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Effects of naltrexone on electrocutaneous pain in patients with hypertension compared to normotensive individuals

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Abstract

An opioid mechanism may help explain hypertensive hypoalgesia. A double-blind placebo-controlled design compared the effects of opioid blockade (naltrexone) and placebo on electrocutaneous pain threshold, pain tolerance, and retrospective McGill Pain Questionnaire ratings in 35 unmedicated patients with essential hypertension and 28 normotensive individuals. The hypertensives experienced less pain than normotensives during the assessment of their pain tolerance; however, this manifestation of hypertensive hypoalgesia was not moderated by naltrexone. These findings fail to support the hypothesis that essential hypertension is characterised by relative opioid insensitivity.

Keywords

Endogenous opioids; hypertension; hypoalgesia; naltrexone; pain

Introduction

In 1980, Zamir and Shuber provided the first evidence in humans that hypertension is characterised by reduced sensitivity to noxious stimulation. Over two decades of research have established the phenomenon of hypertensive hypoalgesia (for review see Ghione, 1996). Numerous studies have documented that, compared to individuals with blood pressure in the normal range, patients with hypertension are characterised by reduced pain in response to various forms of noxious stimulation, including electrical tooth pulp (e.g., Guasti, Grimoldi, Diolisi, Rosaria, Petrozzino, Gaudio, Grandi, Rossi, & Venco, 1998), thermal (e.g., Sheps, Bragdon, Flint Gray, Ballenger, Usedom, & Maixner, 1992), and electrocutaneous (e.g., Rosa, Vignocchi, Panattoni, Rossi, & Ghione, 1994) stimulation.

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Despite a large number of studies demonstrating hypertensive hypoalgesia, limited progress has been made in establishing the mechanism underlying this phenomenon. Animal experiments have provided clear support for involvement of the opioid system; differences in sensitivity to noxious stimulation between hypertensive and normotensive rodents are abolished by the administration of opioid antagonists (Zamir & Segal, 1979; Zamir, Simantov & Segal, 1980; Saavedra, 1981; Maixner, Touw, Brody, Gebhart & Long, 1982; Sitsen & de Jong, 1983; 1984; Naranjo & Fuentes, 1985). Sitsen and de Jong (1984) showed that the insensitivity to pain typical of hypertensive rats was not abolished by a peripherally-acting methylated form of naloxone. This key study revealed that opioid receptors within the central nervous system mediate hypertensive hypoalgesia in rodents. In humans, the evidence is less compelling. Several studies have noted that hypertensives have higher levels of beta-endorphins in the peripheral circulation (e.g., Farsang, Vajda, Kapocsi, Malisak, Alfoldi, Varga, Juhasz & Kunos, 1983; Guasti, Cattaneo, Daneri, Bianchi, Gaudio, Bonora Regazzi, Grandi, Bertolini, Restelli & Venco, 1996; Hughes, Ringer, Francom, Caswell, DeLoof & Spillers, 1991; McNeilly & Zeichner, 1989; Sheps et al., 1992). It has been proposed that a relative opioid insensitivity of paraventricular hypothalamic corticotrophin-releasing factor neurons may account for the phenomenon of hypertensive hypoalgesia in humans (see France & Ditto, 1996; France, 1999). These neurons regulate the release of adrenocorticotrophin hormone and beta-endorphin from the pituitary, and, moreover, project to spinal sympathetic fibres. Along with the possibility of sympathetic influence, there is evidence to suggest that hypertension is associated with exaggerated hypothalamic-pituitary-adrenocortical activity (al'Absi, Lovallo, McKey, Sung, Whitsett & Wilson, 1998; Litchfield, Hunt, Jeunemaitre, Fisher, Hopkins, Williams, Corvol & Williams, 1998). However, there is limited evidence on the comparative effects of pharmacological blockade of opioid receptors on pain in hypertensive and normotensive individuals.

The current study used a double-blind, placebo-controlled design to examine the effects of the opioid antagonist, naltrexone, on electrocutaneous pain threshold, pain tolerance and retrospective pain reports. Several pain experiments have investigated the effects of opioid antagonists on pain in individuals with normal or high-normal blood pressure. However, their results have yielded either little (McCubbin & Bruehl, 1994; McCubbin et al., 2006) or no (Bruehl, Chung, Ward, Johnson & McCubbin, 2002; Schobel, Hanwerker, Schmieder, Heusser, Dominiak, & Luft, 1998; France et al., 2005) support for an opioid mechanism underlying variations in sensitivity to pain with blood pressure status. It is possible that these studies failed to find support for an opioid mechanism because they tested young adults with blood pressures in the normal range, and therefore, research on patients with confirmed essential hypertension offers a more definitive test. However, a recent study of essential hypertensive patients found that neither cold nor ischemic pain was affected by opioid blockade with naltrexone (Ring et al., 2007). To further investigate the mechanism underlying hypertensive hypoalgesia, the current study determined the influence of endogenous opioids on electrocutaneous pain sensitivity to maximal tolerable stimulation intensities, a procedure likely to cause opioid release, in patients with hypertension. It was hypothesised that differences in pain between hypertensives and normotensives would be moderated by opioid blockade with naltrexone.

Method

Participants

Sixty-three individuals completed this double-blind placebo-controlled study. The sample comprised 35 newly diagnosed (M = and unmedicated hypertensive and 28 normotensive individuals. Their characteristics are summarized in Table 1. Patients with newly diagnosed essential hypertension were recruited from the hypertension clinic at University Hospital,

Birmingham, UK, and were tested prior to the initiation of pharmacological treatment. Normotensive volunteers were recruited from the general population of Birmingham, UK, and screened in the same way as the hypertensive group. The study was approved by the local ethics committee and volunteers gave written consent prior to participation.

Screening

Exclusion criteria—In an initial screening session, each participant's medical status and eligibility were determined. The following exclusion criteria were applied: current use of medication (e.g., non-steroidal anti-inflammatory), diabetes mellitus, cerebrovascular disease (including transient ischemic attack or stroke), angina, myocardial infarction, peripheral vascular disease, neurological disease (e.g., multiple sclerosis), chronic liver disease, alcohol intake >28 units (1 unit = 284 ml of beer, 125 ml of wine, or 25 ml of spirits) of alcohol per week in men, >21 units of alcohol per week in women, major psychiatric disorder, secondary hypertension including chronic renal failure, renal artery stenosis, Conn's syndrome, or phaeochromocytoma.

Blood pressure status—British Hypertension Society guidelines were used to establish blood pressure status (Ramsay, Williams, Johnston, MacGregor, Poston, Potter, Poulter, & Russell, 1999). Each participant's blood pressure was measured for 24 hours using an ambulatory blood pressure monitor (ABPM) (SpaceLabs Medical, Madison, USA, Model 90207). Patients with a systolic blood pressure of ≥ 160 mmHg or a diastolic blood pressure of ≥ 100 mmHg at referral, and confirmed at clinic and on ABPM (mean daytime pressure) were diagnosed as hypertensive; this category comprised 94% of patients. Patients with a systolic blood pressure of 140–159 mmHg and/or a diastolic blood pressure of 90–99 mmHg at referral, clinic, and on ABPM, were diagnosed as hypertensive if their 10 year coronary heart disease risk was ≥ 15% and/or there was evidence of left ventricular hypertrophy on a 12 lead electrocardiograph or echocardiograph, or there was other evidence of end organ damage. The cardiovascular risk profile was calculated using the Joint British Societies Cardiac Risk Assessor computer program (Wood, Durrington, McInnes, Poulter, Rees, & Wray, 1998). Blood was sampled to determine renal function, potassium, glucose, cholesterol, high-density lipoprotein, and triglycerides. Urinalysis was also performed. If clinically indicated, patients were screened for evidence of secondary hypertension with renal ultrasound and 24 hour urinary collection for catecholamine, renin and aldosterone levels. Participants were classified as being normotensive if they had a clinic systolic blood pressure of < 140 mmHg and a clinic diastolic blood pressure of < 90 mmHg, confirmed on ABPM, and < 15% risk of coronary heart disease in the next 10 years.

Physiological Measurements

Participants sat upright in a comfortable chair with their left ankle supported so the knee was flexed at 35°. Systolic blood pressure (mmHg), diastolic blood pressure (mmHg), and heart rate (bpm) were obtained using an oscillometric sphygmomanometer (Dinamap, Critikon) and a brachial cuff (Dura-cuf, Johnson & Johnson Ltd) attached to the participant's upper left arm. 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.

Procedure

The study employed a double-blind placebo-controlled design in which participants completed two morning sessions that were separated by at least 2 days and that commenced at around 9:00 a.m. They were instructed to refrain from caffeine, alcohol, and vigorous exercise for 2 hours, and analgesic medication for 24 hours prior to testing. They were paid for participating. At the start of each session, participants sat and relaxed during an initial formal rest period (10

min) while their blood pressure was measured at 30, 210, 390, and 570 s. The investigator then administered a tablet to the participant, which contained either a 50 mg dose of naltrexone or placebo. The order of tablet administration was counterbalanced across participants. The participant was asked to relax for one hour to allow for the drug to reach peak circulating levels (Gonzalez & Brogden, 1988). During this time the sites were prepared and electrodes attached. They then completed a second formal rest period (10 min) while their blood pressure was measured at 30, 210, 390, and 570 s. Participants were then familiarised with electrocutaneous stimulation and the use of the pain rating scale (described in detail below). In three practice trials, their sural nerve was stimulated (2, 4, 6 mA) and participants provided a pain rating. Nociceptive flexion reflex thresholds were then measured (data reported elsewhere; Edwards et al, 2007). Following a 5 min rest, pain threshold and tolerance were determined.

Pain Threshold and Tolerance Assessment

Pain threshold and tolerance were determined using an ascending method of limits. Brief electrocutaneous stimulation (five 1-ms square-wave pulses at 250 Hz), was applied to the sural nerve, at intensities that increased in 2 mA steps from 2 mA. The participant rated each stimulation using a 0 – 100 scale (0 = no sensation, 25 = uncomfortable, 50 = just noticeable pain, 75 = very painful, 100 = maximum tolerable pain). A delay of approximately 20 s separated stimulations. The current intensity increased until either the participant rated the electrocutaneous stimulation as 100 using the 0–100 rating scale or 40 mA, the predetermined maximum allowable current, was reached. The stimulation intensity (mA) that was associated with a rating of 50 (“just noticeable pain”) indicated their pain detection threshold. The stimulation intensity (mA) that was associated with a rating of 100 (“maximal tolerable pain”) indicated the limit of their pain tolerance. Participants then completed Melzack’s (1987) short-form McGill Pain Questionnaire to indicate retrospectively the overall pain associated with the electrocutaneous stimulations delivered during the assessment of pain threshold and tolerance. The reliability and validity of this questionnaire are well established (see McDowell & Newell, 1996; Wright, Asmundson, & McCreary, 2001; Grafton, Foster & Wright, 2005). Participants rated 11 sensory and four affective descriptors on an intensity scale of 0 (none), 1 (mild), 2 (moderate), and 3 (severe), that were summed to yield the total pain rating index..

Data Reduction and Analysis

The set of four resting blood pressure recordings, taken after resting for 1 hour, were averaged to provide measures of resting laboratory systolic blood pressure, diastolic blood pressure and heart rate for each session; these were then averaged to provide overall laboratory cardiovascular activity. Partial 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.

Results

Group Characteristics

The blood pressure status of the two groups is presented in Table 1. A series of 2 Group (hypertensive, normotensive) analyses of variance (ANOVAs) confirmed that, compared to the normotensive group, the hypertensive group exhibited significantly higher ambulatory systolic blood pressure, $F(1, 56) = 78.98$, $p < .001$, $\eta^2 = .59$, ambulatory diastolic blood pressure, $F(1, 56) = 46.73$, $p < .001$, $\eta^2 = .46$, resting laboratory systolic blood pressure, $F(1, 61) = 42.56$, $p < .001$, $\eta^2 = .41$, and resting laboratory diastolic blood pressure, $F(1, 61) = 27.86$, $p < .001$, $\eta^2 = .31$. Resting laboratory heart rates did not differ between groups, $F(1, 61) = 1.93$, $p = .17$, $\eta^2 = .03$. The demographics of the two groups are also shown in Table 1. A Chi-square analysis revealed no significant difference in the proportion of men and women in each group, $\chi^2 (1) = 1.21$, $p = .27$. Finally, 2 Group ANOVAs showed that the two groups had similar

heights, $F(1, 61) = 1.19$, $p = .28$ $\eta^2 = .02$, weights, $F(1, 61) = 0.29$, $p = .59$, $\eta^2 = .01$, and body mass indices, $F(1, 61) = 0.02$, $p = .88$, $\eta^2 = .00$, but the hypertensive group was older than the normotensive group, $F(1, 61) = 6.30$, $p < 05$, $\eta^2 = .09$. Accordingly, age was entered as a covariate in the analyses that follow.

A series of Group (hypertensive, normotensive) × 2 Sex (male, female) × 2 Drug (naltrexone, placebo) ANCOVAs, with age as a covariate, were performed on the blood pressures and heart rates recorded in each laboratory session (see Table 2). These analyses confirmed significant main group effects for systolic blood pressure, $F(1, 58) = 32.01$, $p < .001$, $\eta^2 = .36$, diastolic blood pressure, $F(1, 58) = 19.23$, $p < .001$, $\eta^2 = .25$, and heart rate, $F(1, 58) = 4.09$, $p < .05$, $\eta^2 = .07$. There were no main or interaction effects for Drug or Sex.

Pain

A series of Group (hypertensive, normotensive) × 2 Sex (male, female) × 2 Drug (naltrexone, placebo) ANCOVAs, with age as a covariate, were performed on the pain detection threshold, pain tolerance level, and the retrospective total pain rating index from the short-form McGill Pain Questionnaire (see Table 3). These analyses revealed that there were no significant group differences in the stimulation intensity associated with the pain detection threshold, $F(1, 58) = 2.14$, $p = .15$, $\eta^2 = .04$, and pain tolerance, $F(1, 58) = 0.89$, $p = .35$, $\eta^2 = .02$. Total pain rating index scores, reflecting the pain experienced during the assessment of pain threshold and tolerance, were lower in hypertensives than normotensives, $F(1, 56) = 5.26$, $p < .03$, $\eta^2 = .09$. Importantly, however, there were no significant Group by Drug interaction effects for the pain detection threshold, $F(1, 59) = 1.98$, $p = .16$, $\eta^2 = .03$, pain tolerance, $F(1, 59) = 0.56$, $p = .46$, $\eta^2 = .01$, or total pain rating index scores, $F(1, 57) = 0.06$, $p = .81$, $\eta^2 = .00$. Further, none of the Drug main effects were significant. Finally, no significant effects for sex emerged.

Discussion

The current study found that hypertensive patients reported less pain associated with the assessment of electrocutaneous pain tolerance than individuals with blood pressure in the normal range. This finding supports many previous observations of hypertensive hypoalgesia reported in the literature (for review, see Bruehl & Chung, 2004; Ghione, 1996). However, using a double-blind placebo control design, the study found that these group differences in pain reporting were not affected by opioid blockade with naltrexone. This null result agrees with the results of most previous opioid blockade studies (Bruehl et al., 2002; Schobel et al., 1998; France et al., 2005; Ring et al, 2007) that have failed to support the hypothesis that hypertensive hypoalgesia is mediated by endogenous opioids (cf. McCubbin & Bruehl, 1994; McCubbin, et al, 2006). Taken together these data suggest that an opioid mechanism cannot explain the phenomenon of hypertensive hypoalgesia.

The contrasting effects of opioid blockade on pain and nociception in relation to hypertension status in human and animal studies may be due, at least in part, to the increased probability of opioid responsivity in animal studies. Animal research provides consistent evidence for naloxone-reversed opiate effects; however, human research using analogous blockade paradigms has yielded inconsistent findings. Animal research suggests that uncontrollability may be a necessary condition for opioid activation; Maier and colleagues have demonstrated the importance of stimulus uncontrollability in their studies of learned helplessness and stress-induced analgesia (Maier, Sherman, Lewis, Terman, & Liebeskind, 1983; Maier, 1990). For example, they observed that only situations that allowed for “learning-of-uncontrollability,” such as 20 min of intermittent footshock or 60 or more trials of tailshock, induced opioid analgesia. In human pain research, participants have more control because they can choose not to participate at all or to discontinue a painful procedure whenever they wish. Moreover, it is likely that laboratory pain paradigms are usually more aversive in animal compared to human

studies, thereby yielding greater endogenous opioid activation. In sum, the combination of greater controllability coupled with less aversiveness may limit the likelihood of producing significant endogenous opiate mediated pain reduction in human studies.

It should be conceded that the current study's effect sizes for differences in pain indices between hypertensives and normotensives were small, and therefore, the failure to find effects of opioid blockade may also be attributed in part to low statistical power. The evidence for hypertensive hypoalgesia was based on the retrospective pain evaluation, which may be criticised for its vulnerability to memory distortion. A measure of concurrent pain to painful stimulation, which might be expected to be more reliable, would have been better. A limitation of the current study that should be recognized was that the groups differed in age, and although this difference was adjusted for in the analyses, it is possible that statistical adjustment does not fully address the potential influence of age in this context. However, residual confounding is most likely to occur when the covariate is either related to the dependent variable in a non-linear fashion or is measured inaccurately (Christenfeld, Sloan, Carroll & Greenland, 2004), neither of which apply in this instance. Another limitation of the current report was that participants underwent additional nociceptive flexion reflex testing (see Edwards et al, in submission). Given that order of tablet administration was counter-balanced across participants in each group, the threshold and tolerance assessments were conducted in the same fixed order for all participants. Therefore, both groups of participants experienced the same potentially interfering effects of the additional reflex testing, and hence it is unlikely that this design feature can explain the current results.

In conclusion, the retrospective pain ratings data concerning the tolerance assessment show that the relative hypoalgesia in hypertension was not mediated by endogenous opioids. Given that the study only assessed pain during electrocutaenous stimulation, future studies could determine pain during other forms of noxious stimulation. Naltrexone is a non-specific opioid receptor antagonist, and, therefore, future studies using receptor-specific antagonists would help to determine the involvement of each opioid receptor (mu, delta, kappa) in hypertensive hypoalgesia. Such studies would benefit from measurement of the levels of plasma opioids, such as beta-endorphin and metenkephalin, to permit the effects of the task on circulating opioids to be determined. Finally, studies would do well to explore other possible mechanisms, such as preferential activation of central pain modulation pathways and baroreceptor-mediated cortical inhibitory pathways that may mediate hypertensive hypoalgesia (e.g., see France & Ditto, 1996).

Notes

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Table 1

Unadjusted Mean (*SD*) Blood Pressures and Demographics of the Hypertensive and Normotensive Groups as well as the Statistical Significance Level of the Group Effects

Variable	Blood Pressure Group		Group Effect
	Hypertensive	Normotensive	*p*
Ambulatory (Daytime)			
Systolic Blood Pressure (mmHg)	149.5 (8.8)	128.0 (9.4)	.001
Diastolic Blood Pressure (mmHg)	94.2 (9.1)	78.7 (7.3)	.001
Laboratory (Resting)			
Systolic Blood Pressure (mmHg)	147.5 (13.1)	123.6 (16.0)	.001
Diastolic Blood Pressure (mmHg)	88.5 (10.4)	74.6 (10.3)	.001
Heart Rate (bpm)	77.0 (11.9)	73.4 (7.6)	.17
Sex			.27
Male	21	12	
Female	14	16	
Height (m)	1.72 (0.10)	1.69 (0.09)	.28
Weight (kg)	77.1 (12.7)	75.2 (14.8)	.59
Body Mass Index (kg/m^2)	26.1 (3.4)	26.2 (4.3)	.88
Age (years)	46.6 (13.7)	38.0 (13.3)	.05

Table 2

Unadjusted Mean (*SD*) Laboratory Cardiovascular Activity for the Hypertensive and Normotensive Groups during Placebo and Opioid Blockade with Naltrexone as well as the Statistical Significance Level of the Group, Drug and Group by Drug Effects Adjusted for Age

Variable	Blood Pressure Group				Group Effect	Drug Effect	Group by Drug Effect
	Hypertensive (N = 35)		Normotensive (N = 28)		*p*	*p*	*p*
	Placebo	Naltrexone	Placebo	Naltrexone			
Laboratory (Resting)							
Systolic Blood Pressure (mmHg)	149.5 (13.6)	146.4 (13.0)	124.1 (15.7)	124.5 (15.6)	.001	.19	.08
Diastolic Blood Pressure (mmHg)	89.0 (10.8)	88.0 (11.2)	74.9 (10.3)	75.1 (10.6)	.001	.48	.33
Heart Rate (bpm)	77.5 (11.0)	77.5 (12.2)	73.7 (8.4)	72.7 (9.1)	.05	.58	.59

Table 3

Unadjusted Mean (*SD*) Pain Tolerance Data for the Hypertensive and Normotensive Groups during Placebo and Opioid Blockade with Naltrexone as well as the Statistical Significance Level of the Group, Drug and Group by Drug Effects Adjusted for Age

Variable	Blood Pressure Group				Group Effect	Drug Effect	Group by Drug Effect
	Hypertensive (N = 35)		Normotensive (N = 28)		*p*	*p*	*p*
	Placebo	Naltrexone	Placebo	Naltrexone			
Pain Detection Threshold (mA)	19.6 (7.6)	20.6 (6.7)	18.3 (7.6)	17.2 (7.0)	.15	.99	.16
Pain Tolerance (mA)	29.5 (8.4)	29.3 (8.1)	27.8 (9.3)	26.4 (8.7)	.35	.29	.46
MPQ Total Pain Rating Index (0–45)	8.4 (4.3)	8.1 (5.2)	11.9 (7.3)	12.2 (7.2)	.03	.80	.81

Note: MPQ: McGill Pain Questionnaire