Conditioned pain modulation (the diffuse noxious inhibitory control-like effect): its relevance for acute and chronic pain states

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Purpose of review

There is a growing body of knowledge on pain modulation in various disease states. This article reviews the state of the art regarding the clinical relevance of pain inhibition as revealed by 'pain inhibits pain' test paradigms, trying to organize the clinically relevant data, and emphasizing the pathophysiology of pain. In line with recent experts' recommendations, the term conditioned pain modulation (CPM) will be used, replacing the previous terms 'diffuse noxious inhibitory control (DNIC)' or 'DNIC-like' effects.

Recent findings

Most of the work in this context was done on the idiopathic pain syndromes, such as irritable bowel syndrome, temporomandibular disorders, fibromyalgia, and tension type headache. The pattern of reduced CPM efficiency seems common to these syndromes and an assertion is made that low CPM efficiency, reflecting low pain inhibitory capacity, is a pathogenetic factor in the development of the idiopathic pain syndromes. Low CPM efficiency was shown to be predictive of acute and chronic postoperative pain, and, in some reports, to be associated with neuropathic pain levels.

Summary

Low CPM efficiency is associated with higher pain morbidity and vice versa. Further work is awaited on clarifying plasticity of CPM and its relevance to selection and efficacy of pain therapy.

Keywords

conditioned pain modulation, diffuse noxious inhibitory control, idiopathic pain syndromes, pro-nociceptive

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Introduction

Having dealt, for many decades, mainly with the static pain parameters of threshold, suprathreshold magnitude estimation, and tolerance, the science of pain psychophysics had shifted, during the last decade, to focus on dynamic parameters. Two dynamic test paradigms, designed to activate and measure pain processing mechanisms, provide a better depiction of a patient's pain modulation system, and allow identification of alterations in this system, along with their clinical relevance: (i) temporal summation, representing excitatory modulation processes, usually performed by measurement of the change in pain perception along a series of similar noxious stimuli and (ii) diffuse noxious inhibitory controls (DNIC), representing the inhibitory modulation, usually performed by a 'pain inhibits pain' test paradigm. Translational research applying these paradigms in the clinic has gained popularity over recent years, emanating in a fairly large body of data. The data gathered on the clinical correlates of DNIC called for this first ever review on this diagnostic/mechanistic test in this clinically oriented journal. Two reviews have been published on this topic during this review period. Pud *et al.* [1] have emphasized the technical details of test performance in various studies in healthy subjects, emphasizing the large methodological variety among studies. Van Wijk and Veldhuijzen [2] wrote a comprehensive review, with emphasis on demographic factors and on the clinical applications.

Terminology and characteristics of normal pain inhibitory patterns

Terms used in the literature to describe the paradigm in which one noxious stimulus is used as a conditioning stimulus to induce reduction in pain perception by another stimulus include 'counter-irritation', 'pain inhibits pain', 'heterotopic noxious conditioning stimulation' (HNCS), and, the most commonly used, DNIC. The last has been formulated describing a specific lower brainstem-mediated inhibitory mechanism. Human-based research, using 'pain inhibits pain' paradigms, has adopted the term DNIC, stretching it into the psychophysical domain, by describing behavior patterns that

could relate to several neural mechanisms. Trying to resolve this nomenclature ambiguity a group of basic scientists and clinicians have recommended new terminology, suggesting the term conditioned pain modulation (CPM) to describe psychophysical paradigms in which a conditioning stimulus is used to affect a test stimulus [3•]. This term will be used hereafter in this article.

The characteristics and extents of the normal CPM, and the specifications of the paradigms used to evoke it, must be defined in order to properly interpret findings in clinical studies. One major unanswered question in that regard relates to whether females have less efficient CPM than males (see [4] for review). A study by Tousignant-Laflamme and Marchand [5•] has contributed to clarifying this issue by showing that while heat pain thresholds and tolerance levels were unchanged throughout the menstrual cycle, the CPM effect did change. Exerted by contact heat pain as the test stimulus and cold water immersion as the conditioning stimulus, a higher CPM effect was seen during the ovulatory phase than during the luteal and menstrual phases. The need to take the menstrual cycle phase into consideration in future studies is clear. Looking at another issue, the predictive role of the magnitude of the conditioning stimulus and the test stimulus on CPM efficiency, Treister *et al.* [6] found a significant effect of both, though the former was for men only. Reports on this issue are still controversial [7] and further research is awaited. The distinction between CPM and distraction was clarified by Moont *et al.* [8] using a psychophysical paradigm that measured pain reduction by noxious stimulus, distracting stimulus and the combination of both. A video demonstration of a CPM paradigm, together with other psychophysical pain testing paradigms, has been recently published [9].

Acute pain

While several articles explored correlations between baseline static pain parameters and acute postoperative pain, showing controversial results [10–17], little is known on the relation between CPM and pain in the acute setting. In thoracotomy patients examined for their CPM effect before surgery (see below for the chronic pain findings of this study), no correlation was found between the CPM effect and any of the acute postoperative pain parameters [18•]. Landau *et al.* [19], using a similar paradigm, did find a correlation of baseline CPM and extent of acute postoperative pain. A possible explanation could be blurring of the CPM effect in the multiple factors involved in pain generation in the acute postoperative state.

Chronic pain

As opposed to acute pain, a large body of data has been developed for various chronic pain states. I have combined the 'idiopathic', medically unexplained pain syndromes, since a common modulation pattern seems to be relevant to all of them.

Idiopathic pain syndromes

Consistent data have accumulated on the CPM pattern in idiopathic pain syndromes. In recent years CPM has been shown to be less efficient in several of the idiopathic pain syndromes [20–24]. In the current review period, several articles have further strengthened this line of thought. Patients with irritable bowel syndrome (IBS) showed lower CPM efficiency than healthy controls; Heymen *et al.* [25] studied 48 female patients with IBS using a series of phasic heat pain to the hand as the test stimulus and cold water immersion of the other hand as the conditioning stimulus. King *et al.* [26] studied 14 women with IBS, using hand tonic heat pain conditioned by foot cold immersion. Another study, on 27 female patients with IBS, had used electrical stimulation as the test stimulus and cold water immersion as the conditioning stimulus [27].

The study by King *et al.* [26] has also evaluated 14 patients with temporomandibular disorder (TMD) studied under the same protocol, showing, similar to IBS patients, a decreased CPM efficiency. A correlation between sleep continuity and architecture on one hand and CPM efficiency has been reported by Edwards *et al.* [28] by measuring the effect of cold water hand immersion on pressure pain thresholds in the hand and shoulder in patients with TMD. The authors raised the possibility that, in these patients, sleep disruption may serve as a risk factor for inadequate CPM function, and that treating sleep in the early course of TMD might benefit patients by reducing their pain.

For tension type headache (TTH), Cathcart *et al.* [29] studied 46 patients, using finger and shoulder mechanical temporal summation as test pain, and cuff compression ischemia as conditioning. Enhanced temporal summation and reduced CPM were found in patients with TTH compared with controls. CPM effect was found independent of prior lingual–arithmetic stress. Looking at the neurophysiological correlates of pain processing in patients with chronic TTH, Buchgreitz *et al.* [30] studied the P200 dipole obtained through EEG recording in response to electrical muscle stimulation. While controls exhibited a decrease in this dipole magnitude under conditioning by painful muscle stimulation, patients did not show such a decrease. The authors interpreted this as evidence for deficient descending inhibition in patients with TTH.

In a study on 48 patients with fibromyalgia, Potvin *et al.* [31] explored changes in pain perception, including CPM, and their possible relation to polymorphism in

the serotonin transporter promoter region. Patients did show reduced CPM effect compared with controls, but no genetic association was found. When looking at polymorphism of the dopamine receptor 3, however, this group did find it to be associated with CPM efficiency in patients with fibromyalgia [32•]. In an additional study from the same group, 52 female patients with fibromyalgia were evaluated for pain inhibition using the spatial summation paradigm of immersing different areas of the upper limbs in an ascending–descending sequence in cold water. Patients had less efficient pain inhibition than controls. Within patients, those with depression had even lower CPM [33]. In yet another article from this group, the effect of pain attenuation through expectation was found to supersede that of CPM, suggesting different mechanisms of action for expectation of pain relief and for CPM [34].

For facial pain, Leonard *et al.* [35] measured CPM in 15 patients with classical trigeminal neuralgia (TGN) and 15 patients with atypical facial pain (the latter is considered an idiopathic pain syndrome). Tonic heat pain was applied to the painful region on the face and was repeated immediately after conditioning by cold water immersion of the hand. Patients with classical TGN had a significant reduction in pain owing to the conditioning (16% reduction), similar to that obtained by the healthy controls (21% reduction). Atypical pain patients, however, had only a minute decrease of 1%, in line with the other reports on less efficient CPM in idiopathic pain syndromes. It is noted that, despite the common findings of low CPM efficiency in the idiopathic pain syndromes, there is usually no correlation between symptom severity and CPM, a puzzling finding, probably suggesting the importance of additional confounding factors involved in determining the clinical picture.

In a study on chronic fatigue syndrome (CFS), Meeus *et al.* [36] compared the pain psychophysics of 31 patients and 31 controls, using a paradigm of gradually increasing and then decreasing areas of upper limb hot water immersion. Patients had overall higher pain ratings. When looking at the CPM effect, a difference was only found during the last 15 s of the 2 min immersions, showing a delay in development of the CPM effect in patients compared with controls. The authors interpreted this finding as indicative of less efficient endogenous analgesia that might play a role in development of pain in CFS.

Chronic pain of defined cause

Twenty-five patients with chronic pancreatitis were evaluated for their CPM, using visceral stimuli, by Olesen *et al.* [37]. Patients had lower CPM efficiency than controls. Neurophysiological recordings showed higher latency for P1 peak in patients than in controls. In a very recent article, Arendt-Nielsen *et al.* [38] have shown a decrease in CPM efficiency in patients with painful knee osteoarthritis using ischemia for conditioning, and pressure pain thresholds as the test stimuli. It is noted that earlier studies have shown a normal CPM efficiency in patients with rheumatoid arthritis [39] and those with trapezius myalgia [40]. Thus, low CPM efficiency is not a uniform feature of this group of disorders.

Neuropathic pain

A single study on CPM and neuropathic pain, focusing on central poststroke pain (CPSP), has been published in this review period. Tuveson *et al.* [41] studied 10 such patients using ischemia as the conditioning stimulus. They found no significant effect of conditioning on spontaneous pain. Allodynia seemed to be reduced by conditioning, but this reduction did not reach significance. In pain-free areas, the extent of pain reduction by conditioning was similar for patients to that obtained for controls. In an abstract form, Nahman *et al.* [42] have shown a correlation between CPM efficiency measured in unaffected upper limbs and pain levels in 27 patients with chemotherapy-induced lower limb painful neuropathy.

Conditioned pain modulation in neurological and psychiatric disorders whose main manifestation is not pain

Patients with Parkinson's disease often have pain, whose mechanism is considered central. Since this is a degenerative disease, a likely mechanism would be a decrease in inhibitory efficiency as part of the degenerative process. Contrary to such expectation, Mylius *et al.* [43] have shown a similar extent of pain inhibition in 15 patients and 18 controls, although patients did show lower pain thresholds. The conditioning stimulus was a train of repetitive contact heat pain stimuli; for the test stimulus both electrical pain threshold and the nocifensor reflex threshold have been used. In schizophrenia, a syndrome in which diminished sensitivity to pain has been clinically described, no difference in CPM efficiency was found by use of contact heat as the test stimulus and cold water immersion as the conditioning stimulus [44]. The authors found lower temporal summation of pain in patients, suggesting a lack of pain sensitization. The findings of these two studies suggest that dopamine is not a major player in the CPM mechanism.

Prediction of chronic postoperative pain

Trying to clarify whether changes in CPM efficiency are a causative factor in pain development, or a result of the presence of pain, Yarnitsky *et al.* [18•] measured CPM efficiency in pain-free patients before thoracotomy, and followed up on chronic postoperative pain at 6–12 months after surgery. CPM was measured by forearm contact heat

as the test stimulus and contra-lateral hand hot-water immersion as the conditioning stimulus. A significant negative correlation between CPM efficiency and chronic postthoracotomy pain scores ($r = -0.429$, $P = 0.001$) was found, with an odds ratio of 0.5 (i.e. for each 10/100 reduction in test stimulus score due to the conditioning, the chances of acquiring chronic pain are halved). These findings demonstrate a pathophysiologic role for CPM in the development of clinical pain, suggesting that a pro-nociceptive state is a causative factor in the generation of chronic pain disorders.

Conditioned pain modulation and pain therapy

To date, no studies have been published on the CPM effect as a predictor of analgesic efficacy. An important work, currently available as abstract only, examined the other dynamic psychophysical test paradigm, temporal summation, in predicting the effect of ketamine, an NMDA receptor blocker, on acute postcesarean section pain [45••]. The reasoning was that ketamine would reduce temporal summation for those with enhanced temporal summation, but would be less effective in those with already normal temporal summation. Lavandhomme and Roelants [45••] have shown ketamine to be effective only in patients whose temporal summation was enhanced at baseline, while no effect was shown for subjects with non-enhanced summation. Using similar reasoning, it can be expected that analgesics that augment descending inhibition, such as SSNRIs, will be more effective in patients whose CPM is less efficient than in those with an already efficient CPM prior to the analgesic. No data are yet available to support or refute this concept.

Evaluating the interaction between opioid use and CPM effect, Ram *et al.* [46•] investigated 110 chronic pain patients, mostly nonmalignant, of whom 73 received opioids and 37 received nonopioid analgesics. Opioid-treated patients had less efficient CPM than nonopioid-treated patients. This effect was significant only in men. The authors suggested, in accordance with previous laboratory-based literature, that opioids decrease the activity of the descending inhibition pathways. This might expose patients to excessive neurophysiological pain activity and provide a mechanism for opioid-induced hyperalgesia.

Conclusion

The evolving body of data on altered CPM efficiency in this variety of clinical situations highlights altered pain inhibition as a pivotal factor in pain pathophysiology. Since most of the data obtained so far are cross-sectional, it cannot prove cause–effect relations between the mechanism and the clinical pain expressions. The study on prediction of postthoracotomy pain, however, does show the pain modulation pattern to be primary to the clinical pain picture; thus, validating the concept that a 'pro-nociceptive' pain modulation pattern predisposes people to acquire pain. Since enhanced summation of pain is reported in many pain syndromes as well, I consider the 'pro-nociceptive' state to be that expressed by either decreased inhibition or enhanced summation, or both. Along this line of thought, and in agreement with the hypothesis published by Edwards in 2005 [47], it is plausible to interpret the association found between pro-nociceptive states and idiopathic pain syndromes as a 'cause and effect' relation; individuals whose pain modulation is 'pro-nociceptive' seem to be more prone to acquiring one or more of the idiopathic pain syndromes. The situation for neuropathic and inflammatory states is more ambiguous, but it seems that, at least in some conditions, clinical pain intensity might be affected by CPM.

Data are still minimal on plasticity of the pain modulation patterns, and whether they change from baseline to the clinical pain state, and then from pain to the relieved pain state. Only one study by Kosek and Ordenburg [48] reported reduced inhibitory efficiency in osteoarthritis patients with pain, and improvement of the CPM efficiency in parallel to pain relief after surgery. Data on therapeutic implication of CPM are still awaited.

The author would like to stress a point often neglected in the context of CPM. The application of this paradigm is done in order to assess the endogenous analgesia capability of the individual being assessed. To that end, a variety of other conditioning stimuli could have been used, including stress, hypnotic suggestion, and such like. The common use of a painful stimulus as the means of conditioning is due to it being an easy and quick way to induce activity in the descending pain modulatory pathways. This article has reviewed only the clinical relevancy of painful conditioning stimuli, but the door remains open to studies using other paradigms to induce such modulation, which might show different aspects of these systems, and, possibly, different clinical correlates.

Acknowledgement

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