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Trait Anger Expressiveness and Pain-Induced Beta-Endorphin Release: Support for the Opioid Dysfunction Hypothesis

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Abstract

The anger management styles of anger-in (inhibition) and anger-out (direct expression) are positively associated with pain responsiveness. Opioid blockade studies suggest that hyperalgesic effects of trait anger-out, but not those of trait anger-in, are mediated in part by opioid analgesic system dysfunction. The current study tested the opioid dysfunction hypothesis of anger-out using an alternative index of opioid function: pain-induced changes in plasma endogenous opioids. Plasma beta-endorphin (BE) was assessed at rest and again following exposure to three laboratory acute pain tasks (finger pressure, ischemic, and thermal) in 14 healthy controls and 13 chronic low back pain (LBP) subjects. As expected, acute pain ratings correlated positively with measures of anger-in (both groups) and anger-out (LBP group; p 's < .05). Greater pain-induced increases in BE were associated with significantly lower pain ratings in both groups (p 's < .05). Hierarchical multiple regression indicated that greater anger-out significantly predicted smaller pain-induced BE increases (p < .05). Subject type did not moderate this association (p > .10). Anger-in did not display significant main or interaction effects on pain-induced BE changes (p 's > .10). The significant association between anger-out and BE release partially mediated the hyperalgesic effects of anger-out on pain unpleasantness, and was not attenuated by statistical control of general negative affect. This suggests unique associations with expressive anger regulation. Elevated trait anger-out therefore appears to be associated with opioid analgesic system dysfunction, whether it is indexed by responses to opioid blockade or by examining circulating endogenous opioid levels. Possible "state $\times$ trait" interactions on these anger-related opioid system differences are discussed.

Keywords

Anger-Out; Anger-In; Opioids; Beta-Endorphin; Pain

Introduction

Research has highlighted the pain-related effects of anger management styles (e.g., Keefe et al., 2001; Kerns et al., 1994; Burns et al., 2003; 2004). A recent review indicated that 16/19 published studies supported relationships between elevated trait anger-out (managing anger via direct physical or verbal expression) and either increased acute pain responsiveness or

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greater levels of chronic pain intensity and dysfunction (Bruehl et al., in press). Elevated trait anger-in (managing anger through inhibition of expression) has similarly demonstrated associations with increased pain responsiveness (Kerns et al., 1994; Gelkopf, 1997; Bruehl et al., 2002; Burns et al., 2004).

Evidence suggests that endogenous opioid system dysfunction may contribute to the pain-related effects of anger-out (Bruehl et al., 2002; 2003). Individuals low in trait anger-out reported greater acute pain intensity following opioid blockade than when under placebo, whereas those high in anger-out did not, suggesting absence of opioid analgesia in the latter (Bruehl et al., 2002). Moreover, opioid blockade responses suggested that opioid dysfunction partially mediates the positive relationship between anger-out and chronic pain intensity (Bruehl et al., 2003). These findings indicate that greater acute and chronic pain responsiveness associated with trait anger-out may be due to impaired ability to elicit endogenous opioid analgesia.

One interpretation of these findings is that individuals elevated in trait anger-out do not release sufficient endogenous opioids when exposed to acute pain stimuli to produce significant analgesia. Consequently, high anger-outs do not exhibit the hyperalgesic responses to opioid blockade exhibited by low anger-outs. Previous work has indexed opioid activity through responses to placebo-controlled opioid blockade, but has not directly assessed opioid levels. Examination of circulating plasma levels of endogenous opioids provides an alternative methodology for testing the opioid dysfunction model of anger-out.

This study therefore examined relationships between anger management style and changes in plasma endogenous opioid levels following a series of acute pain stimuli. The target of this study was plasma beta-endorphin (BE), an endogenous mu opioid receptor agonist with known analgesic properties (Millan, 2002). Circulating plasma BE has previously shown associations with acute pain responses (e.g., Bragdon et al., 2002; Cleeland et al., 1984; Guasti et al., 1996; Miller et al., 1993; Rosa et al., 1988; Sheps et al., 1995; Szyfelbein et al., 1985). Therefore, plasma BE levels were assessed at baseline and again following three laboratory acute pain stimuli in a series of subjects participating in a larger study examining alpha-2 adrenergic pain regulatory mechanisms. Given previous opioid blockade results (Bruehl et al., 2002; 2003), we hypothesized that subjects higher in anger-out would demonstrate smaller pain-induced increases in plasma BE than would individuals lower in anger-out. We further expected that anger-in would not be associated significantly with pain-induced BE changes based on prior findings indicating nonsignificant links between anger-in and responses to opioid blockade (Bruehl et al., 2002; 2003). Finally, given the possibility that chronic pain itself may alter endogenous opioid levels (Bruehl et al., 1999), we considered the possibility that chronic pain status might moderate relationships between anger-out and BE responses to pain.

Method

Design

Data were obtained as part of a larger study using double-blind, placebo-controlled crossover administration of yohimbine, an alpha-2 adrenergic receptor antagonist. In order to permit clear interpretation of BE responses to pain unconfounded by yohimbine administration, the current study examined only placebo condition data. Order of drug administration was randomized and counterbalanced. Between-subject variables were anger management style (anger-in and anger-out) and participant type, and the within-subject variable was placebo condition change in plasma BE levels from pre-drug baseline to the assessment period following the three acute pain tasks.

Sample

The sample consisted of 27 subjects (n=13 chronic low back pain and n=14 healthy pain-free controls). All subjects were recruited through advertisements posted in newspapers or on-line advertisements on a university e-mail system. General criteria for participation included age between 18–55 years; no history of cardiovascular disease, hypertension, liver or kidney disorders, or opiate dependence; and no current use of anti-hypertensive or antidepressant medications. To minimize extraneous differences between the two groups and minimize the possibility of drug side effects, all subjects were further required to be free of current DSM-IV major depression, panic disorder, or posttraumatic stress disorder based on results of a structured clinical interview conducted by a trained interviewer using the mood disorders module of the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 1997). Potential subjects who were pregnant were excluded and all participants were asked to refrain from use of analgesics, NSAIDs, or any medications potentially affecting blood pressure (e.g., pseudoephedrine) for 12 hours prior to study participation. Subject characteristics are summarized in Table 1. Both groups were statistically comparable in terms of age, gender, and race/ethnicity (primarily white non-Hispanic). No subjects in either group were using opioid analgesics (daily or as-needed) or neuroleptic medications.

Similar to our past work (Bruehl et al., 2002; 2003), additional inclusion criteria for low back pain (LBP) subjects were persistent lower back pain of at least 3 months duration and a typical daily pain intensity of at least 3/10 (0 = “No Pain” and 10 = “Worst Pain Possible”). LBP subjects on average reported moderately severe pain (39.5 ± 4.44 mm on a 100mm visual analog scale of past month chronic pain intensity) and had a high overall level of pain chronicity (median = 81 months). All LBP subjects underwent a medical evaluation conducted by a pain physician to document their pain complaints, with 39% determined to be experiencing signs and symptoms consistent with a likely contribution of neuropathic pain mechanisms (e.g., referred pain in a radicular pattern).

Procedure

All procedures were performed at the Vanderbilt University General Clinical Research Center and were approved by the university Institutional Review Board. All subjects provided informed consent prior to participation. During an initial screening, subjects provided demographic and background information, and completed a questionnaire packet that included the Anger Expression Inventory (Spielberger et al., 1985), the Beck Depression Inventory (Beck et al., 1961), and the trait form of the State-Trait Anxiety Inventory (Spielberger et al., 1970). All subjects then participated in two laboratory sessions one week apart, at the same time of day to control for circadian rhythms. Subjects remained seated upright in a comfortable chair throughout all laboratory procedures.

During each laboratory session, subjects initially completed a 10-minute seated rest period, followed by a series of five blood pressure (BP) determinations using an oscillometric blood pressure cuff. During these BP determinations, continuous finger blood pressures were also obtained with a Portapres device (Finapres Medical Systems, Amsterdam, The Netherlands) while cardiac function data were simultaneously obtained with a 5-lead electrocardiogram. Similar cardiovascular data were obtained during a subsequent 5-minute pre-drug orthostatic challenge, and immediately prior to, during, and for 20 minutes following drug administration. In the interests of space and given the focus of the current study, these cardiovascular data will be detailed elsewhere.

A research nurse under physician supervision next placed an indwelling venous cannula in the participant's dominant arm, followed by a 25-minute adaptation period during which subjects rested quietly. At the end of this resting adaptation period, a 2mL blood sample was obtained

through the cannula for assessment of pre-drug resting baseline beta-endorphin (BE) levels. A 10ml dose of normal saline (placebo) or a 0.4mg/kg dose of yohimbine hydrochloride (in 10ml saline vehicle) was then infused over a 10-minute period using an automated infusion pump. As noted above, order of drug administration was randomized and counterbalanced, and the current study examined data only from the placebo session.

After a 20-minute rest following drug infusion to allow peak blood levels to be achieved, subjects participated in a one-minute pressure pain task using a Forgione-Barber finger pressure pain stimulator that applied 2000 grams of pressure to the dorsal surface of the second phalanx of the index finger of the dominant hand (Forgione & Barber, 1971). Immediately upon cessation of this task, acute pain ratings were obtained using the McGill Pain Questionnaire-Short Form (MPQ; Melzack et al., 1987). Subjects next participated in a forearm ischemic pain task based on procedures described by Maurset et al. (1992). As in our past work (Bruehl et al., 2002), subjects engaged in two minutes of dominant arm exercise using a hand dynamometer at 50% of maximum, and then a blood pressure cuff was immediately inflated on the subject's dominant upper arm to 200 mmHg. The cuff remained inflated until subjects indicated that their pain tolerance had been reached, up to a maximum of five minutes. Substantial ceiling effects precluded valid statistical analysis of ischemic tolerance data (63% of subjects reached the five-minute maximum). After completing this task, subjects again provided acute pain ratings using the MPQ. Finally, subjects participated in a thermal pain task using a Medoc Thermal Sensory Analyzer (TSA-II, Medoc, Inc., Ramat, Israel). This computer-controlled device was used to apply a controlled heat stimulus to the nondominant ventral forearm using a 30×30mm Peltier thermistor probe as reported in prior studies (e.g., Fillingim et al., 2005). A series of four pain tolerance trials was conducted, with the probe applied to a slightly different target site for each trial to avoid local sensitization. For each trial, the probe started at an adaptation temperature of 40°C, with the temperature increasing at a ramp rate of 0.5°C/sec until the subject indicated tolerance had been reached. Immediately following the last thermal pain trial, subjects again completed the MPQ to describe the pain experienced during this task. A final 2mL blood sample was then obtained for assessment of post-pain BE levels. Thus, post-pain BE levels reflected the aggregate BE response to the three pain tasks. Procedures for the second laboratory session were identical to the first session, although procedural instructions were abbreviated.

Beta Endorphin Assays

Blood samples (in purple-top Vacutainer tubes with EDTA) were immediately stored on ice. Within 30 minutes of collection, samples were processed in a cool centrifuge (0–4°C) at 3000rpm for 15 minutes. Plasma was then extracted and stored at –70°C until assays were conducted. Plasma BE levels were determined using a commercially-available radioimmunoassay kit following standard published procedures (Phoenix Pharmaceuticals, Belmont, CA). The detection limit was 0.1 ng/ml, with 0% crossreactivity with met-enkephalin, alpha-MSH, or ACTH. All BE assays were run in duplicate, with the mean across runs used in data analyses.

Measures

McGill Pain Questionnaire – Short Form (MPQ)—The MPQ is a well-validated measure that allows assessment of the sensory and affective qualities of pain (Melzack, 1987). In addition to providing separate Sensory (MPQ-S) and Affective (MPQ-A) pain scores, the MPQ includes a 100mm visual analog scale of overall pain intensity (VAS). For purposes of this study, a parallel VAS measure of pain unpleasantness (anchored with “not unpleasant at all” and “the most unpleasant possible”) was appended to the MPQ. As in past work, written instructions for completing the MPQ asked subjects specifically to describe the acute pain experienced during the laboratory pain tasks (e.g., Bruehl et al., 2002).

Spielberger Anger Expression Inventory (AEI)—The AEI is a validated self-report measure of anger management style (Spielberger et al., 1985). It includes separate subscales assessing Anger-In (AIS) and Anger-Out (AOS). High scores on the AIS reflect a tendency to deal with anger when it is experienced by inhibiting expression and hiding the emotion from others. High AOS scores indicate a tendency to deal with anger through outward expression (e.g., physically or verbally). Both the AIS and AOS have demonstrated adequate internal consistency (Spielberger et al., 1985). AOS scores but not AIS scores have demonstrated significant relationships in prior work with opioid blockade effects on acute pain responses (Bruehl et al., 2002; 2003).

Measures of General Negative Affect—Two measures of general negative affect were administered to permit tests of whether any associations between anger management styles and BE release were specific to anger management style, or rather, due to overlap with negative affect. These measures included the trait form of the State-Trait Anxiety Inventory (STAI; Spielberger et al., 1970), a widely used standardized measure of the tendency to experience anxiety symptoms, and the Beck Depression Inventory (BDI), a common standardized measure of depressive symptoms (Beck et al., 1961). Both instruments have demonstrated adequate psychometric properties and validity (Beck et al., 1961; Spielberger et al., 1970).

Statistical Analysis

All analyses were conducted using the SPSS for Windows Version 13 statistical package (SPSS, Inc., Chicago, IL). Preliminary analyses used Pearson correlation coefficients, t-tests for group mean comparisons, and as appropriate, chi square or Fisher's exact test for categorical measures. Primary analyses were conducted to examine the relationship between measures of anger management style (AOS or AIS) and changes in plasma BE levels in response to the acute pain tasks. These primary analyses consisted of two hierarchical multiple regressions (one for anger-in and one for anger-out). Each analysis included Participant Type, AOS or AIS, and the two-way interaction of these variables as the independent variables, with the dependent measure being a derived BE change variable. BE change was calculated as baseline BE levels subtracted from post-pain BE levels, and thus a positive BE change score indicated increases in circulating BE in response to the acute pain stimuli. Preliminary analyses used similar hierarchical regression techniques to evaluate relationships between anger management style measures and responses to the acute pain stimuli.

Regressions entered control variables in step one, main effects of interest in step two (Subject Type, AOS or AIS scores), and the relevant AOS $\times$ Subject Type or AIS $\times$ Subject Type multiplicative interaction term in step three. Control variables included drug administration order and BE assay set (assays were run in two batches). To permit examination of baseline adjusted BE change scores, resting baseline BE levels were also entered as a control variable. The source of significant AOS $\times$ Subject Type or AIS $\times$ Subject Type interactions was clarified by calculating simple slopes separately for healthy controls and LBP subjects (Aiken & West, 1991). All probability values reported are two-tailed with a $p < .05$ criterion for significance.

Results

Pain and BE Responses to Pain

To help characterize the intensity of the pain stimuli eliciting the BE release that is the focus of this study, Table 2 displays mean pain ratings and pre- and post-pain BE levels by subject type. LBP subjects reported significantly more intense acute pain in response to the thermal task (MPQ-S) than did pain-free controls, with similar nonsignificant trends for the finger pressure (FP) and ischemic tasks. VAS pain intensity ratings (on a 0–100 scale) indicated that all three tasks produced moderate intensity pain in both groups. Inspection of Table 2 indicates

that BE levels increased from baseline to post-pain in both control and LBP subjects alike, although these overall mean changes were nonsignificant in both groups (p 's $>.10$).

As expected based on prior research, zero-order correlations indicated that in both groups, greater BE release tended to be associated with greater analgesia. In healthy subjects, significant inverse correlations were observed between BE change scores and FP MPQ-A [$r(12) = -0.70, p < .01$], ischemic MPQ-A [$r(12) = -0.56, p < .05$] and thermal task MPQ-A ratings [$r(12) = -0.60, p < .05$], with a similar nonsignificant trend noted for thermal task VAS unpleasantness ratings [$r(12) = -0.48, p < .10$]. Among LBP subjects, a significant inverse correlation was observed between BE change scores and FP VAS unpleasantness ratings [$r(11) = -0.57, p < .05$], although thermal task VAS intensity ratings were correlated positively with BE change [$r(11) = 0.60, p < .05$]. This latter effect may have been influenced by that fact that in the LBP group, greater BE release was associated with somewhat higher thermal pain tolerance [$r(11) = 0.45, p < .13$]. The positive correlation between BE change and thermal VAS intensity ratings may therefore have been a function of exposure to higher thermal stimulus temperatures.

Effects of Anger Management Style on Pain Responses

Subsequent preliminary analyses examined whether the two anger management style measures demonstrated hyperalgesic effects on pain responses as expected based on previous studies. Hierarchical multiple regressions revealed significant AOS $\times$ Subject Type interactions for FP VAS unpleasantness ratings (R^2 increment = 0.21, F change (1,22) = 6.99, $p < .05$) and ischemic task MPQ-S ratings (R^2 increment = 0.23, F change (1,22) = 8.76, $p < .01$). Similar nonsignificant two-way interaction trends were noted for FP MPQ-S (R^2 increment = 0.11, F change (1,22) = 3.32, $p < .10$) and FP VAS intensity ratings (R^2 increment = 0.13, F change (1,22) = 3.47, $p < .10$). Simple effects analyses indicated that the significant interaction for FP VAS unpleasantness was due to a nonsignificant negative slope between AOS scores and VAS unpleasantness in healthy controls [$\beta = -0.33, t(11) = -1.21, p > .10$], but a significant positive slope in the LBP group [$\beta = 0.71, t(10) = 2.52, p < .05$]. The significant interaction on ischemic MPQ-S ratings was similarly due to a nonsignificant negative slope between AOS scores and MPQ-S ratings in healthy normals [$\beta = -0.23, t(11) = -0.78, p > .10$], but a positive slope approaching significance in the LBP group [$\beta = 0.53, t(10) = 1.87, p < .10$]. Thus, the pain-enhancing effects of trait anger-out often noted in past work was confirmed, but was restricted to those subjects with chronic low back pain. Other analyses for AOS scores were nonsignificant (p 's $>.10$).

Analyses of anger-in scores revealed significant AIS $\times$ Subject Type interactions on FP MPQ-A ratings (R^2 increment = 0.11, F change (1,22) = 5.49, $p < .05$) and FP VAS intensity ratings (R^2 increment = 0.14, F change (1,22) = 4.18, $p < .05$). Simple effects analyses revealed that the former interaction resulted from a nonsignificant positive slope between AIS scores and MPQ-A ratings in healthy normals [$\beta = -0.33, t(11) = 1.18, p > .10$], but a larger and significant positive slope in the LBP group [$\beta = 0.77, t(10) = 3.45, p < .01$]. The latter interaction resulted from a nonsignificant negative slope between AIS scores and VAS intensity ratings in healthy normals [$\beta = -0.16, t(11) = -0.53, p > .10$], but a significant positive slope in the LBP group [$\beta = 0.64, t(10) = 2.44, p < .05$]. In addition to the interactions above, significant main effects were observed for AIS scores on MPQ-A ratings for both the ischemic task [$\beta = 0.50, t(22) = 2.75, p < .05$] and the thermal task [$\beta = 0.41, t(22) = 2.42, p < .05$]. Both effects indicated that higher anger-in was associated across groups with greater pain intensity. Similar nonsignificant trends were noted for FP MPQ-S ratings [$\beta = 0.34, t(22) = 1.75, p < .10$], FP VAS unpleasantness ratings [$\beta = 0.37, t(22) = 1.93, p < .10$], and ischemic task VAS intensity ratings [$\beta = 0.35, t(22) = 1.74, p < .10$]. All other analyses for AIS scores were nonsignificant (p 's $>.10$). In sum, while greater anger-in was associated with elevated

acute pain sensitivity as expected, there was some evidence that, as with anger-out, this effect was stronger in individuals with low back pain. The significant Subject Type X Anger Management Style interactions above remained significant even after controlling for gender, suggesting that the modestly greater proportion of females in the LBP group did not account for these differences in effects across subject types.

Anger Management Style and BE Responses to Pain

Primary analyses addressed the issue of whether anger management style measures were associated with degree of BE release in response to the acute pain stimuli. Multiple regression of pain-induced changes in BE revealed a significant main effect for AOS scores [$\beta = -0.43$, $t(21) = -3.05$, $p < .01$]. The scatterplot of the relationship between AOS scores and BE changes is presented in Figure 1. Inspection of this figure indicates that individuals lower in anger-out displayed increases in BE in response to pain whereas those higher in anger-out tended to experience no BE increases. The AOS X Subject Type interaction was not significant ($p > .10$), indicating similar effects of anger-out on pain-induced BE changes regardless of chronic pain status. Inclusion of gender as an additional control variable in step one of this analysis did not reveal significant gender effects on BE nor did it alter the observed anger-out main effects.

To explore whether the significant positive relationship between AOS scores and FP VAS Unpleasantness ratings among LBP subjects (see above) was due to this association between greater anger-out and diminished pain-induced BE changes, a mediation analysis was conducted using hierarchical regression methodology recommended by Baron and Kenny (1986). This type of analysis is described in detail in Bruehl et al. (2003). In brief, among the LBP subjects, results of regressions indicated that AOS scores accounted for 28% of the variance in FP unpleasantness ratings, and the incremental variance accounted for by AOS was significant [F change (1,8) = 6.43, $p < .05$]. When pain-induced BE changes were statistically-controlled, however, the variance in FP VAS Unpleasantness ratings accounted for by AOS was reduced to 6.6% and was no longer significant ($p > .10$). These findings suggest that, at least in the case of FP unpleasantness, diminished BE release partially mediated the hyperalgesic effects of anger-out observed in LBP subjects.

For AIS scores, both the main effect for AIS and the AIS $\times$ Subject Type interaction for BE changes were nonsignificant, and thus tests of mediation were inappropriate.

Potential Confounding Effects of General Negative Affect

As in past work regarding relationships between anger management styles and opioid system function (Bruehl et al., 2002; 2003), the possibility was considered that effects of anger-out on BE release may be best accounted for not by anger-out per se, but rather, by shared variance with general negative affect. In the current study, anger-out was moderately correlated with STAI ratings of trait anxiety [$r(25) = 0.35$, $p < .10$], but was only weakly related to BDI depression scores [$r(25) = 0.17$, $p > .10$], possibly due to restricted range in this latter measure as a result of stringent study inclusion criteria. The hierarchical multiple regression for AOS scores described above was rerun with BDI and STAI scores statistically-controlled. Results indicated virtually no change in the effect size for the main effect of AOS scores on BE changes when general negative affect was controlled [$\beta = -0.42$, $t(19) = -2.65$, $p < .05$]. Thus, differences in pain-induced BE release associated with anger-out appeared to be specific to this anger management style rather than merely being due to overlap with underlying general negative affect.

Discussion

Based on the contribution of the anterior cingulate cortex to both opioid-mediated pain regulation as well as emotional regulation (Davidson et al., 2000; Dougherty et al., 1999; Casey et al., 2000; Price, 2000), we hypothesized that impaired central opioid inhibitory function might simultaneously account for the exaggerated pain responsiveness and more overt anger expression style in high anger-out individuals (through reduced opioid inhibition of arousal and anger expressive behaviors; Bruehl et al., 2002; in press). Prior work using an opioid blockade methodology provided preliminary support for this hypothesis, suggesting that the pain-related effects of trait anger-out, but not trait anger-in, were in part mediated by endogenous opioid dysfunction (Bruehl et al., 2002; 2003). Findings that opioid analgesic medications eliminate the positive association between trait anger-out and chronic pain intensity have also been cited as indirect support for the opioid dysfunction hypothesis (Burns & Bruehl, 2005). The current study provided a further direct test of this hypothesis using an alternative index of opioid function: pain-induced endogenous opioid release.

Results indicated that greater trait anger-out was associated both with significantly greater perceived pain intensity (among the LBP group) and significantly less pain-induced BE release (across groups). Moreover, diminished BE release in LBP subjects higher in anger-out was found to partially mediate the positive relationship observed between anger-out and finger pressure unpleasantness. These findings provide additional support for the hypothesis that anger-out is linked to hyperalgesic effects in part due to an association with deficient opioid analgesic systems. In contrast, anger-in was found in the current study to have hyperalgesic effects but no association with pain-induced BE release. This finding supports previous conclusions based on an opioid blockade methodology that the pain-related effects of anger-in are not opioid-mediated (Bruehl et al., 2002; 2003).

The current results shed further light on the nature of anger-related opioid dysfunction. Specifically, past results showing relationships between trait anger-out and pain-related effects of opioid blockade could have been due to either differences in availability of endogenous opioid receptor agonists or due to differences in opioid receptor sensitivity between people high and low in trait anger-out. In light of the current findings, it appears likely that at least part of the hyperalgesic effects of elevated anger-out arises from diminished release of endogenous opioids rather than receptor sensitivity differences. However, previous findings that the effects of anger-out on acute clinical pain may be moderated by the A118G mu opioid receptor polymorphism suggest the possibility that both altered opioid release and opioid receptor differences may contribute to the pain-related effects of anger-out (Bruehl et al., 2006).

It should be noted that studies directly testing the opioid dysfunction hypothesis have each examined this issue in an experimental context absent of anger and behavioral anger expression (Bruehl et al., 2002; 2003). Such studies neglect the possibility of important trait $\times$ state interactions (Bruehl et al., in press). Specifically, study designs evoking anger and its active behavioral expression appear to produce *diminished* pain and cardiovascular stress responding in high anger-out individuals rather than the typically reported exaggerated responding (Burns et al., 2003; 2006; Engebretson et al., 1989; Faber & Burns, 1996). Whether the analgesia apparently produced by behavioral anger expression in those higher in anger-out is opioid-mediated has not been directly tested, although it is certainly plausible. That is, elevated anger-out may be associated not with absolute opioid dysfunction, but rather a higher threshold for triggering opioid release, with behavioral anger expression serving as the trigger. This opioid triggering hypothesis is currently under evaluation.

Several potential study limitations should be mentioned. Pain-induced changes in circulating plasma BE were assessed, but this measure cannot directly be equated with pain-induced changes in spinal or supraspinal BE. Given that central opioid mechanisms for anger-out are posited, assessment of central BE changes (in cerebrospinal fluid) would have been preferable. This approach, however, was not feasible. That the plasma BE measure assessed has some relevance to pain is suggested by the significant inverse correlations observed between BE change and pain responses both in the current study and in previous work (e.g., Bragdon et al., 2002; Cleeland et al., 1984; Guasti et al., 1996; Miller et al., 1993; Rosa et al., 1988; Sheps et al., 1995; Szyfelbein et al., 1985). At the very least, results do confirm diminished peripheral opioid release in high anger-outs following noxious stimuli, even if the correspondence with central BE release is unclear. An additional limitation is the relatively small sample size of the study and related statistical power limitations. The primary null finding in the study, the absence of a significant relationship between anger-in and BE responses, was predicted based on prior blockade results. Moreover, the extremely small effect size for anger-in on BE change ($\beta = -0.02$) suggests that the absence of a significant relationship between anger-in and BE changes was not a result of statistical power issues. BE findings for anger-out were also consistent with a priori predictions, and were statistically significant despite the small sample. A final potential limitation relates to generalizability issues. Mean scores for both depressive symptoms (BDI) and trait anxiety (STAI) were low in both groups, a result which may seem particularly surprising for a sample with chronic pain. Study inclusion criteria designed to maximize group comparability and minimize drug side effects (e.g., no major depression, panic, or posttraumatic stress disorder, no daily opioid analgesics or antidepressants) are likely to have produced a relatively functional chronic pain sample. While this sample may be representative of the general population with chronic pain as a whole, it may be quite different than the tertiary care chronic pain population. Whether findings would have been different in the latter population remains to be determined.

In summary, elevated trait anger-out and anger-in are both associated with increased acute pain responsiveness, but only anger-out is associated with diminished endogenous opioid release in response to noxious stimuli. These opioid differences appear specific to anger-out rather than being due to overlap with general negative affect. The current findings are consistent with prior tests of the opioid dysfunction hypothesis of anger-out using opioid blockade methodology (Bruehl et al., 2002; 2003). Situational factors that may influence expression of these anger-related opioid effects remain to be elucidated.

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Figure 1.
Scatterplot of AOS scores and residualized beta-endorphin change scores.

Table 1

Subject Characteristics.

Variable	Subject Type	
	Healthy Control (n=14)	LBP (n= 13)
Age (years)	35.4±2.43	37.6±2.93
Gender (% Female)	42.9	61.5
Race/Ethnicity (%):		
White Non-Hispanic	85.7	92.3
African-American	7.1	7.7
Other	7.1	0.0
AIS	18.3±1.16	21.1±1.62
AOS	19.3±1.41	18.8±0.80
BDI	1.4±0.44	2.3±0.69
STAI	27.6±1.75	31.3±2.43

Note: All means are presented as mean ± S.E. All statistical comparisons between groups are nonsignificant ($p>.10$). LBP = Chronic Low Back Pain, AIS = Anger-In Subscale, AOS = Anger-Out Subscale, BDI = Beck Depression Inventory, STAI = Spielberger Trait Anxiety Inventory.

Table 2

Mean ($\pm$ SE) placebo condition pain task ratings and beta-endorphin levels pre- and post-pain across subject type.

Variable	Healthy Control	LBP
Baseline BE (ng/ml)	1.24 $\pm$ 0.23	1.07 $\pm$ 0.19
Post-Pain BE (ng/ml)	1.36 $\pm$ 0.15	1.25 $\pm$ 0.22
FP MPQ-S	7.5 $\pm$ 1.02 [†]	11.6 $\pm$ 2.08
FP MPQ-A	0.57 $\pm$ 0.20 [†]	2.08 $\pm$ 0.69
FP VAS Intensity	49.3 $\pm$ 4.58	53.5 $\pm$ 6.56
FP VAS Unpleasant	48.4 $\pm$ 4.66	56.4 $\pm$ 5.83
Ischemic MPQ-S	7.5 $\pm$ 1.05 [†]	12.4 $\pm$ 2.51
Ischemic MPQ-A	1.4 $\pm$ 0.32	2.4 $\pm$ 0.87
Ischemic VAS Intensity	52.6 $\pm$ 5.47	52.4 $\pm$ 9.08
Ischemic VAS Unpleasant	59.0 $\pm$ 4.37	54.5 $\pm$ 9.62
Thermal MPQ-S	4.6 $\pm$ 0.59 [*]	11.0 $\pm$ 2.22
Thermal MPQ-A	0.7 $\pm$ 0.35 [†]	2.1 $\pm$ 0.72
Thermal VAS Intensity	58.8 $\pm$ 3.83	66.2 $\pm$ 4.29
Thermal VAS Unpleasant	55.3 $\pm$ 3.84	60.8 $\pm$ 6.40
Thermal Pain Tolerance (°C)	47.3 $\pm$ 0.40	47.4 $\pm$ 0.55

[†]
p<.10

^{*}
p<.05

Note: Significance values reflect comparisons across participant types at each assessment point. LBP = Chronic Low Back Pain, BE = Plasma Beta-Endorphin, FP = Finger Pressure Task, MPQ-S = McGill Pain Questionnaire-Sensory Subscale, MPQ-A = McGill Pain Questionnaire-Affective Subscale.