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Analysis of Meaningful Conditioned Pain Modulation Effect in a Pain-Free Adult Population

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Abstract: Conditioned pain modulation (CPM) encompasses the effects of inhibitory and facilitatory pain modulatory systems and is inefficient in some chronic pain states. A proportion of healthy subjects also exhibit little or no CPM, perhaps suggesting that inherent factors such as gender or genetics may be influential. However, there is no consensus on how best to determine a meaningful CPM effect. This study aimed to determine the proportion of pain-free subjects exhibiting a meaningful CPM effect. Analyses of associations between 5HTTLPR (serotonin transporter-linked polymorphic region) polymorphisms on the serotonin transporter gene (*SLC6A4*), gender, and CPM effect were also carried out. A total of 125 healthy subjects (47 male; 78 female) underwent pressure pain threshold testing before, during, and after a cold pressor conditioning stimulus. A buccal cell sample was collected for analysis of 5HTTLPR genotype. Meaningful CPM effect was determined as an increase in pressure pain threshold values from baseline greater than the inherent error of measurement, calculated as 5.3%. During the conditioning stimulus, 116 subjects (92.8%) exhibited a CPM effect whereas 9 did not. CPM effect did not differ significantly between genders or between 5HTTLPR genotypes. This provides a clear basis on which to determine the proportion of patients with a chronic pain disorder that exhibit a meaningful CPM effect.

***Perspective:** This study proposes a method for calculating meaningful CPM effect and reports the proportion and magnitude of effect elicited in a large sample. Associations between CPM, gender, and genotype were also analyzed. Clarification of normal CPM response may help to elucidate the mechanisms driving CPM inefficiency in chronic pain.*

***Key words:** Conditioned pain modulation, diffuse noxious inhibitory controls, serotonin transporter gene, gender, healthy adults.*

It is recognized that pain perception is complex and multifactorial, involving not only biological mechanisms but also psychological and social factors.[1] However, there is growing evidence for a specific impairment of pain inhibitory/facilitatory pathways that results in the diffuse hyperalgesia that characterizes a number of chronic pain disorders.[17,18]

The original concept of diffuse noxious inhibitory controls identified a mechanism whereby the central nervous system modulates inhibitory and facilitatory signals in order to focus on the most significant nociceptive input.[20] Numerous studies have demonstrated that application of a second nociceptive stimulus to a distant body region will result in inhibition of an initial test stimulus.[33] This phenomenon has more recently been renamed "conditioned pain modulation" (CPM) in order to encompass the overall effect of multiple inhibitory and facilitatory pain mechanisms.[41] A painful conditioning stimulus activates A∂ and C-fibers in an area distant to the initial tested or painful area.[19] This activates descending neuronal

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networks. All spinal and trigeminal multireceptive neurons not directly affected by the conditioning stimulus are inhibited, thereby increasing pain threshold at the test stimulus site.[40] The extent of increase in pain threshold reflects the CPM effect. The most efficient CPM effect appears to be elicited by using the cold pressor test (CPT) as the conditioning stimulus, combined with use of pressure pain thresholds (PPTs) as the test stimulus.[30]

Although inefficient CPM effect has been reported for a range of clinical pain states,[21,37] it is apparent that the extent of CPM may vary considerably among individuals, depending on a range of factors.[2,10,18] Evaluation of CPM effectiveness may therefore be of value in understanding the mechanisms underpinning chronic pain states. However, study comparison is difficult because a variety of CPM methodologies have been used.[40] To date, there is no consensus on a standard protocol for the induction of CPM or for measurement of extent of CPM effect, and sample sizes have been limited.[32] Normative studies involving larger sample sizes and a standardized method for CPM induction and measurement of a clinically meaningful effect are needed. This will provide consistency among studies[30,32,40] and will allow the characteristics of a normal response to be clarified, thereby enabling better understanding of how CPM is altered in individuals with chronic pain.

Given that a proportion of pain-free healthy individuals have exhibited diminished or no CPM effect,[13,22] it may be that inherent factors such as gender or genetics may play a role. The evidence for the influence of gender on CPM is limited to small studies with mixed findings, and a recent systematic review has advised the need for studies with larger sample sizes.[31] 5-Hydroxytryptamine (5-HT) or serotonin has been shown to have an important role in modulating cold pressor pain.[25] Genetic influences on CPM have recently become a focus of research.[11] The 5HTTLPR (serotonin transporter-linked polymorphic region) polymorphisms on the serotonin transporter gene, *SLC6A4*, have been shown to influence transcription of the serotonin transporter.[28] The short allele of 5HTTLPR has been linked to reduced SLC6A4 expression, decreased serotonin transporter transcription, and reduced serotonin effectiveness, which could potentially decrease the CPM effect.[23] A recent in vivo study reported decreased inhibitory CPM in individuals with short allele 5HTTLPR genotypes, but only with a non-noxious conditioning stimulus and not with a noxious conditioning stimulus. The interaction between CPM and genetics is therefore still unclear, because of the conflicting findings of current research and limited available data.

This study therefore aimed to determine the proportion of healthy adults exhibiting a meaningful CPM effect by applying a standardized methodology for induction of CPM and calculation of effect greater than the inherent measurement error. The influences of gender and serotonin transporter gene polymorphisms on the extent of CPM effect were also analyzed.

Methods

Participants

One hundred thirty-two healthy, pain-free adult volunteers were recruited via advertisements posted on community notice boards in the South Perth, Victoria Park, and Canning districts in Perth, Western Australia. Further subjects were recruited via a social media event page. Volunteers were provided with an information sheet and a screening questionnaire, e-mailed prior to the testing date.

Exclusion criteria included current illness or serious medical condition; contraindications to cold application (cold urticaria, diabetes, Raynaud's syndrome, circulation deficiencies, skin conditions); current musculoskeletal pain of greater than 4 weeks' duration; chronic pain disorders (fibromyalgia, temporomandibular joint disorder, irritable bowel syndrome); or current or long-term history of medication for pain or depression. Subjects also needed to be able to understand written and spoken English.

The study was approved by Curtin University Human Research Ethics Committee, approval number HR 154/2011, and informed consent was obtained from all subjects prior to commencing testing.

Protocol

Eligible subjects attended for a single test session and followed the testing protocol illustrated in Figure 1. PPTs at the right forearm was used as the test stimulus with submersion of the left hand in temperature-controlled ice water, which provided the painful conditioning stimulus.

Test Stimulus: PPT

PPT was tested using a hand-held algometer (Somedic, Hörby, Sweden), with a stimulation area of 1 cm^2. Pressure was applied at a standard rate of 40 kPa/s. Subjects were asked to press a control switch when they first perceived painful pressure.[27] PPT has been shown to be highly consistent and repeatable, both on the same day and across subsequent days (intraclass correlation coefficient [ICC]: day 1 = .94; day 2 = .96; day 3 = .97; and day 4 = .96).[16]

PPT was carried out on the left forearm for familiarization and then on the right at a location 2 cm proximal to the dorsal wrist crease, in the midline. Subjects were seated at a table with the forearm supported in pronation. Seat height was controlled so that the table remained at a comfortable elbow height. The site over the right wrist was tested at 4 time points: prior to conditioning stimulus cold immersion for a baseline measurement, after 1 minute of immersion in order to measure CPM effect, and at 2 minutes and 5 minutes postimmersion to assess time taken for subjects to return to baseline. The primary outcome measure was PPT after 1 minute of immersion. At each time point, PPT was measured 3 times with a 20-second pause between trials.