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Role of endogenous pain modulation in chronic pain mechanisms and treatment

David Yarnitsky

Abstract

Development and application of psychophysical test paradigms to assess endogenous pain modulation in healthy controls and in patients yielded large body of data over the last 2 decades. These tests can assist in predicting pain acquisition, in characterizing pain syndromes and related dysfunctions of pain modulation, and in predicting response to treatment. This chapter reviews the development of thought on pain modulation in the clinical setup, focusing on conditioned pain modulation, and update on accumulated data regarding the mechanism, protocols of administration, and applications in the clinic.

Key words: Psychophysical test paradigms, Endogenous pain modulation, Pain acquisition, Conditioned pain modulation

1. Concept

Endogenous pain modulation is a wide-ranging term, delineating the array of actions that the central nervous system can use to reduce, or, at times, augment pain. Generally, the action of different brain regions, derived by a spectrum of manipulations, converge at the brainstem pain control centers, which, in turn, send descending messages to the spinal cord, which can be either inhibitory or facilitatory, to reduce or augment, respectively, the incoming nociceptive messages from the periphery. Anatomy and physiology of these systems have been reviewed.[48,55] The descending pain-controlling pathways can, thus, be activated at such "top down" mode, ie, from brain to brainstem, for example, by psychological interventions. In addition, a "bottom up," ie, from peripheral and spinal cord to a brainstem mode of action can also be evoked, for example by noxious stimuli. The latter, often referred to as "counter-irritation," or "pain inhibits pain" phenomena, are time honored, and had been explored scientifically already more than 70 years ago.[23,70] Animal-based meticulous research on this phenomena was initiated by Le Bars et al., who coined the term "diffuse noxious inhibitory controls," abbreviated as DNIC to describe the inhibition inflicted on the response to one nociceptive stimulus by a concomitant another one, administered remote from the first. The series of publications by this group ignited a relatively extensive work in animal laboratories, and soon after in humans. The latter yielded a flurry of publications around the turn of the century, and since. A consensus of experts in the field recommended the use of the term "conditioned pain modulation" (CPM) for human application of protocols that assess human DNIC-like phenomena.[91] A current PubMed search for article titles that include CPM reveals some 50 articles, with additional ones of at least 3-fold the number of articles dealing with the phenomenon without mentioning it in the title. In this monograph, I review the development of the concept reflected by the work done in my laboratory and give a "state of the art" description on the concept and its applications. For uniformity of the discussion, I will use the term CPM for all human application of the test protocols, also for articles published before 2010.

A large body of data has accumulated around the turn of the century showing that less efficient CPM is typical for groups of patients with idiopathic pain syndromes when compared with healthy controls. This observation was shown for fibromyalgia (FM),[40,46] irritable bowel syndrome (IBS),[12] migraine,[80] tension-headache,[82] temporomandibular disorder (TMD),[51] osteoarthritis (OA) and muscle pain,[41] and whiplash[17,61]; see also the review by Lewis et al.[50] Typically, a CPM protocol includes a test stimulus that is given 1 time as a stand-alone, and 1 time during, or immediately after, a conditioning stimulus. The CPM effect is the net change in pain rating, obtained psychophysically or neurophysiologically, between the 2. Cold or hot water immersion is most commonly used for conditioning, and a variety of thermal, mechanical, or electrical stimuli are used for the test stimulus.[76] It is of interest to note, that although a group level difference in CPM was found in all the articles between patients and controls, there was usually no association between CPM and the parameters that characterize the pain within the patients groups. My interpretation of this puzzling point is that the CPM testing uncovers a "hidden" potential feature of pain modulation of the individual, which is not necessarily related to the current pain syndrome, but relates to wider characteristics of pain in the individual patient, such as the risk of acquiring pain in the future, a point that requires further research.

The finding of less efficient CPM prevailing in patients across a variety of pain syndromes calls for an explanation, which, theoretically, poses a "chicken and egg" question suggesting that either (1) patients had a normal CPM efficiency to begin with, but had exhausted their pain inhibition capacity because of a long-standing effort to overcome the ongoing chronic pain, to the point of not being able to reduce pain in the laboratory setting of the CPM protocol, or (2) that patients had a less efficient CPM to

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begin with. In other words, one possibility is that less efficient pain inhibition is secondary to the presence of pain, and the other is that less efficient pain inhibition is primary to the clinical pain, being a risk factor for development of pain. Because cross-sectional studies cannot answer this kind of a question, we explored these relationships in a prospective study, where prethoracotomy pain-free patients were examined for their pain modulation, and were followed up for acquisition of chronic pain after surgery.[92] Conditioned pain modulation efficiency was found to predict chronic postthoracotomy pain; patients with less efficient CPM had higher risk to develop chronic pain and vice versa. The findings of this study were replicated by Wilder-Smith et al.,[89] in their study on chronic pain after abdominal surgery. These longitudinal studies reasonably establish causative relations, suggesting less efficient CPM to be a pathogenetic factor for future clinical pain. Thus, having a less efficient CPM when being pain-free, suggests that upon a pain-generating event, such as surgery, the person is at a higher risk to develop pain than subjects showing an efficient CPM at baseline. These findings, however, do not rule out the possibility that CPM itself can change during, and possibly due to, the presence of chronic pain.

Involvement of CPM efficiency in generation of pain calls for its possible role in treatment of pain as well. The theoretical framework suggested here is that a dysfunctional mechanism of pain modulation should be targeted by a drug capable of rectifying that dysfunction. This way, patients with less efficient CPM, having an inhibitory pronociceptive pain modulation profile (PMP) (**Fig. 1**), should benefit from agents that augment descending inhibition of pain by spinal monoamine reuptake inhibition such as Serotonin-Noradrenaline Reuptake Inhibitors (SNRIs). Patients whose CPM is efficient to begin with will probably benefit little from trying to improve a well-functioning modulation line. To examine this assertion, we measured CPM in painful diabetic neuropathy patients before and after administration of the SNRI duloxetine. We found that CPM efficiency predicted the efficacy of the drug; patients with less efficient pretreatment CPM expressed high efficacy of the drug with pain reduction, whereas those with efficient pretreatment CPM did not gain from the drug.[94] Furthermore, for the first group, an improvement in CPM efficiency was found along with pain reduction, whereas no change in CPM was found for the latter. Findings were recently reproduced by Niesters et al.,[63] in a study on painful diabetic neuropathy using tapentadol, a combined SNRI and opioid molecule.

Having discussed thoroughly the line of pain inhibition, I would like to now add the line of pain facilitation. Application of a series of short noxious stimuli typically results in a continuously increasing perception of pain along the series. This is the phenomenon of temporal summation (TS), believed to represent features of central sensitization of pain pathways, equivalent to the wind-up physiological phenomenon. Enhanced TS has been described in many idiopathic pain syndromes, including FM,[82] OA,[3] migraine,[88] and TMD.[81] These patients will be described as having a facilitatory pronociceptive PMP. It is noted that several articles have also reported co-occurrence of both enhanced TS and less efficient CPM in patients with pain, such as in patients with OA,[3] cluster headache,[71] and chronic postmastectomy pain.[21] A double pronociceptive PMP might indicate a more robust change, which could imply more intense pain phenotype, and possible higher resistance to treatment (**Fig. 2**). The same question as above, of whether enhanced TS is primary to or secondary to pain can be asked here as well. Some evidence supports the first possibility, for example in, our thoracotomy cohort, TS predicted acute postoperative pain, such as subjects whose preoperative TS was enhanced had higher acute post-operative pain.[87]

The next question, in line, is whether TS can be used in prediction of analgesic efficacy. To this end, a study by Lavand'homme and Roelants[47] used ketamine in post-cesarean section pain. They found that patients with enhanced TS are those that benefited from ketamine, which attenuates neuronal sensitization, thus rectifying a dysfunctional pain modulation mechanism. Patients with non-enhanced TS, however, did not benefit from the drug, whose potential effect was unnecessary facing well function summation. In a study by Olesen et al.,[67] pregabalin, a calcium channel ligand, expected to reduce neuronal sensitization, was given to patients with chronic pancreatitis. The ratio of electrical pain thresholds between painful and nonpainful body regions predicted the drug's efficacy. Pain thresholds were measured by a slowly increasing stimulus, which, in a similar way to a series of repetitive stimuli, had probably induced wind-up of pain afferents, again showing that in the presence of enhanced summation, pain is better treated by drugs that reduce sensitization. Interesting, and providing a complementary support to the concept presented here, are the finding on the no efficacy in these studies—in our duloxetine study, TS did not predict efficacy, probably because it does not affect neuronal sensitization; in the Olesen study, CPM did not predict effect of pregabalin, probably due to this drug's noninvolvement in the CPM process. It is noted that the drug–mechanism coupling concept may be criticized for being oversimplified, because many drugs have more than 1 mode of action, and psychophysical test paradigms are not exclusively testing only 1 phenomenon, yet, evidence so far is supportive of the concept, and more solid understandings will develop as more data will be gathered.

Taking together the 2 features, CPM and TS, that characterize the way an individual processes pain, as measured in nonpainful body sites, one can try and construct a profile of the modulation of painful stimuli for the tested person. Such profile should have the potential of predicting important features of clinical pain behavior for this person. We proposed the term pain modulation profile, representing a spectrum between the pronociceptive and the antinociceptive ends.[93] We propose that one can be categorized as pronociceptive if one expresses either less efficient CPM,

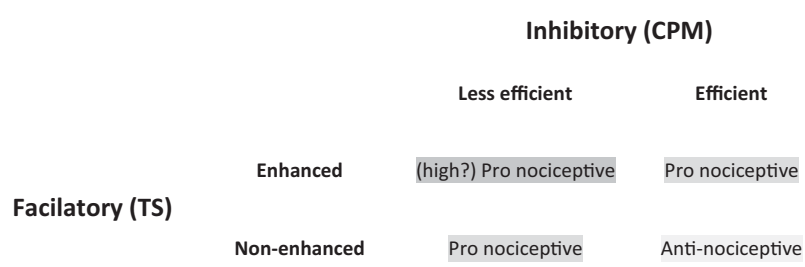

Figure 1. Pain modulation profile possibilities based on psychophysical laboratory testing.

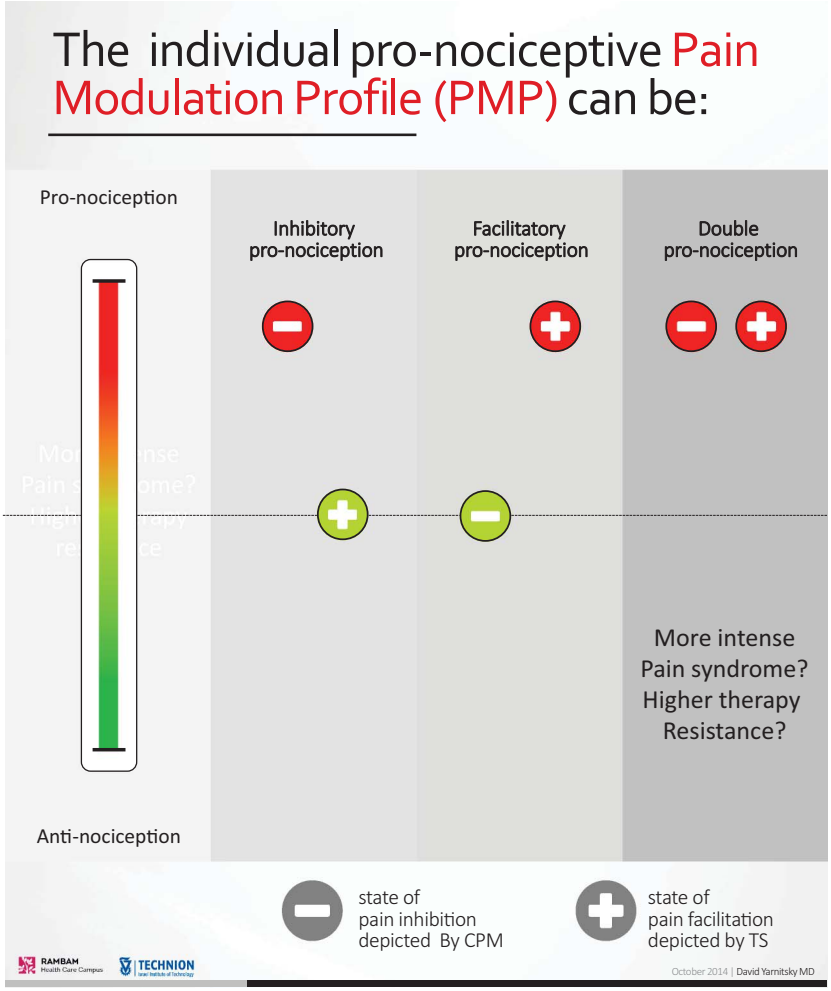

Figure 2. Pronociceptive profiles. Pronociception can be either inhibitory, due to less efficient conditioned pain modulation (CPM) (left pane), facilitatory, due to enhanced summation (middle pane) or double, with both less efficient CPM and enhanced temporal summation (right pane).

a state of inhibitory pronociception, or enhanced TS, a state of facilitatory pronociception. It is likely that some people will express both, potentially having a higher risk profile for pain. However, one can have an antinociceptive PMP for either efficient CPM, an inhibitory antinociception, or for nonenhanced or even adapting TS, a facilitatory antinociception. The suggested concept is that being on the pronociceptive end means higher risk for acquiring pain, and probably higher intensity of clinical pains, and vice versa, being antinociceptive probably means lower changes of acquiring pain, and lower intensity of pain syndromes. Implications toward pain therapy are seen to depend on the subtype of pronociceptive or antinociceptive profile of the patient, as previously explained. We assert that antinociceptive state is desired for pain prevention, such as in migraine or in preemptive treatment of operative pain (**Fig 3**). There is, of course, a need for methodological assessment of the relative weight and relevance of each of these parameters in determining the PMP of each patient. I would like to mention 2 additional test protocols, which could make important contribution to a comprehensive PMP protocol; offset analgesia is a test protocol in which a transient increase in stimulus intensity is given along a constant intensity nociceptive stimulation. Typically, a drop in pain rating immediately after end of the transient is seen, representing pain inhibition.[95] Suprathreshold magnitude estimation of experimental pain is a simple-to-perform protocol, shown to be relevant in predicting acute postoperative pain.[1]

The text will now update on the CPM phenomena, regarding methodology, mechanism, and clinical applications in diagnosis and in therapy for pain.

2. Methodology

A variety of test protocols can be found in the literature.[76] The main parameters are the timing, modality, intensity, duration, and location of the stimuli. For timing, there are 2 main approaches—parallel and sequential. For the first, test stimulus is typically given as a stand-alone, and then, in parallel to administration of the conditioning stimulus. This approach yields higher CPM effect than the sequential approach, but poses questions, mainly when done in a research setup, regarding the distinction between the nociceptive-specific effect and distraction, and when performing imaging study, in differentiating between the central effects of the conditioning from those of the test stimulus. The sequential protocol applies the second test stimulus immediately at the end of the conditioning stimulus, so that there is no time overlap, mitigating the above-mentioned reservations.

Regarding the modalities, test stimulus is typically applied through thermal, mechanical, or electrical stimuli, whereas for the

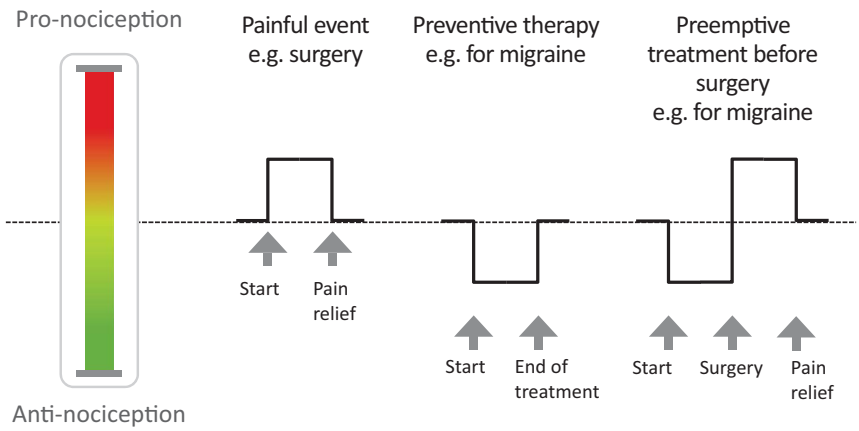

Figure 3. Antinociceptive pain modulation profile (PMP). (a) Pronociception caused by painful event, and reversed at its termination. (b) Pharmacologically induced antinociception for prevention of clinical pain events. (c) A major pain event shifts PMP toward pronociceptivity, but because start point was antinociceptive, the final PMP, and probably consequent pain syndrome, is lowered compared with (a).

conditioning, researchers had used painful cold or hot water immersion, cuff inflation, capsaicin injection, and other stimuli. Water immersion of a limb, upper or lower, seems to be the most popular way of inducing the conditioning stimulus.

Stimulus intensity of test stimulus is typically chosen such that it is painful enough, leaving room for measurable reduction of pain during the procedure, yet not too painful such that subjects in the study will comfortably endure it. A common approach is to use psychophysically anchored stimuli, which apply pain at a certain point between 40 and 60 on a 0 to 100 scale. This approach requires a short presession series of stimuli to measure, for the individual subject, what stimulation energy is required to evoke pain at the desired level. For conditioning, it is widely accepted that the stimulus needs to be painful, with some conflicting results on the influence of its intensity on the CPM efficiency.[27,64]

Duration—test stimulus can vary between short transients lasting tens to hundreds of milliseconds typically used to evoke recordable brain potentials and trapezoid stimuli of several tens of seconds during which several pain ratings can be reported. For conditioning, stimuli up to several minutes had been used.

Location—the 2 stimuli need to be remote from each other. Typically, 2 separate limbs are used for the test and the conditioning stimuli.

The use of 2 upper limbs is convenient, but is criticized for possibly reflecting a segmental spinal inhibitory effect, rather than an ascending–descending long tract activity.[28] In many protocols, thus, 1 upper and 1 lower limb are used, each can serve for test or for conditioning stimuli, limbs can be ipsilateral or crossed.

Test-to-test reliability was tested by several groups, generally showing acceptable reliability. This reliability was shown by Biurrun Manresa et al.[5] for nociceptive withdrawal reflexes as test stimulus; Jurth et al.[35] found good reliability for both psychophysical and electrophysiological measures of the same reflex. Less good reliability was reported by Olesen et al.[68] for psychophysical measurements.

3. Mechanism

The question of distraction as a possible nonpain-specific explanation for pain reduction during CPM is commonly brought up. Moont et al.[56] have recently shown that pain reduction due to simultaneous administration of both conditioning pain and distracting task is greater than the extent of pain reduction due to conditioning pain alone, suggesting that CPM acts independently from distraction, though with possible partial overlap. Lautenbacher et al.[45] have reached similar conclusions based on a computational model of CPM. Another pertinent issue is the interrelations of CPM and expectation, suggestion, and placebo. Nir et al.[65] found in healthy controls that suggestion of change in the intensity of the conditioning stimulus affected CPM efficiency; subjects who believed that the unchanged conditioning stimulus was lowered, reduced their CPM effect, emphasizing the influence of brain processes over the spinal–bulbo–spinal CPM effect. Cormier et al.[15] showed that CPM efficiency is influenced by suggestion to its efficiency. Two articles examined the influence of dispositional optimism on CPM, which found that healthy controls reporting optimism had more efficient CPM,[25,26] with possible influence of pain catastrophizing on this association. Very recently, Rainville et al.[52] reported that pain inhibition is associated with the capacity for cognitive inhibition in healthy aging, such that generalized age-related decline in inhibitory capacity is expressed in both Stroop and CPM results. These results concur with those of Edwards et al.[20] and Grashorn et al.[29] showing less efficient CPM in older age.

4. Clinical applications

4.1. Idiopathic pain syndromes

As briefly mentioned above, there is a substantial body of knowledge showing CPM to be less efficient in idiopathic pain syndromes. Fibromyalgia seems to be the disorder most extensively explored in this regard, with several articles reporting reduced or deficient pain reduction under the CPM protocol in these patients.[33,83] de Souza[19] reported that patients with FM with depression have less efficient CPM than those without depression. Patients with FM show lower activation of rostral Anterior Cingulate Cortex (rACC) during the CPM protocol compared with controls,[31] their less efficient CPM is not associated with serotonin transporter genes,[75] and they do not show pain reduction during exercise as do healthy controls.[44] Chalaye et al.[11] has recently shown that patients with FM show less increase in blood pressure during CPT, associated with less efficient CPM, raising the possibility that the CPM effect might be, at least in part, mediated by change in the autonomic balance. These authors have shown that for patients with FM, the dominant autonomic tone is sympathetic, as opposed to parasympathetic dominance in controls Chalaye et al.[10]

For IBS, Coffin et al.[13] have shown that using a rectal balloon as conditioning stimulus did not reduce the RIII response in patients compared with controls. King et al.[37] found CPM to be reduced in

IBS compared with controls, but to a smaller extent than TMDs. Piche et al.[72] found an association between CPM, which was less efficient than in healthy controls, and a variety of psychological parameters. The study by Bouhassira et al.[6] was among the few that described a correlation between CPM and clinical severity, but this correlation was found only for the group of patients with facilitatory CPM. Recently, Williams et al.[90] found reduced CPM in girls with IBS. Temporomandibular disorder has also been explored in this regard. King et al.[37] reported less efficient CPM in these patients; Garrett et al.[24] reported CPM similar to healthy controls, whereas Kothari et al.[42] reported reduced CPM in TMDs after surgery. Oono et al.[69] reported reduced CPM in TMD, but only when measured from affected sites. For other disorders, a report on interstitial cystitis found reduced CPM,[60] whereas 2 reports on vestibulodynia found normal CPM.[32,84] In summary, most studies found less efficient CPM in patients with idiopathic pain, providing some possible common ground for the mechanism of these disorders.

4.2. Nociceptive

Conditioned pain modulation was reported to be less efficient in patients with painful hip OA and to improve after surgery that alleviated the clinical pain.[41] This article provided the first evidence that CPM can change along time in patients, and furthermore, that this change is related to the presence or absence of clinical pain. It suggests that CPM can be altered, with its dysfunction reversed back toward normal when the clinical status is improved. This concept was reproduced for knee OA by Graven-Nielsen et al.[30] Arendt-Nielsen et al.[3] have also shown less efficient CPM in patients with OA. Cruz-Almeida et al.[16] found CPM reduction in patients with OA to be prevalent mostly in whites compared with African Americans. Olesen et al.[66,68] explored patients with chronic pancreatitis, showing reduced CPM and central sensitization but low repeatability of CPM. Bouwense et al.[7] found reduced CPM for these patients. Patients with whiplash-associated disorder had reduced CPM.[17] For rheumatoid arthritis, Meeus et al.[53] found normal exercise-induced analgesia, whereas Lee et al.[49] reported reduced CPM, noting that the association might have been mediated by sleep disturbances.

4.3. Neuropathic

Several studies measured CPM in patients with neuropathic pain. Mylius et al.[57] reported reduced CPM in patients with Parkinson disease, which was unrelated to their clinical pain. Granovsky et al.[28] found a correlation between CPM and disease severity, but CPM did not differ from controls. Conditioned pain modulation was found to be unchanged in patients with shoulder pain who have had stroke.[79] Patients with chemotherapy-induced neuropathy showed changes in CPM and TS, which were conversely interrelated, and both were related to clinical pain.[59] In painful diabetic neuropathy, Knauf and Koltyn[38] found that patients do not reduce experimental pain in response to exercise as do healthy controls. Brock et al.[9] found a correlation between tactile thresholds and CPM, but only in patients with nonpainful diabetic neuropathy. Niesters et al.[63] found a null CPM response in these patients, which reversed after treatment with tapentadol. Pickering et al.[73] reported impaired CPM in patients who have had herpetic neuralgia.

For migraine, several reports suggested less efficient CPM, tested by psychophysics and RIII[80] or by blink reflex,[86] whereas others found no change in CPM.[14,85] Nahman-Averbuch et al.[58] reported CPM to wane along repeated applications in migraineurs, while controls were able to maintain the pain inhibitory capacity, which suggests that there is only a subtle dysfunction of CPM in migraineurs. Conditioned pain modulation was found to be reduced in chronic tension type headache[74] and headache after mild traumatic brain injury.[18]

5. Pharmacological and therapeutic applications

Several research groups applied pharmacological interventions in healthy volunteers to explore the mechanism of CPM. Koppert et al.[39] reported blocking of the CPM effect by naloxone, suggesting an important role of opioids in the CPM mechanism. King et al.[36] reported reduction of CPM by naltrexone in controls and found the effect to be moderated by pain catastrophizing. On the same note, Julien and Marchand[34] reported reduction in spatial summation–induced pain inhibition by naloxone. In a study on opioids induced hyperalgesia, Ram et al.[77] reported that CPM is reduced by opiates in patients with chronic pain. Arendt-Nielsen et al.[2] reported enhancement of the CPM effect by opioids in controls. Conditioned pain modulation was not affected by lorazepam,[43] nor by oral contraceptives.[78] Ketamine, however, was reported by Niesters et al.[62] to turn CPM into being more facilitatory. Alpha2 agonists inhibit CPM, in a dose-dependent manner.[4]

The ability of CPM to predict analgesic effect was examined in healthy controls by Eisenberg et al.,[22] finding that CPM did not predict efficacy of oxycodone, whereas heat pain thresholds (HPT) and TS did. Use of CPM in prediction of analgesic effect was reported by these authors, as described above.[94] In a nutshell, patients with painful diabetic polyneuropathy with less efficient CPM gained more from duloxetine than those with efficient CPM. In a very recent article, Niesters et al.[63] showed the same effect for tapentadol (an additional analysis made by the author on request, not reported in article; correlation between pretreatment visual analog scale and pain levels at 4 weeks after treatment was at $r = 0.66$, $P = 0.01$ for low responders, and $r = 0.88$, $P = 0.02$ for high responders). Conditioned pain modulation did not predict the effect of pregabalin on pain in patients with chronic pancreatitis.[67]

Does CPM change by the use of analgesics? Our supposition is that it should change if the medications used have a specific effect on pain inhibitory modulation. This way, in our above-mentioned article on painful diabetic neuropathy, patients who benefited from the drug also improved their CPM consequent to its use. Similarly, as mentioned above, Niesters et al.[63] also reported improvement in CPM after tapentadol. Another drug whose mode of action includes augmentation of descending inhibition of pain, and, in line, should improve CPM, is paracetamol; a study by Meeus et al.[54] showed an improvement in CPM after paracetamol in patients with rheumatoid arthritis. A question that comes to mind is whether the improvement in CPM is specific to the drug used, or a more generalized response to pain alleviation. A study by Bouwense et al.[8] showed no change in CPM after treatment of chronic pancreatitis pain by pregabalin, suggesting the effect is specific to the treated mechanism.

It is important to note the difficulties and pitfalls related to use of CPM. It is usually a psychophysical test, whose results might differ intra- and inter-individually, might be a subject for feigning for various purposes such as secondary gain, and might be misperformed because of misunderstanding of instructions. It is essential that laboratories and clinics performing the protocol make sure they took care of these points before drawing conclusions. Second, different laboratories use different protocols, and the exact limits of what is normal, and what is a mild of a more severe deviation from the norm are not yet well delineated.

The fact that results of protocols using different stimulation parameters do not intercorrelate is, aside offering a source for rich physiological data, also a source of difficulties in interpretation of the test results. I would like to encourage researchers in the field to further enrich our understanding by generating more and more relevant data, to allow build up of a solid body of knowledge.

6. Conclusions

Endogenous analgesia mechanisms seem to play an important role in shaping clinical pain pictures. Evidence was raised showing that dysfunctional CPM is primary to acquisition of pain, that CPM can be altered, and that its efficiency seems to react to clinical pain—an improvement in CPM is seen upon reduction in clinical pain levels, maybe more so by drugs that improve CPM. It is likely, although not yet proved, that CPM becomes less efficient upon acquisition of clinical pain. The role of CPM in pain generation calls for its perusal in improving pain treatment and in its prevention. The sought after target of individualizing pain treatment can be served by coupling the dysfunctional modulation pattern with a drug that can improve that dysfunction. Regarding CPM, it is the SNRIs, TCAs, and tapentadol that act by reuptake inhibition of 5HT and NE that are expected to improve dysfunctional CPM, but to be less useful for patients whose CPM is efficient to begin with. Many questions remain open, such as the lack of correlation of CPM to the current clinical pain parameters in most studies, the relative role of expectation and distraction in the effect and the more practical questions of what is the most suitable CPM protocol for any specific study. The role of CPM in relation to psychosocial aspects of pain and pain-related disability is very minimally explored, and it is certainly a field of research that deserves immediate attention in the near future. I do hope that future research will answer these questions and improve our ability to better treat pain by better understanding how to best use descending inhibition in the service of pain alleviation.

Conflict of interest statement

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