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Conditioned Pain Modulation: A Predictor for Development and Treatment of Neuropathic Pain

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Abstract Psychophysical evaluation of endogenous pain inhibition via conditioned pain modulation (CPM) represents a new generation of laboratory tests for pain assessment. In this review we discuss recent findings on CPM in neuropathic pain and refer to psychophysical, neurophysiological, and methodological aspects of its clinical implications. Typically, chronic neuropathic pain patients express less efficient CPM, to the extent that incidence of acquiring neuropathic pain (e.g. post-surgery) and its intensity can be predicted by a pre-surgery CPM assessment. Moreover, pre-treatment CPM evaluation may assist in the correct choice of serotonin-noradrenalin reuptake inhibitor analgesic agents for individual patients. Evaluation of pain modulation capabilities can serve as a step forward in individualizing pain medicine.

Keywords Central sensitization · Chronic pain · Conditioned pain modulation (CPM) · Personalized pain medicine · Neuropathic pain · Pain facilitation · Pain inhibition · Psychophysics

Introduction

Adequate relief of neuropathic pain is still a major unaccomplished goal, with most agents having a low efficacy of 30–50 % pain reduction, and a low number needed to treat (NNT) of about 3–4 [1, 2]. Currently, the treatment choice is solely at the physician's discretion, regardless of any individual patient-related parameters, such as pain modulation capabilities [3–6]. In addition to the need to choose the most appropriate drug for a specific patient in general, there is the need to pre-operatively assess and identify patients who are at higher risk for development of chronic post-operative pain. This prediction can possibly be done by taking into consideration the individual patient's characteristics, including those that relate to the patient's pain modulation. Hopefully, this will help develop efficient treatment-choice strategies. This may spare patients the long "trial and error" process of treatment titration, often needed before substantial relief, if any, is achieved.

Chronic neuropathic pain represents a heterogeneous group of diseases in which pain is caused by nerve damage owing to various etiologies. The most common are metabolic abnormalities, such as diabetes, and traumatic or surgical injuries. The common symptoms characterizing the neuropathic changes are spontaneous pain, mostly of burning character, and sensory loss, as well as allodynia and/or hyperalgesia [7]. With regard to the neurophysiological basis of neuropathic pain, the following underlying mechanisms are described: (1) abnormally excessive peripheral inputs resulting in changes in the central properties of second-order neurons at the dorsal horn, mostly wide dynamic range neurons. These changes are expressed by increased spontaneous firing, lowered activation threshold, and expanded receptive fields [8], resulting in ascending facilitation of the nociceptive input; (2) enhanced activation of descending pain facilitatory pathways originating in the rostroventromedial medulla and/or the periaqueductal grey [9]; (3) reduced descending pain inhibitory control of the wide dynamic range [10]. Importantly, the activation of both descending facilitatory and inhibitory supraspinal pain control systems requires intense noxious stimulation, resulting in activation of these brainstem centers to finally activate the descending arm of this spino-bulbo–spinal circuit [9]. Imbalance between facilitatory

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and inhibitory systems, with higher activity in the former and lower in the latter, contributes to central neuronal sensitization, and to the development and maintenance of pain, reduction in pain thresholds, and spreading or radiation of pain to uninjured sites.

One of the most studied mechanisms of the supraspinally-mediated descending pain inhibition system is diffuse noxious inhibitory control (DNIC). DNIC engages the "bottom-up" activation of the endogenous analgesia system where, upon arrival of data to the brainstem, the ascending pain activates descending pain inhibitory pathways, exerting effects on incoming nociceptive inputs. This is a physiological phenomenon originally described in animals in the late 1970s [11, 12], where one noxious stimulus—the "conditioning stimulus"—inhibits a concomitant or subsequent "test stimulus". This results in the "pain inhibits pain" phenomenon, corresponding with the time-honored concept of "counterirritation" [13]. In humans, if a patient is asked to rate the intensity of a certain "test stimulus", and then given the combination of a noxious "conditioning stimulus" and a repeated similar "test stimulus", the perceived intensity of the latter "test stimulus" will generally be lower than when given alone. The term conditioned pain modulation (CPM) has recently been coined for the psychophysical protocols that explore the DNIC phenomenon in humans [14•]. CPM represents the new generation of "dynamic" pain psychophysical testing, in this case evaluating inhibitory pain modulation processes [15]. Complementary to assessment of pain inhibition via CPM, there is a psychophysical method for evaluation of ascending pain facilitatory pathways. This can be done using a temporal summation (TS) protocol, where pain increases along a series of repeated identical noxious stimuli representing the physiological phenomenon of wind-up—the central neuronal sensitization in response to noxious activation [16]. We hypothesize that at the clinical level, a facilitatory state of pain modulation systems (i.e. less efficient CPM, enhanced TS, or both) identifies the individual patients as having a pro-nociceptive pain modulation profile that is associated with higher pain morbidity. In contrast, an inhibitory state of pain modulation (i.e. more efficient CPM, diminished TS, or both) corresponds to an anti-nociceptive pain modulation profile and, consequently, to lower pain morbidity. Indeed, specifically for endogenous pain inhibition, less efficient CPM was described for a variety of idiopathic and other chronic pain conditions, including fibromyalgia [17•, 18–20], osteoarthritis [21–24, 25••], migraine and tension-type headaches [26–29], irritable bowel syndrome [30–32], and post-whiplash pain [33•]. Many of these reports were summarized in recent review articles by van Wijk and Veldhuijzen [34••], Yarnitsky [35••], and Lewis et al. [36••].

Whether the less efficient CPM is a result of ongoing chronic pain, or it predisposes to the pain syndrome, remains, to a large extent, an open question. In the laboratory animal set-up, the results of a recent study suggest that the efficient engagement of descending inhibition provides protection against the development of experimental chronic neuropathic pain [37••]. However, the pain modulation profile seems to be a flexible feature, being pro-nociceptive in the presence of substantial clinical pain, but reversing to anti-nociceptive pain modulation upon pain alleviation [21, 25••].

Psychophysical and Neurophysiological Characteristics of CPM in Neuropathic Pain

Despite the widely recognized fact that neuropathic pain models in animals are characterized by central neuroplastic changes of pain pathways, research on human neuropathic pain previously focused on the assessment of neurological deficits, mostly of peripheral nerve origin. This was done using mainly the "static" psychophysical measures, such as sensory and pain thresholds, referenced either to control body sites, or to healthy control participants. Such "static" pain measures prove useful in the diagnosis of the negative signs required for diagnosis of pain as neuropathic. Dynamic pain parameters, however, can illuminate the question of how the CNS facilitates or inhibits pain. This can be done by assessment of pain modulation on pain-free body-sites, remote from painful injured areas. Using this testing approach, enhanced TS was reported for chemotherapy-induced pain [38] and for post-surgical neuropathic pain patients [39, 40]. For inhibitory modulation, as expressed by CPM, the findings are ambiguous and relate to where the "test" or "conditioning" stimuli were delivered to painful or non-painful body sites.

"Test" and "Conditioning" Stimuli are Delivered to Unaffected Body Areas. Compared with healthy controls, less efficient CPM was reported for chemotherapy-induced neuropathic pain [38]. In line with this, Tuveson et al. [41] reported less efficient CPM in chronic peripheral neuropathy patients; ischemic pain was inefficient in increasing heat pain thresholds, but was efficient in increasing pressure pain thresholds. Similarly, less efficient CPM in modulating heat pain sensation and efficient CPM in increasing pressure pain thresholds was reported for patients with central post-stroke pain [42].

"Test Stimulus" is Delivered to Allodynic Skin, and "Conditioning Stimulus" is Delivered to Unaffected Body Area. Cold pressor test induced efficient CPM on noxious contact heat delivered on the painful face area in trigeminal neuralgia patients, but it was less efficient for pain reduction in patients with atypical facial pain [43]. Further, it

efficiently reduced mechanical allodynia in chronic peripheral neuropathy patients [41, 44], and increased electrical and mechanical pain thresholds assessed on the affected arm in post-stroke shoulder pain patients [45]. In contrast to the effect of cold pressor test, ischemic pain did not reduce allodynia in chronic peripheral neuropathy patients [41].

"Test Stimulus" is the Ongoing Clinical Pain, and "Conditioning Stimulus" is Delivered to Unaffected Body Area. Cold pressor test and ischemic pain applied to pain-free body sites were inefficient in reducing the ongoing pain [42, 44]; the latter was also inefficient in reducing allodynic intensity in central post-stroke pain patients [42].

"Test Stimulus" is Delivered to an Unaffected Body Area, and "Conditioning Stimulus" is Delivered to Allodynic Body Area. Light mechanical pressure applied within the allodynic area efficiently reduced the amplitude of the nociceptive reflex, and the concomitant painful sensation in peripheral traumatic injury pain patients. The extent of the aforementioned CPM responses was similar to those obtained in response to the application of "conditioning" pain stimulus in pain-free remote body areas [46]. These surprising findings are in line with several reports from studies on animal models of sciatic injuries, mononeuropathy, and monoarthritis. In those studies, the "conditioning stimulus" was applied to the painful extremity and induced augmented DNIC compared with the application of "conditioning stimulus" to a non-painful extremity [47, 48]. Looking into the mechanisms of CPM augmentation in neuropathic pain [49], likely explanations relate to the fact that some of the A-delta and C-fibers, at the site of application of the "conditioning stimulus", remain intact despite the nerve injury [50] and may become chronically sensitized [51]. This contributes to excessive ascending sensory input, inducing, in turn, higher descending inhibitory "test stimulus" is applied to allodynic skin. In these cases, intense sensory input from the "test stimulus" itself could generate endogenous pain inhibition. In addition to the peripheral mechanisms leading to neuronal sensitization, there are several spinal mechanisms possibly related to enhanced DNIC in neuropathic pain. Among these factors are loss of spinal or segmental inhibition [52–55], sprouting of low threshold afferent endings into superficial layer of the dorsal horn [56], activation of central N-methyl-D-aspartate receptors, and of protein kinase C [57] and compensatory up-regulation of the descending inhibitory noradrenergic innervation to the dorsal horn [58].

The mixed findings on the CPM responses in neuropathic pain may lead to the following conclusions. (1) Congruent with reports of less efficient CPM in various idiopathic pain syndromes, CPM is less efficient in neuropathic pain patients compared with normal controls when both "test" and "conditioning" stimuli are applied to unaffected body sites, truly reflecting reduced capabilities of central pain inhibitory mechanisms. (2) If we look at the ongoing clinical pain as a part of the pain-inhibits-pain loop, and consider it as a conditioning stimulus, it seems not to exert any inhibitory effect for both neuropathic and non-neuropathic pain. That is because no differences were reported in pain responses to experimental pain administered to pain-free areas in pain patients versus healthy participants [41, 46, 59, 60]. (3) Similarly, for the reverse situation, when the ongoing neuropathic pain is conceptually considered as a "test stimulus", and an experimental "conditioning" pain is administered, no inhibitory effects are observed [42, 44]. The application of a "conditioning stimulus", however, efficiently reduced the capsaicin-induced intensity of pain and allodynia in healthy participants [61] in a well-known model of neuropathic pain, thus supporting the concept of dysfunctional descending inhibition in neuropathic pain, possibly due to central neuronal reorganization. (4) The findings on CPM deficiency in neuropathic pain are strongly dependent on the CPM-evoking methodology. The methodological discrepancies among different laboratories in inducing CPM were summarized by Pud et al. [62] and were found to be related to (i) the type of the "test stimulus" (pain thresholds, tonic, or repeated suprathreshold pain, pain tolerance); (ii) the modality of both "conditioning" and "test" stimuli (thermal: cold, contact-heat, laser; mechanical, ischemic, or chemical); and (iii) the combinations of both. In line with this, beyond the described effects of the stimulated body site (affected or unaffected), application of same "conditioning stimulus" exerts efficient CPM on some of the "test stimuli", but not on the others [41, 42, 44, 46]. These ambiguous findings are not specific to neuropathic pain states and were also reported for inflammatory pain, such as osteoarthritis [21], raising the potential need to tailor the best combination of "test" and "conditioning" stimuli to each type or sub-type of the pain syndromes.

An additional point relates to the question of whether the presence of neuropathic lesions, when non-painful, is sufficient to impair inhibitory function, or whether clinical pain is required for it. One could assume that reorganization in the central nervous system due to neuronal damage is the driving force for reducing the efficiency of pain inhibition. There are no data on inhibitory pain modulation in non-painful peripheral neuropathies, but possible insight is available from data on patients with pain-free brain lesions. More specifically, efficient CPM was reported in pain-free patients with central neuropathic changes, such as non-painful thalamic lesions [63], in patients with neurodegenerative diseases of the basal ganglia, such as Huntington's disease [64] and Parkinson's disease [65, 66]. Thus, without experiencing ongoing pain, it seems that the structural changes in regions related to the brain pain-network are not sufficient to affect the CPM response, suggesting that the presence of clinical pain stands as the basis of reduced capabilities of the pain inhibitory system.

CPM as Predictor of the Development of Neuropathic Pain

Experimental pain, administered in well-defined and quantitative ways, has served over the recent decades as a model for clinical pain and served for its prediction. Facing our inability to objectively measure the patient's endogenous clinical pain, pain threshold and pain tolerance became major players on the pain psychophysics literature stage. Pain threshold, suprathreshold estimation, and pain tolerance are "static" parameters of experimental pain, which give a quantitative value to a certain point along the pain continuum, for the tested patient [67]. Quite a long list of studies has shown significant correlations between the static parameter of suprathreshold pain magnitude estimation, as obtained before surgery, and the acute clinical pain that develops soon after surgery [68–73]. Steps forward in pain psychophysics are the stimulation protocols that seem to bring us closer to the patient's pain experience. The protocols for "dynamic" tests (CPM and TS), are designed to evoke a process of endogenous pain inhibition or pain facilitation. I proposed that the extent of inhibition or facilitation expressed in response to the painful stimuli, as may be demonstrated by psychophysical assessment, would faithfully reflect the modulation inflicted upon "real life" pain messages in pain patients. More specifically, I expected that intra-individual variability in pain modulation relates to likelihood for developing chronic pain, hypothesizing that patients with less efficient CPM would be "at risk" for pain disorders when exposed to pain-generating perturbations. To investigate this assertion, I chose the post-operative chronic pain model, as patients can be assessed at a pain-free stage before surgery, with a ""aïve" pain modulation system not yet affected by the presence of clinical pain. I explored this question on a group of 64 patients—candidates for thoracotomy. The study results confirmed my hypothesis and demonstrated a significant association between the less efficient CPM at the pre-operative pain-free state and more intense chronic post-operative pain (CPOP), as assessed more than 3 months after surgery. Furthermore, among various demographic and static psychophysical pain parameters, the extent of CPM efficiency was the only pre-operative predictor of incidence and severity of CPOP. Thus, the ability to modulate experimental pain in the laboratory setting translates, in the clinical setting, to the susceptibility of developing future pain, including the neuropathic pain states [74].

Similar results were obtained by Wilder-Smith et al. [75••] in a pilot study, where 20 candidates for elective major abdominal surgery were assessed pre-operatively with several CPM-evoking protocols. The patients were followed-up to rate their pain 1 day, and 1, 3, and 6 months post-operatively. The results indicated that patients reporting CPOP 6 months after surgery were characterized by less-efficient pre-surgical CPM. Moreover, enhanced post-operative deep tissue hyperalgesia was associated with pre-operatively assessed less-efficient deep tissue CPM, measured as a change in pressure pain tolerance thresholds with cold pressor pain [75••]. In line with the findings on abdominal surgery, less efficient pre-operative CPM and enhanced TS were associated with greater extent of post-surgical hyperalgesia assessed within 48 h of elective cesarean section [76].

The Role of CPM in Treatment of Neuropathic Pain

A growing body of evidence points to the important role of spinal serotonin (5-HT) and noradrenaline (NA) in mediation of pain inhibition via DNIC/CPM [77–79]. Accordingly, pharmacologic spinal NA denervation enhanced hyperalgesic behavior and reduced the anti-nocicpetive effects of morphine in neuropathic animals [80], and increased spinal 5-HT concentration was associated with reduced mechanical allodynia [81]. Expanding these findings to clinical research, I propose that the recruitment of endogenous pain modulation networks will determine the choice of drugs likely to reduce pain.

Duloxetine (DUL), a serotonin-noradrenalin reuptake inhibitor (SNRI) agent, is currently used for treatment of painful diabetic neuropathy (PDN) [6, 82] and other chronic pain conditions. DUL is expected to augment descending inhibition by increasing synaptic norepinephrine and serotonin via reuptake inhibition [83]. Thus, it is likely that CPM efficiency will be associated with efficacy of DUL; DUL should be more efficacious in patients with less efficient endogenous pain inhibition than in those with efficient inhibition. Based on this theory, I conducted a study on 30 PDN patients who were assessed for a battery of psychophysical testing, including CPM, before and after 5 weeks of treatment with DUL (60 mg/day). The results of this study confirmed my proposal and pointed at a significant correlation between the pre-treatment CPM efficiency and DUL effect: less efficient CPM predicted better drug efficacy. Importantly, pre-treatment CPM remained the only predictor for DUL efficacy after controlling for initial clinical pain, pre-treatment level of depression, neuropathy severity, and the placebo effect. Furthermore, my findings revealed that the greater improvement in CPM was associated with higher drug efficacy, mainly owing to those patients with less-efficient pre-treatment CPM. In line with the theory of coupling between the less efficient pain inhibition (as measured by CPM) and higher pain-reducing efficacy of medication that restores the deficient level of NA/5-HT, no correlation was observed between the DUL effect and the extent of pre-treatment TS [84••].

In addition to linking the SNRI's efficacy to pre-treatment CPM efficiency, importance of this coupling may be further enrolled in the concept of additive effects of drugs coming from families with different mechanisms of action. Thus, animal studies report on the relationship between deficient NA

transmission and reduced morphine-induced behavioral changes [85], including morphine-induced analgesia [86]. Re-establishment of NA signaling reversed these changes [85]. In line with this, NA and 5-HT reuptake inhibition by tricyclic antidepressants was shown to increase the intensity and duration of morphine analgesia [87, 88], as well as the analgesic efficacy of calcium channel blockers in animal models of nerve injury [89]. It seems, therefore, that pre-treatment CPM assessment may be relevant for prediction of analgesic drug interaction and additive effects.

In line with my theory of prediction of the analgesic effect of SNRIs by pre-treatment psychophysical assessment of pain inhibitory pathways with CPM, I propose that the effect of pain medications acting to reduce central neuronal excitability may be predicted by the assessment of pain facilitatory pathways via TS. There are several reports favoring this assumption. Lavand'homme and Roelants [90] published an abstract in 2009 on use of ketamine in post-cesarean pain; they found that those patients with pre-operatively enhanced TS gained more analgesia from ketamine, an NMDA receptor blocker expected to reduce central neuronal sensitization. The patients with non-enhanced pain summation did not benefit from the drug [90]. Later, Eisenberg et al. [91•] reported that pre-treatment enhanced TS was associated with higher tolerance to cold pressor test after oxycodone treatment. Another important finding came from a recently published study on chronic painful pancreatitis, which demonstrated that patients hypersensitive to a train of electrical stimuli gained more analgesia from treatment with the Ca++ blocker gabapentin [92••]. The results of these studies confirm my assertion about the predictive value of facilitatory pathway assessment.

Conclusions

As a whole, theory supports selecting and tailoring pain medication based on individual pain modulation profiles. This is a significant step forward toward personalized pain medicine. Needless to say, further work is required in improving the protocols used for the CPM, as well as for other dynamic psychophysical tests for individual pain assessment, to optimize reliability, sensitivity, and specificity in describing various clinical pain events, and optimizing specific test paradigms for particular clinical situations, including neuropathic pain states.

Compliance with Ethics Guidelines

Conflict of Interest Dr Yelena Granovsky is a paid consultant of Medoc Ltd. Dr Granovsky reports receiving a grant from the Israeli Scientific Foundation (ISF #147/08) and an IIT grant from Eli Lilly Inc.

Human and Animal Rights and Informed Consent With regard to the author's research cited in this paper, all institutional and national guidelines for the care and use of humans and laboratory animals were followed. In addition, all procedures were followed in accordance with the ethical standards of the responsible local committee of Rambam Health Care Campus, Haifa, Israel.

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