ for SBP and DBP, respectively). Overall, these analyses indicated that the harassment task was associated with significantly increased physiological arousal and self-reported negative affect, suggesting that it was appropriate to examine effects of arousal of negative emotions (i.e., Task Order) on associations between SBP and pain responses in primary analyses.

Ischemic pain task

For the analysis with MPQ-Affective ratings as the dependent measure, all main and interaction effects involving Gender and Task Order were nonsignificant ($F < 1.0$). However, as hypothesized, a significant Drug $\times$ SBP interaction was noted [$F(1,146) = 6.45, P < .01$]. The effect of opioid blockade on the SBP/pain association is depicted graphically in Fig. 1 based on procedures described by Aiken and West (1991). That is, the regression equations computed for each drug condition were solved for hypothetical low and high SBP values (-1 SD and $+1$

SD from the mean SBP level; 99.1 and 122.9 mmHg, respectively). Pain ratings were then predicted for these representative low and high SBP values and were plotted by drug condition. Simple effect analyses indicated that in the placebo condition, the association between resting SBP and MPQ-Affective ratings was inverse and approached significance ($r = -0.21$, $P < .06$). In contrast, the comparable association in the naltrexone condition was positive and approached significance ($r = 0.21$, $P < .06$). Thus, the significant Drug $\times$ SBP interaction on MPQ-Affective ratings indicated opposite effects of BP on pain responses in the placebo versus opioid blockade conditions.

A similar analysis of MPQ-Sensory ratings failed to reveal any significant main or interaction effects (all $F < 1.6$).

A GLM analysis of VAS Intensity ratings revealed a significant four-way Gender $\times$ Drug $\times$ SBP $\times$ Task Order interaction [$F(1,144) = 4.04$, $P < .02$]. Dissection of this complex gender interaction by simple effects analysis indicated that for male participants, opioid involvement in BP-related hypoalgesia was significantly dependent on whether participants were emotionally aroused [Drug $\times$ SBP $\times$ Task Order interaction: $F(1,72) = 4.77$, $P < .05$]. For male participants undergoing pain in the absence of emotional arousal (Pain/Maze order), those receiving placebo exhibited a moderate inverse SBP/pain association as expected, although this was nonsignificant due to cell size limitations ($r = -0.32$, n.s.). For male participants in the Pain/Maze order receiving naltrexone, the association between SBP and VAS intensity was positive and nonsignificant ($r = 0.14$, n.s.). This effect of opioid blockade is depicted graphically in Fig. 2a in a manner comparable to Fig. 1. That is, for men in the Pain/Maze order, the regression equations computed for each drug condition were solved for hypothetical low and high SBP values. Pain ratings were then predicted for these representative low and high SBP values and were plotted by drug condition.

For male participants in the Maze/Pain task order (in which participants were angered before undergoing pain induction), the pattern of correlations was quite different. Under placebo, the association between SBP and VAS Intensity was moderate in magnitude and positive ($r = 0.34$, n.s.), but under naltrexone, this relationship was small and negative ($r = -0.14$, n.s.).

In female participants, the Drug $\times$ SBP $\times$ Task Order interaction approached significance [$F(1,72) = 3.42$, $P < .07$], but reflected a different pattern than in male participants. Specifically, for female participants in the Pain/Maze order receiving placebo, a correlation near zero was observed between SBP and VAS intensity ($r = -0.08$, n.s.), whereas comparable female participants receiving naltrexone displayed a moderate positive correlation approaching significance ($r = 0.39$, $P < .10$). For comparison with Fig. 2a in men, this effect of opioid blockade on the SBP/pain relationship among female participants in the absence of emotional arousal is depicted graphically in Fig. 2b. In the Maze/Pain task order, women receiving placebo exhibited a moderate positive correlation between SBP and VAS intensity ($r = 0.31$, n.s.), with women receiving naltrexone in this task order demonstrating a correlation near zero ($r = -0.05$, n.s.). The pattern of findings in female participants described above was not altered by inclusion of main and interactive effects of menstrual cycle phase (dummy coded 1 or 2 to reflect follicular versus luteal phase).

Examining the correlations above within cells as a reflection of effect size magnitude rather than tests of significance (Cohen 1988), the pattern above indicates that moderate magnitude BP-related hypoalgesia occurred only in men with intact endogenous opioid function (placebo condition) who were not angered prior to experiencing pain (Pain/Maze task order). Results suggested that both opioid blockade (for women not emotionally aroused) and negative emotional arousal (for men and women with intact endogenous opioid function) can be associated with moderate magnitude resting BP-related *hyperalgesia*.

Discussion

Results of this study are consistent with prior work indicating that elevated resting BP in healthy normotensive individuals is associated with reduced pain responsiveness (Bruehl et al. 1992; McCubbin and Bruehl 1994; Fillingim and Maixner 1996; Page and France 1997; Ditto et al. 1998; al'Absi et al. 2000; Edwards and Fillingim 2001; Edwards et al. 2001, 2003; Lewkowski et al. 2008). Moreover, pharmacological blockade of endogenous opioids with naltrexone eliminated this BP-related hypoalgesia, suggesting that it is at least partially mediated by endogenous opioids. This finding is consistent with numerous animal studies supporting a role for endogenous opioids in BP-related hypoalgesia (Zamir et al. 1980; Maixner et al. 1982; Sitsen and DeJong 1983, 1984; Naranjo and Fuentes 1985). The current findings are also consistent with prior human research indicating that opioid blockade can eliminate hypoalgesia associated with elevated BP on cold pressor pain responses (Lewkowski et al. 2008; Frew and Drummond 2009) and work suggesting greater endogenous opioid analgesia in individuals at increased risk for hypertension (McCubbin et al. 2006). Other human studies similarly hint at possible opioid mediation of BP-related hypoalgesia, but did not directly test this possibility empirically. For example, within a normotensive sample, higher resting BP was associated with both greater cold pressor pain tolerance and higher circulating levels of beta-endorphin, an endogenous opioid peptide with known analgesic properties (Rosa et al. 1988). Similarly, two other studies reported that hypertensive participants displayed both diminished responsiveness to acute pain and higher circulating levels of beta-endorphin when compared to normotensive controls (Sheps et al. 1992; Guasti et al. 1996). Taken together, the studies above all suggest that endogenous opioid activity can contribute to BP-related hypoalgesia in some circumstances.

This conclusion is not, however, universally supported by the existing literature. Several studies indicate that hypoalgesia related to elevated normotensive BP levels (McCubbin and Bruehl 1994; Bruehl et al. 2002), increased parental hypertension risk (France et al. 2005; al'Absi et al. 2006), and presence of clinical hypertension (Ring et al. 2008) can occur even when opioid systems are pharmacologically blocked. While in some cases relatively small sample sizes in past work may have contributed to negative results (Bruehl et al. 2002; McCubbin and Bruehl 1994), other studies had sample sizes nearly as large as the current study and incorporated a more powerful within-subject design (e.g., France et al. 2005). Although several of the studies above with negative findings employed the same opioid antagonist as the current study (oral naltrexone; France et al. 2005; al'Absi et al. 2006; Ring et al. 2008), these studies all used an electrocutaneous pain stimulus rather than the ischemic (current study) or cold pressor (McCubbin et al. 2006; Lewkowski et al. 2008; Frew and Drummond 2009) pain stimuli used in studies supporting opioid mediation. It is possible that such methodological differences could have contributed to the discrepant findings regarding effects of opioid blockade. Although determinants of whether BP-related hypoalgesia is expressed with or without an opioid-mediated component remain to be elucidated, the neurohumoral contributors to this hypoalgesia are likely to be multifactorial, and may include alpha-2 adrenergic, serotonergic, and other mechanisms as well (Maixner and Randich 1984; Randich and Maixner 1984; Taylor et al. 2000; Tsukamoto et al. 2000; Chung et al. 2008).

The current results are consistent with several prior studies suggesting that BP-related hypoalgesia may be moderated by gender. Significant gender interactions observed on VAS intensity ratings supported previous work suggesting that BP-related hypoalgesia may be more prominent in men (e.g., Fillingim and Maixner 1996; Girdler et al. 1998; al'Absi et al. 1999), and further indicated that this hypoalgesia in men has an opioid-mediated component. That is, the moderate magnitude inverse association observed in male participants between resting SBP and pain intensity under placebo was absent under opioid blockade. This finding is consistent with brain imaging work indicating greater endogenous opioid analgesia in men (Zubieta et

al. 1999), although it is in contrast to other work suggesting greater opioid analgesia in women (al' Absi et al. 2004, 2006; France et al. 2005; Frew and Drummond 2007). Statistical control for menstrual phase (follicular versus luteal) did not alter the observed pattern of results, so this potential confound would not appear to explain the absence of BP-related hypoalgesia on pain intensity among female participants in this study.

Based on the fact that arousal of negative emotions may increase endogenous opioid analgesia (Bandura et al. 1988; Frew and Drummond 2007, 2008), we hypothesized that undergoing pain stimulation after induction of negative emotions might exaggerate BP-related analgesia if it were opioid-mediated. Thus, to the extent that individuals with higher resting BP displayed hypoalgesia due to more effective endogenous opioid systems, we expected that experiencing pain after arousal of negative emotions might exaggerate opioid-mediated hypoalgesic effects. Results failed to support this hypothesis. Under placebo, hypoalgesia on the VAS pain intensity measure related to higher resting BP was apparent only when pain was experienced in the absence of emotional arousal (and only in men). Inclusion of an emotional arousal manipulation in the current work would therefore not appear to explain why the present results suggested opioid mediation of BP-related hypoalgesia whereas past studies without an emotional arousal manipulation did not (McCubbin and Bruehl 1994; Bruehl et al. 2002; France et al. 2005; al' Absi et al. 2006).

Results of this study may have implications for understanding altered functional associations between the cardiovascular and pain regulatory systems that appear to occur in individuals with chronic pain. Several studies suggest that BP-related hypoalgesia is absent in individuals with chronic pain (Brody et al. 1997; Maixner et al. 1997; Bragdon et al. 2002; Bruehl et al. 2002, 2008, in press; Chung et al. 2008;). Given the possibility that endogenous opioids may contribute to expression of BP-related hypoalgesia, it is notable that prior work indicated reduced endogenous opioid function and opioid levels in many individuals with chronic pain (Bruehl et al. 1999, 2004). Results of brain imaging studies (using PET scan with mu opioid radiotracers) of individuals with chronic pain also can be interpreted as suggesting opioid receptor downregulation (Sprenger et al. 2005), which would in turn imply a reduction in opioid analgesic capabilities. Based on the assumption that opioid dysfunction is a key feature of chronic pain, we previously hypothesized that these chronic pain-related opioid changes would account for alterations in BP-related hypoalgesia in individuals with chronic pain. The only previous test of this hypothesis (Bruehl et al. 2002) failed to demonstrate opioid-mediation of BP-related hypoalgesia in healthy controls, thereby making it impossible to determine whether the absence of BP-related hypoalgesia observed in a parallel chronic low back pain sample was influenced by opioid system changes. The current results support at least partial opioid mediation of BP-related hypoalgesia in healthy individuals. Therefore, further exploration may be merited regarding how chronic pain-related opioid changes might contribute to alterations in overlapping systems modulating cardiovascular and pain regulation.

The current study has several limitations. It employed a between-subjects design due to the ethical necessity of revealing immediately after the study session the deception used in the anger induction manipulation, rendering a more powerful (and more common) within-subjects opioid blockade design impossible. Whether differences between separate naltrexone and placebo groups can be interpreted the same as more traditional within-subject blockade effects remains unclear. Although a relatively large overall sample size was available, the relatively lower power of the between-subjects design led to inadequate power for evaluating the complex four-way interaction we found for pain intensity. Cell size limitations likely contributed to the lack of significance of within-cell correlations used to explore this four-way interaction. Several of these within-cell correlations would have been significant with only small increases in cell sizes. However, small cell sizes might also lead to unstable patterns of findings within-cells due to the influence of a few extreme cases. Another potential limitation is that all

participants, regardless of weight, received the same standard clinical dosage of naltrexone. The possibility that some heavier participants may have experienced incomplete opioid blockade due to inadequate naltrexone dosage (by weight) cannot be ruled out. Given all of the limitations above, findings of this study require replication.

In summary, results of this study indicated that the association between elevated resting BP and reduced affective pain intensity was eliminated by pharmacological blockade of opioid receptors. This suggests that BP-related hypoalgesia has an opioid-mediated component at least under some circumstances. This hypoalgesia was absent under conditions in which pain was experienced in the context of negative emotional arousal. Observed gender interactions on overall pain intensity support previous work hinting that BP-related hypoalgesia may be stronger in men, and further suggest that this hypoalgesia in men is at least partially opioid-mediated. Identification of situational factors that may determine whether BP-related hypoalgesia is opioid rather than non-opioid mediated may be a useful focus of future work. The current findings may potentially be relevant to understanding mechanisms that contribute to chronic pain-related changes in functional interactions between the cardiovascular and pain regulatory systems.

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Fig. 1.

Relationships between resting SBP and MPQ-Affective subscale scores across placebo and opioid blockade conditions. SBP values plotted are hypothetical values representing one standard deviation (SD) below and above the sample mean

Fig. 2.

a, b Relationships between resting SBP and VAS pain intensity in male (**a**) and female (**b**) participants across placebo and opioid blockade conditions in the absence of emotional arousal. SBP values plotted are hypothetical values representing one standard deviation (SD) below and above the sample mean

Table 1

Sample characteristics by drug condition

Variable	Drug condition	
	Placebo (n = 79)	Naltrexone (n = 84)
Age (years)	27.5 ± 0.67	26.8 ± 0.57
Gender (% female)	50.6	50.0
Body mass index ***	26.0 ± 0.53	24.0 ± 0.32
Race (%)		
Caucasian	78.9	79.8
Asian	9.2	13.1
African-American	11.8	4.8
Other	0.0	2.3
Ethnicity (%) *		
Non-Hispanic	89.5	98.8
Hispanic	10.5	1.2
Resting SBP (mmHg)	111.5 ± 1.30	110.0 ± 1.28
Resting DBP (mmHg)	66.6 ± 1.03	64.9 ± 0.85

All means are presented as mean ± SE

SBP systolic blood pressure, DBP diastolic blood pressure

*
 $P < .05$ ***
 $P < .001$