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The effect of a mental stressor on conditioned pain modulation in healthy subjects

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ABSTRACT

Background and purpose: In animal studies, enhanced sensitivity to painful stimuli succeeding chronic stress has been reported, while acute stress is reported to induce analgesia. Human studies on the effect of mental stress on pain are more equivocal. A disturbed stress-response resulting in an increased sensitivity to painful stimuli has also been discussed as a potential mechanism for e.g., the fibromyalgia syndrome. Endogenous analgesia may be studied in humans by measuring the analgesic effect of heterotopic noxious conditioning stimulation. In neurophysiological animal studies this phenomenon was originally denoted "diffuse noxious inhibitory controls" (DNIC), but for human studies it has been suggested to use the term conditioned pain modulation (CPM).

The clinical relevance of aberrances in CPM is not clear. Inhibitory CPM is reported as being reduced in several medically unexplained syndromes with musculoskeletal pain aggravated by mental stress. However, whether the reported reduced CPM effects are causally related to clinical pain is unknown.

In the present study the effect of a mental stressor on CPM is studied.

Methods: With tourniquet-induced pain as the conditioning stimulus we estimated the CPM effect in twenty healthy subjects. Heat pain threshold (HPT), supra-threshold heat pain level (SHPL) and pressure pain threshold (PPT) were used as test stimuli. Measurements were performed at baseline, after a stressful task and after a non-stressful task presented in a blinded cross-over design. We used repeated-measures ANOVAs in the analysis with simple contrasts for post hoc analysis.

Results: With a ANOVA repeated measures model we found a significant task effect ($F = 18.5$, $p \leq 0.001$), indicating that CPM was successfully induced. In our ANOVA model, we found a significant effect of stress in the contrast analysis ($F = 5.2$, $p = 0.037$), indicating that CPM was affected by the stressful task. The effects on PPT could not be analyzed due to a significant carry-over effect (for PPT only).

Conclusions: In the present blinded crossover study, we found a significant small to medium inhibitory effect of mental stress upon the CPM of thermal pain.

Implications: Our results suggest that previously reported reduced inhibitory CPM in several medically unexplained syndromes with musculoskeletal pain aggravated by mental stress possibly can be related to confounding or clinically relevant stress level differences. However, the result might be modality-specific. Further studies in patients are obviously needed, and the impact of mental stress on CPM should be investigated also with other stressors.

1. Introduction

A reduced ability to engage endogenous analgesia is one potential mechanism for the fibromyalgia syndrome [1–6]. A disturbed stress-response resulting in an increased sensitivity to painful stimuli has also been discussed as a potential mechanism [7]. Both social stress [8] and low-grade mental stress [9] increase pain in fibromyalgia patients. However, a recent paper has challenged this

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view by reporting that emotional distress does not predict subsequent pain in fibromyalgia, at least not in day-to-day perspective [10].

The relation between stress and pain is complicated. In animal studies, enhanced sensitivity to painful stimuli succeeding chronic stress has been reported [11–14], while acute stress is reported to induce analgesia [13]. Human studies are more equivocal. Mental stress has been reported to induce increased sensitivity to painful cold stimulation [15,16]. In other studies, mental stress has led to a decreased sensation of pain using electrocutaneous [17,18] and pressure pain stimulation [18].

Heterotopic noxious conditioning stimulation (HNCS) can induce "counterirritation analgesia." In neurophysiological animal studies this phenomenon was originally denoted "diffuse noxious inhibitory controls" (DNIC). DNIC is thought to depend on a spino-bulbo-spinal network which modulates the transmission of signals from primary to secondary afferent neurons in the spinal cord [19–21]. In order to induce "DNIC-like effects" [22] in human experimental settings, both cold-pain [23], heat-pain [24], and tourniquet-induced pain [3,25], as well as mechanical stimulation [26,27] have been used as conditioning stimuli. Moreover, it has been suggested that the term conditioned pain modulation (CPM) should be used in human experimental studies of this phenomenon [28].

The clinical relevance of inhibitory CPM is not clear [29]. This effect is reported as being reduced in patients with migraine [30], tension type headache [31], fibromyalgia [1–3], osteoarthritis [32], irritable bowel syndrome [33] and temporomandibular disorder [34], as well as in patients using oral opioids [35]. However, whether the reported reduced inhibitory CPM is causally related to their pain or not is unknown.

Furthermore, it is incompletely known if reduced inhibitory CPM in patients is caused by, or related to, a (group) difference in perceived stress or stress response magnitude. In one CPM model perceived stress during conditioning stimulation correlated with hypoalgesia in men only [36], while another study found no effect of one hour mental stress, neither in healthy subjects nor in chronic tension-type headache patients [37]. Indeed, if mental stress is able to modify CPM one should control for this in future CPM studies, especially in studies involving patients who may perceive the experimental situation as stressful.

As a first step, we aimed to study whether CPM is affected by a mental stressor in healthy subjects. We hypothesized that mental stress induced immediately before the conditioning stimuli would modulate the CPM effect.

2. Materials and methods

2.1. Subjects

Subjects were recruited by email and direct inquiry among fellow students. Written informed consent was obtained from all subjects. Exclusion criteria were: (1) any pain that had reduced the general health or the function level during the last two weeks or caused a need for analgesics in the last five days before the trials, (2) headache more than two days per month, (3) present somatic or psychiatric illness, and (4) pregnancy. None of the invited subjects were excluded and all included subjects completed the experimental procedure.

Sample size calculations revealed that (in the case of no carry-over effects) 20 subjects would be enough to detect a population mean difference of at least 70% of the standard deviation with 5% significance level and a power of 80%. Twenty subjects (ten males and ten females, age 20–28 years, median age 24.2 (SD 2.1)) years were included after written informed consent. The project was approved by the Regional Committee for Research Ethics and by the Norwegian Social Sciences Data Services. The study was conducted according to the Helsinki Declaration.

2.2. Procedure

We used tourniquet induced pain as the conditioning stimulus and measured the inhibitory CPM with two different heat pain measures (heat pain threshold (HPT), supra-threshold heat pain level (SHPL)) and pressure pain threshold (PPT) as test stimuli, following a stressful and a non-stressful task in a blinded cross-over design.

2.2.1. Time, place and investigators

The subjects were tested on two different days at an interval of maximum three days. On day one, the procedure was explained and performed once (without the stressful and non-stressful tasks) to accustom subjects to the procedure. On day two, the order of stress- and non-stressful tasks was randomized while the complete procedure (Fig. 1) was performed by another experienced technician who was blinded for the task order: (1) Recording of baseline HPT, SHPL and PPT. (2) Stressful task or non-stressful task. (3) Recording of HPT, SHPL and PPT during the painful conditioning stimulus. (4) Recording of HPT, SHPL, and PPT ("recovery-1"). (5) Non-stressful or stressful task, 5 min. (6) Recording of HPT, SHPL, and PPT during a conditioning stimulus. (7) Recording of HPT, SHPL, and PPT ("recovery-2"). The recording of test stimuli (HPT, SHPL, and PPT) lasted approximately 3 min, and were performed in the order indicated above each time and started immediately after the desired pain level of the conditioning stimulus was reached. Blood pressure and heart rate were measured before and after each session with stressful or non-stressful task, as well as before the experiment started (Fig. 1).

2.2.2. Experimental equipment and conditions

HPT and SHPL were measured with a Somedic MSA (SenseLab equipment, Hörby, Sweden). The thermode was a rectangular 25 mm × 50 mm Peltier element. The baseline temperature was 32.0 °C, the maximal temperature was 55.0 °C, and the rate of change was 1 °C per second. A pressure algometer (Somedic Sales AB, Sweden) with a 1 cm^2 tip was used [38] to assess PPT. The subjects were lying on a bench with the upper part of their body raised 30° during the measurements. They were sitting in an upright position in a chair during the stress- and non-stressful tasks. Blood pressure and heart rate was measured with an automatic oscillometric device (CAS 740, MAX NIBP, Bollbrügg, Germany). A cuff width of 14 cm was used, and all subjects had an arm circumference within the range specified for the use of this cuff for blood pressure measurements.

2.2.3. Pressure pain threshold measurements

Pressure pain threshold (PPT) was recorded by pushing the tip of the algometer with gradually increasing pressure (30 kPa/s) towards the belly of the temporalis muscle on the right side of the forehead. The subjects were instructed to say stop when the pain threshold level was reached. The mean value of three consecutive measurements was used for analysis.

2.2.4. Heat pain measurements

A stop button was placed in the right hand of the subjects, who were instructed to press it immediately when the desired threshold was reached. Three warm stimuli (with a random interval between 4 and 6 s) were applied to the ventral side of the right forearm. The thermode was moved proximally 5 cm after each stimulus to prevent burns. HPT and SHPL were calculated as the average of three stimuli.