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Effects of opioid blockade on nociceptive flexion reflex thresholds and nociceptive responding in hypertensive and normotensive individuals

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Abstract

Hypertension and risk for hypertension have been associated with reduced pain sensitivity. It has been hypothesised that endogenous opioids contribute to this hypertensive hypoalgesia. The nociceptive flexion reflex can be used as a tool to investigate modulation of nociceptive transmission at spinal level. The current study employed a double-blind placebo-controlled design to compare the effects of naltrexone, an opioid antagonist, and placebo on nociceptive flexion reflex thresholds and nociceptive responding in unmedicated patients with essential hypertension and normotensive individuals. Neither nociceptive flexion reflex thresholds nor nociceptive responding differed between hypertensives and normotensives during placebo or naltrexone. These data provide no support for the hypothesis that essential hypertension is characterised by higher levels endogenous opioids in the central nervous system and reveal no association between blood pressure status and nociceptive flexion reflex responses.

Keywords

Endogenous opioids; Hypertension; Naltrexone; Nociceptive flexion reflex threshold; Nociceptive responding

1. Introduction

Elevated blood pressure has been associated with decreased sensitivity to pain (Ghione, 1996). Moreover, normotensive individuals at increased risk for developing high blood pressure have also demonstrated reduced pain sensitivity (France, 1999). A number of mechanisms have been proposed to account for these effects, including differences in baroreflex sensitivity, endogenous opioid responsivity and activation of inhibitory pain

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pathways which modulate nociceptive transmission (see France and Ditto, 1996). The nociceptive flexion reflex response is a polysynaptic spinal withdrawal response elicited in the ipsilateral biceps femoris muscle by electrocutaneous stimulation of A-delta nociceptive fibres in the sural nerve (Sandrini et al., 2005; Skljarevski and Ramadan, 2002). Electromyographic activity in the biceps femoris can be used either to determine the threshold for eliciting a withdrawal response or to quantify the amount of nociceptive responding (Rhudy and France, 2006). Studies of young normotensive adults have reported that thresholds for eliciting the nociceptive flexion reflex were higher in individuals with a positive parental history of hypertension compared to those with a negative parental history (France et al., 2002; France and Suchowiecki, 2001; Page and France, 1997). However, nociceptive flexion reflex thresholds were found not to differ between patients with essential hypertension and normotensive individuals, and moreover, activation of supraspinal pain inhibitory pathways did not vary with blood pressure status (Edwards et al., 2007). Further, this group of hypertensive patients also reported less pain than normotensives at maximum tolerable intensities of electrocutaneous stimulation (Ring et al., 2008). Given that nociceptive flexion reflex thresholds are elicited at stimulation intensities close to pain threshold, it remains to be determined whether hypertension influences nociceptive transmission at higher levels of noxious stimulation. Accordingly, one of the purposes of the current investigation was to assess nociceptive flexion reflex responding at moderately and extremely painful levels of electrocutaneous stimulation in hypertensive and normotensive individuals.

It has been hypothesised that a relative opioid insensitivity of paraventricular hypothalamic corticotrophin-releasing factor neurons that leads to exaggerated release of endogenous opioids in the central nervous system may be responsible for causing hypertensive hypoalgesia in humans (see France, 1999; France and Ditto, 1996). Animal studies have provided compelling evidence that differences between hypertensive and normotensive rodents in sensitivity to uncontrollable and highly aversive noxious stimulation are abolished during opioid blockade (Maixner, et al., 1982; Naranjo and Fuentes, 1985; Saavedra, 1981; Sitsen and de Jong, 1983; 1984; Zamir et al., 1980; Zamir and Segal, 1979). Moreover, it has been demonstrated that opioid receptors within the central nervous system mediate hypertensive hypoalgesia in rodents; a peripherally-acting methylated form of naloxone did not abolish the insensitivity to pain that characterises hypertensive rats (Sitsen and de Jong, 1984). To date, human studies provide less convincing evidence for opioid dysfunction in hypertension. Although numerous studies have detected higher levels of beta-endorphins in the peripheral circulation of hypertensives (e.g., Farsang et al., 1983; Guasti et al., 1996; Hughes et al., 1991; McNeilly and Zeichner, 1989; Sheps et al., 1992), measurement of such markers in the plasma can not indicate levels of opioids in the central nervous system. Pharmacological blockade studies examining the effects of opioid antagonists on pain in individuals with normal or high-normal blood pressure have yielded little support for an opioid hypothesis for hypertensive hypoalgesia. Evidence supporting an opioid mechanism for hypertensive hypoalgesia comes from a recent study in normotensives by McCubbin et al. (2006) that reported a significant interaction between drug and blood pressure group: opioid blockade increased cold pain in individuals with high-normal blood pressure but reduced pain in those with low-normal blood pressure. Conversely, other studies in normotensive participants have reported that endogenous opioids did not mediate the inverse relationship between resting blood pressure and cold pain (McCubbin and Bruehl, 1994), noxious mechanostimulation (Bruehl et al., 2002; Schobel et al., 1998), ischemic pain (Bruehl et al., 2002), and electrocutaneous pain (France et al., 2005). Further, recent blockade studies have also failed to find opioid mediation of cold, ischemic or electrocutaneous pain in patients with essential hypertension (Ring et al., 2007; Ring et al., 2008). In addition, France et al. (2005) have observed that nociceptive flexion reflex thresholds were not affected by naltrexone in young normotensive adults at varying risk for hypertension. However, to date, no studies have investigated the role of opioids on nociception flexion reflex activity in patients with essential hypertension. Accordingly, the current study

used a double-blind, placebo-controlled design to determine the influence of the opioid antagonist, naltrexone, on nociceptive flexion reflex thresholds and nociceptive responding at moderately and extremely painful stimulation intensities in hypertensive and normotensive individuals. If hypertensives are characterised by higher levels of endogenous opioids in the central nervous system it may be hypothesised that they would exhibit higher nociceptive flexion reflex thresholds and less nociceptive responding than normotensives, due to the dampening effect of opioids on spinal nociceptive transmission. It would be further hypothesised that opioid blockade may cause nociceptive flexion reflex activity to become similar in the hypertensive and normotensive groups, indicative of increased nociceptive transmission at the spinal cord in hypertensives.

2. Materials and Methods

2.1. Participants

Unmedicated patients with newly diagnosed essential hypertension were recruited from the hypertension clinic at the University Hospital, Birmingham, UK. Normotensive volunteers were recruited from the general population of Birmingham, UK. Their characteristics are summarized in Table 1. British Hypertension Society guidelines were used to establish blood pressure status (Ramsay et al., 1999). Each participant's blood pressure was measured for 24 hours using an ambulatory blood pressure monitor (ABPM) (SpaceLabs, Model 90207). Patients with a systolic blood pressure of ≥ 140 mmHg or a diastolic blood pressure of ≥ 90 mmHg at referral, and confirmed at clinic and on ABPM (mean daytime pressure; average of measurements obtained every 30 min between 9:00 am and 11:00 pm) were diagnosed as hypertensive (see Edwards et al., 2007 for further details). Participants were classified as being normotensive group if they had a clinic systolic blood pressure of < 140 mmHg and a clinic diastolic blood pressure of < 90 mmHg, confirmed on ABPM. The study protocol was approved by the local research ethics committee and individuals gave informed consent to participate prior to their inclusion in the study.

2.2. Physiological measurements

Participants sat with their left ankle supported and knee flexed at 35° . Blood pressure and heart rate were measured using an oscillometric sphygmomanometer (Dinamap, Critikon) and a brachial cuff attached to the upper left arm. Electromyographic activity of the left biceps femoris muscle was recorded at 2000 Hz using a Bagnoli-2 amplifier (20–450 Hz, $\times 10000$) and single differential surface electrode (Delsys) with a separate reference electrode. The sural nerve was stimulated using a constant current stimulator (DS7A, Digitimer) and bar electrode (Nicolet) that was secured posterior to the ankle with the anode superior. Sites were prepared until electrode impedance was < 10 k Ω .

2.3. Procedure

In a double-blind placebo-controlled design, participants completed two sessions that began at around 9:00 a.m and that were scheduled at least 2 days apart. They were instructed to refrain from caffeine, alcohol, and vigorous exercise for 2 hours, as well as analgesic medication for 24 hours before testing. All participants were instructed to eat breakfast before attending the study session. At the start of each session, participants sat and relaxed during a 10-min formal rest period while their blood pressure was measured four times. The participant consumed a tablet that contained either a 50 mg dose of naltrexone or placebo, with order of tablet administration counterbalanced across participants. A one hour rest allowed for the drug to reach peak circulating levels (Gonzalez and Brogden, 1988). Participants then completed a second 10-min formal rest period while their blood pressure was again measured four times. To familiarise participants with the electrocutaneous stimulation and pain rating scale, their sural nerve was stimulated at 2, 4 and 6 mA and a pain rating was obtained. After each sural

nerve stimulation, the participant rated the intensity using a 1–100 scale, with anchors of 1 (sensory threshold), 25 (uncomfortable), 50 (just noticeable pain), 75 (very painful) and 100 (maximum tolerable pain). Each participant's nociceptive flexion reflex threshold was determined during three consecutive conditions (rest, arousal/distraction, and rest), with a 5 min rest after each threshold determination. Finally, their nociceptive responding was measured while pain threshold and pain tolerance were determined.

2.4. Nociceptive flexion reflex threshold

A 4-2-1 up-down staircase method was used to determine the nociceptive flexion reflex threshold (Edwards et al., 2001). The sural nerve was stimulated by five 1-ms square-wave pulses at 250 Hz. The nociceptive flexion reflex was operationally defined as a mean rectified electromyographic response in the 90–150 ms post-stimulus interval that exceeded mean rectified electromyographic activity during a 60 ms pre-stimulus baseline interval by 1.5 *SD*. Starting at 4 mA, the stimulus intensity increased in 4 mA steps until the nociceptive flexion reflex was first detected and then decreased in 2 mA steps until the reflex was not detected. The staircase continued in 1 mA steps for four more reversals. An inter-trial interval of 15, 20 or 25 s was used. Maximum stimulation intensity was 40 mA. This maximum was reached by 1 normotensive and 3 hypertensive participants. In such cases, the computer algorithm designated 40 mA as a reflex and a reversal point. Thresholds were determined under three conditions: while resting (rest 1), while playing a computer game (data not reported here), and while resting (rest 2).

2.5. Pain threshold and tolerance

An ascending method of limits was used to determine pain threshold and tolerance. Starting at 2 mA, the sural nerve was stimulated in 2 mA steps until the maximum tolerable pain was reported or 40 mA was reached. This maximum was reached by 5 normotensive and 8 hypertensive participants. The stimulation intensity (mA) that was associated with a rating of 50 (“just noticeable pain”) indicated their pain detection threshold whereas the intensity associated with a rating of 100 (“maximal tolerable pain”) indicated their pain tolerance. A measure of nociceptive responding, defined as the mean rectified electromyographic response in the 90–150 ms post-stimulus interval, was calculated for each stimulation intensity.

2.6. Data reduction and analysis

The blood pressure recordings, taken after resting for 1 hour, were averaged to provide measures of resting laboratory systolic blood pressure and diastolic blood pressure. The nociceptive flexion reflex threshold (mA) was computed as the average of the last four reversals of the staircase method in each condition of each session. The two resting nociception flexion reflex thresholds (rest 1 and rest 2) were averaged to generate a mean resting nociceptive nociception flexion threshold for each session. A 2 Group (hypertensive, normotensive) $\times$ 2 Sex (male, female) $\times$ 2 Drug (naltrexone, placebo) repeated measures analysis of covariance (ANCOVA), with group and sex as between-subject factors, drug as a within-subjects factor, and age as a covariate, were performed on these resting nociceptive flexion reflex thresholds. To compare the effects of opioid blockade on nociceptive responding elicited by sural nerve stimulation at the same intensity, the current associated with the pain threshold in each session was identified, and the amount of nociceptive responding (μ V) at the lower of the two intensities was determined (e.g., if pain threshold was 18 mA on one session and 20 mA on the other session, then nociceptive responses to the 18 mA stimulation were determined for each session). The same procedure was performed for the pain tolerance data. These procedures allowed for a direct comparison of nociceptive responding to the same stimulation intensity in each session (see France et al., 2007). To this end, separate Group $\times$ Sex $\times$ Drug repeated measures ANCOVAs, with ages as a covariate, were performed on nociceptive responding at

intensities corresponding to the pain detection threshold and to the pain tolerance level. For pain threshold analyses the mean (*SD*) stimulation intensities were 18.1 (5.6) mA for hypertensives and 15.8 (6.7) mA for normotensives, whereas for the pain tolerance analyses they were 27.0 (8.3) and 25.5 (9.4) mA, respectively. Age was used as a covariate in these analyses. Eta-squared (η^2), a measure of effect size, is reported. Differences in the reported degrees of freedom reflect occasional missing data. Data were analysed using Statistica 99.

3. Results

3.1 Group characteristics

Separate 2 Group (hypertensive, normotensive) analyses of variance (ANOVAs) confirmed blood pressure differences between the hypertensive and normotensive groups: ambulatory systolic blood pressure ($F(1,56) = 78.98, p < .001, \eta^2 = .59$), ambulatory diastolic blood pressure ($F(1,56) = 46.73, p < .001, \eta^2 = .46$), laboratory systolic blood pressure ($F(1,61) = 42.56, p < .001, \eta^2 = .41$), and laboratory diastolic blood pressure ($F(1,61) = 27.86, p < .001, \eta^2 = .31$). The blood pressures and demographics of the two groups are shown in Table 1. A Chi-square revealed no significant difference in the proportion of men and women in each group ($\chi^2(1) = 1.83, p = .18$). The 2 Group ANOVAs showed that the groups had similar body mass indices ($F(1,61) = 0.02, p = .88, \eta^2 = .00$), but different ages ($F(1,61) = 6.30, p < .05, \eta^2 = .09$). Accordingly, age is entered as a covariate in the subsequent analyses.

3.2. Nociceptive flexion reflex thresholds

A 2 Group (hypertensive, normotensive) $\times$ 2 Sex (male, female) $\times$ 2 Drug (naltrexone, placebo) ANCOVA, with age as a covariate, on the nociceptive flexion reflex thresholds (see Fig. 1, top) yielded non-significant effects for group ($F(1,55) = 0.62, p = .43, \eta^2 = .01$), drug ($F(1,56) = 0.00, p = .98, \eta^2 = .00$), and group by drug ($F(1,56) = 1.78, p = .19, \eta^2 = .03$). No sex effects were detected.

3.3. Nociceptive responding at pain threshold and pain tolerance intensities

A 2 Group $\times$ 2 Sex $\times$ 2 Drug ANCOVA, with age as a covariate, performed on nociceptive responding associated with stimulation intensities at pain threshold (see Fig. 1, middle) produced non-significant effects for group ($F(1,56) = 2.00, p = .16, \eta^2 = .04$), drug ($F(1,57) = 0.03, p = .86, \eta^2 = .00$), and group by drug ($F(1,57) = 0.42, p = .52, \eta^2 = .01$). Similarly, ANCOVA on nociceptive responding elicited by stimulation at pain tolerance (see Fig. 1, bottom) yielded no significant group ($F(1,56) = 0.06, p = .81, \eta^2 = .00$), drug ($F(1,57) = 0.65, p = .81, \eta^2 = .00$), or group by drug ($F(1,57) = 0.08, p = .78, \eta^2 = .00$) effects. No significant effects for sex emerged.

4. Discussion

The current study was the first to assess nociceptive flexion reflex thresholds and responding in hypertensives and normotensives during opioid blockade in order to test the hypothesis that hypertensives exhibit higher levels of endogenous opioids in the central nervous system, leading to a state of hypoalgesia. The finding that opioid blockade did not alter nociceptive flexion reflex thresholds in either group suggests that nociceptive neurotransmission at spinal level is not abnormally affected by endogenous opioids in hypertensives. The current findings are congruent with recent pharmacological blockade studies which failed to find opioid mediation of cold, ischemic or electrocutaneous pain in patients with essential hypertension (Ring et al., 2007; Ring et al., 2008). In addition, these results concur with previous blockade studies examining the effects of opioid antagonists on pain in individuals with normal or high-normal blood pressure that have also yielded little (McCubbin and Bruehl, 1994; McCubbin et al., 2006) or no (Bruehl et al., 2002; France et al., 2005; Schobel et al., 1998) support for an opioid hypothesis for hypertensive hypoalgesia. The absence of opioid antagonist effects on

the nociception flexion reflex has also been noted in previous research examining the effects of opioid blockade in young, presumably normotensive, healthy adults. For example, studies have found that nociceptive flexion reflex thresholds were unaltered by naloxone (Sandrini et al., 1999; Willer et al., 1982) or naltrexone (France et al., 2005). Other studies have reported that the infusion of naloxone can lower nociceptive flexion reflex thresholds in special circumstances that activate the opioid system. In these studies, stress-induced elevations in nociception flexion reflexes were reversed by administration of the opioid blocker (Willer and Albe-Fessard, 1980; Willer et al., 1981). Taken as a whole, the findings from this and previous blockade studies in humans indicate that altered endogenous opioid responsivity does not characterize essential hypertension, which contrasts with the animal literature. One criticism which can be levelled at the current study was that circulating opioid levels were not measured. However, it is difficult to know how useful the measurement of such markers in the plasma would be as they do not indicate levels of opioids in the central nervous system. However, the measurement of circulating opioids could be used to determine whether differences in nociception between hypertensives and normotensives are apparent during stressful situations when the opioid system is known to be activated. Another potential criticism of the current study was that, even though participants were instructed to eat breakfast before the study appointment and would have had similar gut contents, the state of the gut was not assessed. However, naltrexone has 100% absorption with 95% broken down in the liver to inactive products leaving 5% active to exert a pharmacological action (Licko, 1981). Accordingly, on the basis of this high absorption and the small amount required for pharmacological action it is unlikely that differences in the state for the gut would have influenced the results of the present study.

Previously, our laboratory has found that hypertensives reported less pain than normotensives at maximum tolerable intensities of electrocutaneous stimulation (Ring et al., 2008), whereas nociceptive flexion reflex thresholds were similar between groups (Edwards et al., 2007). Given that nociceptive flexion reflex thresholds are elicited at stimulation intensities close to pain threshold, the current study also investigated if hypertension may begin to influence nociceptive transmission at higher levels of noxious stimulation. However, nociceptive responding associated with moderate and extremely painful levels of electrocutaneous stimulation was found to be similar between hypertensive and normotensive groups. The effect sizes for group differences in nociceptive responding were very small (Cohen, 1992) for stimulation intensities corresponding to the nociceptive flexion reflex, pain threshold and pain tolerance level. The current study was the first to measure nociceptive responding in response to moderately and extremely painful levels of electrocutaneous stimulation in patients with essential hypertension. The finding that nociceptive responding elicited by both moderate and extremely painful stimulation was similar between groups is compatible with previously reported data describing similar nociceptive flexion reflex thresholds between hypertensive and normotensive groups (Edwards et al., 2007). However, prior studies which measured nociceptive flexion reflex thresholds in young normotensive adults at risk for developing hypertension were found to exhibit blunted nociceptive flexion reflexes compared to those with a negative parental history in most (France et al., 2002; France and Suchowiecki, 2001; Page and France, 1997) but not all (France et al., 2005) studies. The reason for the discrepancy between these null and positive studies is not obvious. Slight methodological differences in the assessment of the nociceptive flexion reflex characterized the different studies. Regardless, the current data seem to indicate that hypertension does not influence nociceptive transmission at the spinal level, even at higher levels of noxious stimulation.

Nociceptive responding associated with stimulation intensities at pain threshold and pain tolerance was not affected by opioid blockade in either group (see Figure 1). The current findings are in line with previous studies which reported opioid blockade had no significant effect on the nociceptive flexion reflex in normal conditions (Sandrini et al., 1999; Willer et

al., 1979), indicating that endogenous opioid systems are not tonically active in humans. However, the current study is at odds with one previous study in young normotensive adults demonstrating, paradoxically, reduced nociceptive responding and lower pain ratings with opioid blockade (France et al., 2007). Given that it has been proposed that hypertensive hypoalgesia is caused by an exaggerated release of endogenous opioids in the central nervous system, due to a relative opioid hyposensitivity in hypothalamic neurons, the current finding that nociceptive responding is similar between groups and is not altered by opioid blockade provides further evidence for normal opioid function in hypertensives, even at higher stimulation intensities when the endogenous opioid system is more likely to be activated.

The current study reported no sex effects for either nociceptive flexion reflex thresholds or responding. Although sex differences in pain ratings have been reported in the literature, we believe the lack of sex differences for the nociceptive flexion reflex is not particularly curious. Indeed, none of our previous studies found sex differences in the nociceptive flexion reflex (e.g., al'Absi et al., 2005; Edwards et al., 2001; France et al., 2005). However, it must be conceded that some other studies have found a sex effect for the nociceptive flexion reflex (e.g., France & Suchowiecki, 2001; Page & France, 1997).

In conclusion, the data from the current study offer no support for the hypothesis that essential hypertension is characterised by abnormal opioid functioning. Clearly, studies are required to uncover the mechanisms behind hypertensive hypoalgesia. In addition, the data reveal no association between blood pressure status and nociceptive transmission at the spinal level, as indexed by nociceptive responding, and suggest that hypertensive hypoalgesia may reflect perceptual processing – studies have shown that hypertensives report less pain than normotensives (e.g., Ghione, 1996; Ring et al., 2008) – rather than somatosensory deficits associated with elevated blood pressures.

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Figure 1.

Mean (standard error) nociceptive flexion reflex thresholds (top), nociceptive responding at pain threshold intensity (middle) and nociceptive responding at pain tolerance intensity (bottom) during placebo and naltrexone for the hypertensive and normotensive groups

Table 1

Mean (standard deviation) blood pressures and demographics of the hypertensive and normotensive groups

Variable	Hypertensives (N = 35)	Normotensives (N = 28)
Ambulatory Systolic Blood Pressure (mmHg)	150 (9)	128 (9)
Ambulatory Diastolic Blood Pressure (mmHg)	94 (9)	79 (7)
Laboratory Systolic Blood Pressure (mmHg)	148 (13)	124 (16)
Laboratory Diastolic Blood Pressure (mmHg)	89 (10)	75 (10)
Sex, Male (%)	21 (60%)	12 (43%)
Body Mass Index (kg/m ²)	26 (3)	26 (4)
Age (years)	47 (14)	38 (13)