PAIN® 154 (2013) 2633–2638

www.elsevier.com/locate/pain

Temporal stability of conditioned pain modulation in healthy women over four menstrual cycles at the follicular and luteal phases

Hilary Wilson [a], Brendan Carvalho [b], Michal Granot [c], Ruth Landau [d,*]

[a] United Biosource Corporation, Outcomes Research, USA
[b] Stanford University Medical Center, Stanford, CA, USA
[c] Department of Nursing, Faculty of Social Welfare and Health Studies, University of Haifa, Haifa, Israel
[d] University of Washington, Seattle, WA, USA

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

ARTICLE INFO

Article history:
Received 6 June 2012
Received in revised form 21 June 2013
Accepted 24 June 2013

Keywords:
Pain
Diffuse noxious inhibitory controls
Conditioned pain modulation
Descending inhibition
Endogenous analgesia

ABSTRACT

Conditioned pain modulation (CPM) is a phenomenon that may be tested with a dynamic quantitative sensory test that assesses the inhibitory aspect of this pain modulatory network. Although CPM has been adopted as a clinical assessment tool in recent years, the stability of the measure has not been determined over long time intervals. The question of stability over time is crucial to our understanding of pain processing, and critical for the use of this tool as a clinical test. The primary objective of this study was to evaluate the stability of a CPM paradigm over time in healthy women. The secondary objective was to determine the potential influence of menstrual cycle phase on CPM. CPM was assessed 8 times in 22 healthy women during the follicular and luteal phases of 4 different cycles. The CPM effect was evidenced by a reduction in the pain rating of a test stimulus (6.3 ± 0.2) with the introduction of a conditioning stimulus (5.0 ± 0.3; $P < 0.001$). The intraclass correlation coefficient for the CPM effect was modest (0.39; CI = 0.23–0.59), suggesting that there is significant variation in CPM over long time intervals. CPM did not vary across phases in the menstrual cycle. Prior to the adoption of CPM as a clinical tool to predict individual risk and aid diagnosis, additional research is needed to establish the measurement properties of CPM paradigms and evaluate factors that influence CPM effects.

1. Introduction

Each individual's perception and experience of pain is the result of a complex modulatory process of ascending and descending input that may be inhibitory or excitatory. Conditioned pain modulation (CPM) is a dynamic quantitative sensory test that assesses the descending inhibition aspect of this pain modulatory network. The CPM technique has been described in the literature using several different terminologies, including heterotopic noxious inhibitory controls, counter-irritation, and most notably, descending noxious inhibitory controls. A group of basic scientists and clinicians have recommended the phrase "conditioned pain modulation" to describe the psychophysical paradigms in which a conditioning stimulus (CS) is used to affect a test stimulus (TS), and we will adopt this terminology for the current manuscript [24]. CPM is performed by a "pain inhibits pain" testing paradigm [11]. Participants rate the pain of a TS alone, and then repeat this pain rating together with a concurrent CS. Both the TS and CS may vary with the sensory modality, stimulus intensity, location of application, and temporal characteristics. A reduction in the pain severity of the TS with concurrent CS is evidence of pain inhibition. Studies comparing patients with chronic pain, particularly patients with idiopathic pain syndromes, with healthy controls reveal growing evidence that patients with chronic pain have a decreased capacity to modulate pain as assessed by CPM [6–8,10,13,19,23].

Despite rapid growth of CPM in clinical research, minimal work has been published evaluating the temporal stability of the measure. Test–retest reliability is the evaluation of the temporal stability of a measure over short time intervals (⩽2 weeks) under circumstances where the construct being measured is perceived to be stable. Cathcart and colleagues [4] and Lewis and colleagues [12] assessed the reliability of 2 different CPM paradigms at 1 hour and 15 minute intervals, respectively, and the test–retest reliability was high [4]. Unfortunately, significant variance among the procedures for assessing CPM hampers the generalization of these findings to other CPM paradigms [18].

* Corresponding author. Address: Department of Anesthesiology and Pain Medicine, University of Washington Medical Center, 1959 NE Pacific Street, Suite BB 1415B, Seattle, WA 98195-6540, USA.
E-mail address: rulandau@u.washington.edu (R. Landau).

0304-3959/$36.00
http://dx.doi.org/10.1016/j.pain.2013.06.038

The assessment of temporal stability over longer time intervals gives information on whether the measure is a "trait" or a "state." An individual's capacity to modulate pain may be understood as a trait if there is high temporal stability over longer time intervals, or as a state if there is low temporal stability. Sex, genetic, ethnic, psychological, and sociocultural differences have been hypothesized to influence the CPM effect; however, the stability of CPM among a homogenous group of individuals under steady conditions and over long time intervals has not been well established.

Sex differences, and in particular hormonal status within menstrual cycles among females, are one factor thought to affect CPM. Contributing to this theory, evidence suggests that CPM effects are more robust in males than females [17]. Evidence evaluating the effects of CPM at different phases in the menstrual cycle, however, is mixed. One study reported that pain inhibition as assessed by CPM was significantly greater during the ovulatory than the luteal phase [22]; however, a second found no differences in CPM at the mid-follicular and late-luteal phases [3]. Both studies used different CPM paradigms, and it is unknown whether the discrepancy between these findings is due to poor test–retest reliability of the CPM paradigms used, differences in the hormonal phases assessed in the studies, or lack of hormonal effects on CPM.

The primary objective of the present study was to evaluate the temporal stability of CPM using a published CPM paradigm [9]. A secondary objective was to evaluate the influence on CPM of phase of the menstrual cycle. CPM data were collected on a cohort of healthy nonpregnant females at 8 different time points and across 4 different menstrual cycles as part of a broader clinical trial designed to evaluate pregnancy-induced analgesia. The present study used these data to address the above-stated objectives.

2. Methods

2.1. Study population

After approval by the institutional review boards of the University of Washington and Stanford University, 30 healthy nonpregnant female volunteers were enrolled in this prospective study (clinicaltrials.gov NCT00867945). The study subjects were recruited via advertisements posted at the University of Washington and Stanford University campuses and medical centers. Subjects were included if they were between 18 and 45 years of age, English speaking, reported regular menstrual cycles (defined as between 21 and 35 days in length) and had a body mass index <35. Women were not eligible for participation in the study if they were taking oral contraceptives or had a hormone-coated implantable uterine device; had ever required medication for a history of anxiety or depression; or had ever chronically consumed opiates, antidepressants, or anticonvulsants. They were also excluded if they had taken opiates, acetaminophen, or nonsteroidal anti-inflammatory drugs in the 48 hours prior to each study visit.

All participants gave written informed consent upon study enrollment. Testing was performed in a designated quiet room. A study visit was scheduled for each subject during the follicular phase (day 4–10) and the luteal phase (day 18–24) of every other menstrual cycle. Four ovulatory cycles were studied and thus subjects completed a total of 8 study visits over the course of 7–10 months. The course of the study sessions is illustrated in Fig. 1. The follicular phase of each cycle was determined by the subject's self-report of the first day of her menstrual period. The luteal phase was determined by urine ovulation test strips (Kurkel Enterprises, Redmond, WA), which the study subjects used at home according to instruction by the study investigators. In the event of a negative ovulation test (indicating a possible anovulatory cycle), the testing session during the luteal phase was cancelled and data gathered during the follicular phase of that cycle were consequently excluded from further analysis and the study subject was re-evaluated at the next menstrual cycle.

2.2. Experimental design

2.2.1. Conditioned pain modulation

The CPM paradigm was conducted as previously described by Granot and colleagues using the US Food and Drug Administration-approved TSA II NeuroSensory Analyzer system (Medoc, Ramat-Yishai, Israel). The methodology has previously been published [4] and is outlined online [5,9] as well as illustrated in Fig. 2. The research personnel (a total of 3 people) administering the tests followed a standardized script on all 8 visits.

2.2.1.1. Training phase. Subjects were given a short training period in order to familiarize them with the devices, the perceived sensations, and the task. First, they were exposed to 2 short heat stimuli applied using the TSA II to their dominant forearm by the contact thermode. The 2 target temperatures, 43°C and 44°C, each lasted 7 seconds. The increasing/decreasing rate and interstimulus interval settings remained at 8°C/second and 3 seconds, respectively, throughout the entire procedure. When not activated, the thermode rested at a baseline temperature of 32°C. Subjects were asked to rate the pain intensity using an 11-point verbal numerical pain scale (VNPS; 0 = no pain, 10 = worst pain imaginable).

2.2.1.2. Test stimulus. The intensity of the TS was determined for each subject, and was defined as the temperature resulting in a painful sensation with a magnitude of 6 on the VNPS. Subjects were exposed to a first series of randomly selected hot stimuli (between 42°C and 48°C) to determine the TS temperature. If the TS temperature was not found after the first trial of randomly selected temperatures, up to 2 additional trials were performed.

The TS temperature was confirmed with an additional 7-second stimulus at that temperature. The baseline TS was applied for 30 seconds, and subjects were asked to rate the level of pain intensity 4 times: at 0, 10, 20, and 30 seconds.

2.2.1.3. Conditioning stimulus. After a 5-minute break, subjects were asked to place their nondominant hand into a 46.5°C hot-water-bath apparatus (Hot Tub 14 L, Boekel Scientific, PA) in a still position with their fingers wide apart for 60 seconds. Subjects were asked to rate the level of pain intensity 4 times: immediately after immersion of the hand into the water (time 0), and after 10, 20, and 30 seconds following immersion. After 30 seconds of the immersion of the hand in the hot-water bath, and subsequent to the fourth pain rating for the CS, the TS was applied as outlined earlier. Subjects were asked to shift their focus to the thermode, and to rate the intensity of the conditioned TS at 40, 50, and 60 seconds while their nondominant hand remained in the hot-water bath. The TS and the conditioned TS were obtained in the same manner in terms of test duration (30 seconds), intensity rating intervals (10 seconds), and instruction to focus the attention on the thermode during the TS.

2.2.1.4. CPM effect. The CPM effect was evaluated by comparing the last TS pain rating (VNPS of the baseline TS at 30 seconds) with the last pain rating during the conditioned TS (VNPS of the conditioned TS at 60 seconds). The CPM score was calculated as follows:

$$\text{CPM score} = \text{VNPS}_{\text{baseline test stimulus at 30sec}} - \text{VNPS}_{\text{conditioned test stimulus at 60sec}}$$