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Cardiovascular influences on conditioned pain modulation

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ABSTRACT

Conditioned pain modulation (CPM) (ie, diffuse noxious inhibitory controls) is characterized by reduced perception of pain caused by intense pain in a remote body area. The conditioning stimuli used to trigger CPM causes pain, but also important cardiovascular responses. Higher blood pressure has been associated with reduced pain sensitivity. Descending pain inhibitory mechanisms such as CPM could be involved in this relationship. We investigated the associations between CPM and cardiovascular responses during the cold-pressor test (CPT). Heat pain threshold and tolerance were evaluated in 26 (13 men, 13 women) healthy subjects. CPM was evaluated by comparing pain intensity produced by a 120-second heat stimulation before and after a CPT (5 minutes, 7°C). Heart rate, blood pressure, and baroreflex sensitivity were monitored at rest and during CPT to evaluate cardiovascular responses. We observed a positive relationship between resting blood pressure and heat pain tolerance. The CPT caused important heart rate and blood pressure increases. CPT also reduced pain intensity during the subsequent heat pain-stimulus, indicating effective CPM. A significant positive association was observed between CPM magnitude and the increase in blood pressure during the CPT. These results show that resting blood pressure values are related to acute pain tolerance, while descending pain inhibition is associated with increases in blood pressure. The rise in blood pressure caused by the conditioning stimulus is an important factor predicting the extent of endogenous pain inhibition in healthy subjects.

1. Introduction

The perception of pain can be amplified or decreased by endogenous pain regulatory mechanisms. Nociceptive conditioned pain modulation (CPM) (ie, counterirritation) is a commonly used paradigm for the assessment of endogenous pain inhibition in psychophysical human studies [46,63]. CPM is thought to reflect the spino-bulbar-spinal loop, originally described in animals, named diffuse noxious inhibitory controls [37,38]. The specific mechanism involved in the CPM effect measured in humans has not been completely elucidated, but is believed to represent the net outcome of descending pain inhibitory mechanisms [53,63].

The clinical relevance of CPM is highlighted by cumulative studies demonstrating less efficient pain inhibition in various chronic pain conditions such as fibromyalgia [14,29,32,35], irritable bowel syndrome [27,52,60], and atypical trigeminal neuralgia [39]. Interestingly, CPM magnitude has been inversely associated with chronic postoperative pain intensity at follow-up [64], indicating that reduced effectiveness of endogenous pain inhibition could be a risk factor for the development of chronic pain.

Different paradigms can be used to study CPM and there is no consensus on a specific methodology. The experimental procedure usually consists of comparing the pain produced by a noxious test-stimulus before and after (or simultaneously with) application of a second noxious conditioning stimulus applied to a remote body area [46]. Stronger (ie, more intense) conditioning stimuli have been associated with greater CPM analgesia [36,55,61]. However, many investigations reported no relationship between the pain intensity produced by the conditioning stimulus and CPM extent [2,25,42,47]. These results suggest that the subjective perception of pain induced by the conditioning stimulus has poor predictive value of the resulting analgesia, but other factors (physiological or psychological) affected by the intensity of the conditioning stimulus could be more closely related to the extent of CPM. Determining these factors could have important clinical implications such as identifying patients at risk of developing chronic pain and gaining a better understanding of the mechanism underlying CPM and its dysfunction.

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One of the most common and effective conditioning stimuli used to trigger CPM is the immersion of the arm in cold water [46], also known as the cold-pressor test (CPT). The CPT is also used in autonomic testing to assess cardiovascular responses [28,56,57,62]. More precisely, cold water immersions are known to cause sympathetically mediated heart rate and blood pressure increases, without significantly affecting baroreflex sensitivity (BRS) [12,51]. Interestingly, inverse associations between pain sensitivity and resting blood pressure have been reported in several studies [6,20,23,50]. Inverse relationships have also been observed between pain sensitivity and resting BRS [10,11]. Furthermore, an inverse association has been observed between heart rate reactivity and ischemic pain ratings [21]. Animal studies have shown that descending pain inhibitory mechanisms are implicated in such relationships [48,65]. However, relationships between CPM and cardiovascular responses have not been extensively investigated. Thus, we hypothesized that the increase in blood pressure and heart rate caused by the conditioning stimulus may be associated with the extent of CPM. The present study aimed at investigating relationships between CPM and cardiovascular responses to the CPT in healthy subjects.

2. Methods

2.1. Subjects

Twenty-seven healthy volunteers participated in this study. One participant did not complete the entire experimental procedure (CPT) and was removed from all analyses based on this criterion. Hence, 26 healthy volunteers (13 men and 13 women) were included in the analyses. None suffered from chronic pain, major depression, cardiovascular or respiratory problems, had diabetes, or were pregnant or breastfeeding. Participants were instructed to refrain from using analgesic or anti-inflammatory medication at least 24 hours prior to testing. All participants signed a written consent form, and all procedures were approved by the Human Ethics Committee of the *Centre Hospitalier Universitaire de Sherbrooke* (CHUS).

2.2. Experimental procedure

Participants were comfortably seated in a quiet room. The French version of Spielberger's State-Trait Anxiety Inventory and Beck's Depression Inventory were administered at the beginning of the experimental session.

2.3. Heat pain threshold and heat pain tolerance

Heat pain threshold and heat pain tolerance were evaluated with a 30 × 30-mm thermode (TSA II, Medoc Advanced Medical Systems, Ramat Yishai, Israel) applied on the volar part of the left forearm. Thermode temperature was initially set at 32.0°C and gradually increased at a rate of 0.3°C/second. Participants were instructed to report when the sensation produced by the thermode changed from heat sensation to pain (heat pain threshold) and when the pain became unbearable (heat pain tolerance). This procedure was done twice for every subject and the mean of the 2 trials is reported. The thermode was placed on adjacent areas of the forearm for every trial to avoid primary skin hyperalgesia.

2.4. Heat test-stimulus

The thermode was applied on the volar part of the left forearm for 120 seconds at constant temperature. However, participants were informed the temperature could increase, decrease, or be stable during the 120-second heat test-stimulus in order to reduce expectations. The temperature was individually adapted to induce a mean pain intensity of 60/100 based on heat pain threshold and tolerance values using the following formula: heat pain threshold + ([heat pain tolerance-heat pain threshold]/2). If the pain intensity produced by this temperature was not approximately 60/100, the temperature was adjusted accordingly (±0.5°C modifications were generally sufficient). Participants continuously evaluated pain intensity with a computerized visual analogue scale (COVAS) ranging from 0 (no pain) to 100 (most intense pain tolerable) during the entire heat test-stimulus. The 120-second heat test-stimulus was done before and after the CPT (using the same thermode temperature). An interval of approximately 1 minute separated the end of CPT and beginning of the second heat test. The thermode was placed on adjacent areas of the forearm to avoid primary skin hyperalgesia.

2.5. Cold-pressor test (CPT)

Participants immersed their right arm (up to the elbow) in circulating cold (7°C) water for 5 minutes. Participants were instructed not to move or contract their arm during the immersion. Subjects provided pain intensity and pain unpleasantness scores using a verbal numeric rating scale ranging from 0 (no pain/not unpleasant) to 100 (most intense pain tolerable/most unpleasant pain). Ratings were provided every 15 seconds during the entire 5-minute immersion period. The CPT was used as a conditioning stimulus to trigger CPM.

2.6. Conditioned pain modulation

CPM magnitude was evaluated by computing the difference in mean pain intensity induced by the heat test-stimulus before and after the CPT (ie, mean COVAS before CPT − mean COVAS after CPT). Thus, effective pain inhibitory mechanisms are represented by higher (positive) values.

2.7. Heart rate

Electrocardiograms (ECG) were recorded and analyzed at baseline (5-minute rest at the beginning of the experimental session) and during CPT (5 minutes). ECG activity was obtained using a standard 3-lead montage sampled at a frequency of 1000 Hz using the PowerLab system and analyzed with Chart software (AD Instruments, Colorado Springs, CO, USA). Mean heart rate was computed from successive R-R intervals of the ECG waveform. Cardiac responses to the CPT were determined by calculating immersion-induced changes in heart rate (ie, mean heart rate during CPT − mean heart rate during baseline).

2.8. Blood pressure

Noninvasive continuous blood pressure (systolic and diastolic) measurements were taken during baseline (5 minutes) and during CPT (5 minutes) using a Nexfin monitor (BMEYE, Amsterdam, Netherlands). The finger cuff was placed on the mid-phalanx of the index or middle finger (with appropriate cuff size) of the left hand. The heart reference system of the Nexfin monitor was used to compensate for differences between finger and heart level. Nexfin monitor showed good accuracy and reliability to track changes in blood pressure compared to invasive intra-arterial pressure measurement [40]. Blood pressure responses to the CPT were determined by calculating immersion-induced changes in blood pressure (ie, mean blood pressure during CPT − mean blood pressure during baseline).