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manifestations and implications for pain progression

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ASSESSMENT OF CONDITIONED PAIN MODULATION IN HEALTHY SUBJECTS AND PATIENTS WITH CHRONIC PAIN – MANIFESTATIONS AND IMPLICATIONS FOR PAIN PROGRESSION

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ABSTRACT (max 200 WORDS)

Purpose of review: To summarize recent findings on conditioned pain modulation (CPM) in humans with a focus on methodology, factors modulating CPM, and the potential for CPM as a clinical marker for pain progression.

Recent findings: CPM can be evoked by combining different stimulus modalities with good reliability, optimism and pain catastrophizing might influence pain inhibition, and sequential CPM-effects are stable over time with limited carry-over effects. Further, studies suggests that the CPM-effect can be improved by gabapentinoids, transcranial direct current stimulation to cortical structures and exercise and that long-term opioid use might impair CPM in patients with chronic pain. Clinically, increasing evidence suggests that preoperative impaired CPM may predict more severe chronic postoperative pain and the effect of pain duration on CPM impairment has been challenged by recent studies.

Summary: The CPM methodology has been optimized and studies are revealing factors, which can modulated the descending pain inhibitory pathways. Understanding these mechanisms will improve the utility of CPM in a clinical setting and potentially lead to improvements in the treatment of chronic pain patients.

INTRODUCTION

The endogenous pain inhibitory system has received increasing attention over the last decade, as its function has been purported to explain discrepancies between tissue injury severity and degree of pain. In humans, the potency of this pain inhibitory system is primarily assessed by investigating the modulatory effect of a tonic painful conditioning stimulus on a painful test stimulus. This 'pain-inhibits-pain' phenomenon was first described by Le Bars et al., in 1979(1), describing that noxious stimulus-elicited activity in convergent wide-dynamic-range neurons in the spinal dorsal horn could be blocked by another tonic noxious stimuli, and termed this effect, "*diffuse noxious inhibitory control*" (DNIC)(2). In 2010, an expert panel recommended to use DNIC when referring to pre-clinical studies and conditioned pain modulation (CPM) when referring to human studies using psychophysical protocols assessing the degree of 'pain-inhibits-pain'(3), but both terms refer to the same presumed underlying descending inhibitory mechanisms. Pre-clinical trials have established that DNIC manifests as the inhibition of wide-dynamic-range neuronal activity by descending adrenergic pathways from the sub-reticularis dorsalis via the locus coeruleus(4). CPM is the human surrogate model for the estimate of this inhibitory effect, in reality giving the net effect of facilitatory and inhibitory systems(5). In most healthy subjects application of the conditioning stimulus will result in decreased pain sensitivity. Increasing evidence suggests that patients with severe and prolonged chronic pain do not demonstrate this decrease in pain sensitivity when a conditioning stimulus is applied(6) (see figure 1), suggesting that pain inhibitory mechanisms are impaired.

The aim of this narrative review is to summarize the recent CPM literature with a focus on CPM methodology, modulation of CPM, and the potential for CPM as a clinical marker for pain progression.

Contemporary findings were defined as studies published within the last years, which also partly drew selection of topics for this review.

ADVANCEMENTS OF CPM METHODOLOGY

The CPM recommendations from 2015(7) highlighted a lack consensus regarding CPM assessments and the need for comparison between protocols. In 2016, a systematic review(8) concluded that the degree of CPM reliability is dependent on stimulation parameters, highlighting the ongoing need for improvement of CPM methodology and the current section highlights recent advancements of CPM methodology.

Multimodal assessment of CPM

Recently, Imai et al.(9) assessed five different test stimuli (heat pain, electrical pain, single-point pressure pain thresholds, and cuff-induced pain detection and tolerance thresholds) with two different conditioning stimuli (the cold pressor test and tonic cuff pressure) in healthy subjects and found that most combinations could evoke a CPM response. In general, pressure-induced test and conditioning stimuli provoked CPM with good reliability (interclass correlations coefficients of approx. 0.50)(9). This study adds to the knowledge that CPM can be evoked using e.g. both thermal and pressure-based test stimuli, which is in line with the current recommendations suggest using multi-modal assessment of CPM(7).

Neurophysiological methods to assess CPM

Advances in the resolution of functional magnetic resonance imaging (fMRI) and source localization of electroencephalography (EEG) have allowed these techniques to be used to assess the functional connectivity of brain regions thought to be involved in descending pain inhibitory pathways. A study has identified that aberrant functional connectivity between the periaqueductal gray (PAG) and brainstem is associated with impaired CPM responses, while high resting connectivity between the cortex and the PAG was associated with enhanced CPM(10). Similarly, differences in regional brain morphology (e.g. in the orbitofrontal cortex) have also been associated to poor CPM efficiency(11). Such work helps to validate mechanisms assumed to underlie descending inhibition, but also highlights the complexity of the CPM-response in humans. Studies assessing both psychophysical CPM paradigms in combination with these neurophysiological measures are therefore strongly encouraged.

Influence of pain catastrophizing and optimism on CPM

Studies have demonstrated that higher levels of optimism is associated with e.g. placebo analgesic response, less temporal summation(12), greater CPM(13), and lower pain ratings to a cold pressor task(14). Two recent studies investigated the influence of optimism on CPM(15,16). Traxler et al.(15) manipulated optimism by using the so-called “best possible self” method, which have been shown to increase optimism temporarily(17), but this had no effect on heat or cold pain sensitivity or CPM, which is in contrast to previous findings. Traxler et al.(15) did find that higher pain catastrophizing was associated with less CPM effect. In contrast, Hinkle and Quiton(16) reported that high optimism

predicted less CPM effect, and together with the Traxler et al.(15) these data challenge the association between the level of optimism and CPM. High pain catastrophizing has previously been found associated with pain severity and poor pain alleviation to treatments(18) and therefore investigating the interplay between pain catastrophizing, optimism and CPM in both experimental and clinical settings is encouraged.

Duration of the conditioning effect on pain sensitivity

Until recently little was known about the temporal dynamics of CPM although it has been suspected to have carry-over effects on subsequent experimental tests, as ongoing reduced pain sensitivity has been documented to last for a few minutes(19). However, Hoegh et al.(20) investigated this by applying four sequential CPM paradigms in five minute blocks using the deep-somatic pressure-cuffs and found that the CPM effect remained stable over time. This could indicate that deep somatic provoked CPM measures are less influenced by carry-over effects than previously thought.

Age and sex influences on CPM

CPM has been suggested to decline with age, as middle-aged to older participants generally show reduced inhibitory responses compared to younger participants(21,22). Females are over-represented in chronic pain populations and sex differences in pain threshold and tolerance measures have consistently been found for pressure pain and cutaneous electrical stimulation(23). Further, a systematic review from 2010 concluded a more efficient CPM to be found in males compared with females(24). To further investigate this, Skovbjerg et al.,(25) conducted a study on 2,199 randomly

selected adults from the general population in Denmark, demonstrating that CPM was less efficient in females compared with males, but that CPM was unaffected by age. This study further increases the awareness that sex influences assessment of pain, and therefore should considered in future studies.

NEUROPLASTIC CHANGES OF PAIN INHIBITORY PATHWAYS

Maladaptive neuroplastic changes can occur from prolonged peripheral drive to the central nervous system(6,26). Impaired CPM is well documented in severe chronic pain patients compared with healthy subjects(6) and recent studies have therefore started to investigate how interventions may influence CPM in a maladaptive or advantageous manner.

Advantageous neuroplastic changes in pain inhibitory pathways

Pregabalin

Pregabalin is a gabapentinoid that has previously been used to modulate central sensitization in e.g. chronic pancreatitis(27). Wodehouse et al.,(28) followed 25 patients with fibromyalgia to whom pregabalin was administrated (75 mg twice daily) for 12 weeks resulting in reduced clinical pain and improved CPM. This study adds to our current knowledge that pregabalin could improve pain inhibitory processes, but it is noteworthy that more than 40% of patients discontinued the pregabalin treatment, hence these results need replication in larger studies to document the same effect. Nonetheless, it is not clear if the CPM improvement was directly caused by the action of pregabalin or because other pain mechanisms were reversed, causing reduced clinical pain and thus increasing efficacy of CPM.

Transcranial direct current stimulation

Recent studies have indicated that transcranial direct current stimulation (tDCS) and other transcranial stimulation methods, such as repetitive transcranial magnetic stimulation (rTMS), can modulate musculoskeletal pain development in experimental settings(29,30) and yield pain relief in patients with fibromyalgia(31,32). As patients with knee osteoarthritis often display impaired CPM compared to healthy subjects(33), a recent study by Ahn et al.,(34) assessed the modulatory effect of tDCS on CPM in patients with osteoarthritis. This study found that tDCS on the primary motor cortex could improve CPM, and reduce pain sensitivity to pressure, mechanical punctuate pain and heat, arguing that pain relief occurred through advantageous neuroplastic changes. It is of note, that this study was controlled by a sham-group but that the sample size was low and while these data are of high interest, these findings need to be replicated in large clinical cohorts. Interestingly, the transcranial stimulation techniques also allow targeting specific structures or brain networks that may be a particular interesting approach to study CPM mechanisms in future studies.

Effect of exercise programs on CPM

Long-term exercise programs provides pain relief for multiple patient groups with persistent pain(35). The mechanisms thought to underlie the pain relieving effects of exercise includes activation of the descending pain inhibitory pathways(36), decreased pro-inflammatory cytokine response(37), and a reduction in psychological distress(38). Beyond this, the mechanisms are largely unknown(36). In a recent study, Heredia-Rizo et al.,(39) evaluated females with neck and shoulder pain before and after

a 5-week upper trapezius eccentric training program. An average of approximately 65% pain relief was reported and this was associated with an improvement in CPM. Future studies are encouraged to investigate if long-term exercise can promote improvements in pain inhibitory pathways and to investigate if the CPM improvements are independent of clinical pain reduction.

Maladative neuroplastic changes of pain inhibitory pathways

Opioids

De Resende et al.,(40) studied DNIC effects in rats by administrating naloxone (an opioid antagonist targeting the μ-receptors) and found this to prevent DNIC responses. Martel et al., (41) studied CPM response in 190 chronic neck and low back pain patients who were either current opioid-users (64 % of the sample) or non-users and found that CPM was impaired in opioid-users compared with non-users. Of note, difference in clinical pain intensities were reported in the Martel et al study(41), which could be the driving factor for the CPM impairment but despite this, these findings are consistent with previous studies in patients with chronic pain(42,43). Interestingly, experimental studies have suggest that acute use of opioids might improve the CPM response(44,45). Overall, this series of studies suggest that the pain inhibitory pathways may be positively impacted by acute opioid use, but that chronic use might cause impairment, which is of high relevance due to the opioid misuse epidemic occurring worldwide and further research within this field is encouraged.

PAIN PROGRESSION AND PAIN INHIBITORY PATHWAYS

In 2008, Yarnitsky and colleagues(46) demonstrated that impaired preoperative CPM was associated with more severe chronic postoperative pain in patients undergoing thoracotomy. Wilder-Smith et al.,(47) followed with a study in patients undergoing abdominal surgery demonstrating similar results. Further, Yarnitsky et al.,(48) demonstrated that the degree of CPM impairment was associated with the drug efficacy of duloxetine (a serotonin-noradrenalin reuptake inhibitor). Together, these studies have formed the foundation of CPM as a measure for personalized pain medicine.

Prediction of chronic postoperative pain

Vaegter et al.,(49) found that impaired CPM prior to total knee arthroplasty was associated with less pain relief six months after surgery, which adds to the growing evidence that patients with severely preoperatively senstized pain mechanisms are in greater risk of chronic postoperative pain(46,47,50). In addition, Vaegter et al.,(49) reported that greater pain relief was associated with normalization of CPM, indicating that high pain intensity, potentially as a result of increased nociceptive activity, could be maintaining the impairment in pain inhibitory pathways. This finding is also supported by older studies in patients undergoing total hip(51) and knee(52) arthroplasty. More recent studies applying similar methodology in larger clinical cohorts have been unable to demonstrate an association between preoperative impaired CPM and chronic postoperative pain after total hip(53) and knee arthroplasty(50,54,55) and therefore the conclusion regarding CPM as a predictor for total joint arthroplasty is still debated.

Transition from acute to chronic pain and back

A recent preclinical monoiodoacetate model of osteoarthritis highlighted that DNIC is functional in early stages of osteoarthritis and abolished in the later stages(56) suggesting that prolonged disease severity is associated with impairment in pain inhibitory pathways.

Studies on patients with musculoskeletal pain have found that intense pain for longer duration can impair CPM(26,57,58) but the causality between pain intensity, pain duration and impaired CPM is unclear. Experimental pain models have been utilized to understand the transition from acute to chronic pain, but these are limited to: 1) intense pain for a short duration (i.e. the hypertonic saline(59) or acid(60) models), or 2) muscle soreness for a longer duration but without spontaneous pain (i.e. delayed on of muscle soreness (DOMS)(61) and nerve growth factor (NGF)(62)). In these cases, intense acute pain (akin to a second conditioning stimulus) has been demonstrated to abolish the usual inhibitory response(63), but experimental back pain induced by eccentric exercise was unable to produce the same impairing effect on CPM(61).

In a recent study, Holden et al.,(64) aimed to investigate pain sensitivity of central pain mechanisms in young females with current and past long-standing patellofemoral pain compared with healthy subjects. Interestingly, the females with current and past history of patellofemoral pain displayed facilitated temporal summation of pain compared to healthy subjects but no difference were found for CPM. Teles et al.,(65) studied adolescents with idiopathic scoliosis and chronic low back pain and found a variation in the CPM results, so that approx. 50% displayed efficient CPM, approx. 20% displayed sub-optimal CPM and approx. 30% displayed impaired CPM. Further, Teles et al., (65) did not find an association between CPM impairment and pain duration, which is similar to

Holden et al.,(64). Since these studies were conducted in young females, this could indicate that CPM is not disrupted in the early stages of pain chronification, but more studies are needed to determine this.

Palsson et al.,(66) investigated subjects who recovered from a previous ankle injury and found these individuals to have enhanced CPM responses compared to subjects without prior trauma, which could indicate that the pain inhibitory systems are highly active when recovering from an injury. This is in line with Holden et al.,(64), demonstrating that individuals who had recovered from adolescent patellofemoral pain showed enhanced CPM compared to those with ongoing pain however it is unclear if the CPM alterations are driven by pain intensities. Currently, there is limited information regarding CPM in the recovery phase or following persistent pain resolution, so studies similar to these are encouraged.

In summary, these new studies(64–66) challenge the hypothesis that longer pain duration is associated with less efficient CPM. Of note, previous studies demonstrating an association between pain duration and less efficient CPM have been conducted in patient populations with pain durations for decades e.g. severe osteoarthritis pain(26,58) and these new studies are all conducted in patient populations with pain durations of a few months or years.

CONCLUSION

This review highlighted that there is large growth in both experimental and clinical CPM-related research (summary found in figure 2). Recent studies show that CPM can be assessed in a multimodal manner, that there is limited carry-over effects of CPM, and that the potency of CPM is lower in

females compared with males. Further, pregabalin seems to improve CPM in fibromyalgia, tDCS may improve CPM in osteoarthritis, endurance training may be more effective at enhancing CPM compared to strength training. Finally, a few studies have investigated CPM in patients with short duration (months to years) chronic pain and found mixed results regarding impairment of the pain inhibitory pathways. Important questions to be studied includes the specific dynamic characteristics of CPM, such as how much and for how long is ongoing pain needed to modulate CPM, and importantly is ongoing pain in patients needed to demonstrate reduced efficacy of the descending pain control system.

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CONFLICT OF INTERST

None.

SUMMARY – BULLET POINTS

1. Conditioned pain modulation (CPM) is a human assessment of descending inhibitory mechanisms, which has shown good test-retest reliability without carry-over effects but might be influenced by psychological factors.
2. Advantageous neuroplasticity can occur due to acute pharmacological modulation, non-invasive brain stimulation and exercise programs.
3. Maladaptive neuroplasticity due to prolonged opioid use, ongoing pain or increasing age.
4. CPM is improved when a painful condition is resolved.
5. Impaired CPM may predict pharmaceutical efficacy and chronic postoperative pain.

Figure legends

Figure 1: Assessment of conditioned pain modulation (CPM) requires a test stimulus (e.g. pressure pain thresholds at the knee) and a painful conditioned test stimulus (e.g. tonic painful pressure). In healthy subjects, the conditioning stimulus will result in reduced pain sensitivity (increased thresholds), indicating an activation of pain pathways under descending noxious control, which are impaired in many chronic pain disorders. Modified based on data from Arendt-Nielsen et al.(26) (24 healthy controls, 24 knee osteoarthritis (KOA) pain patients). * indicate significant difference between the conditioned on unconditioned test stimuli.

Figure 2: Recent findings on conditioned pain modulation (CPM) in humans with a focus on **(A)** methodology, **(B)** factors modulating CPM, and **(C)** the clinical use of CPM. **(A)** A conditioned test stimulus (e.g. pain threshold) will change (e.g. increased pain threshold) compared with an unconditioned test stimulus in healthy subjects (illustrated in blue), which does not occur in chronic pain patients (illustrated in red), the assessment show good reliability with no carry-over effect but might be influenced by pain catastrophizing or optimism. **(B)** Acute pharmacological interventions (e.g. Pregabalin), non-invasive brain stimulation (e.g. transcranial direct current stimulation and repetitive transcranial magnetic stimulation), and long-term exercise might enhance descending pain control whereas ongoing pain, prolonged use of opioids, and increasing age might impair descending pain control. **(C)** CPM is improved when pain is resolved and impaired CPM might be utilized to predict poor pain relief to surgery and certain pharmacological interventions.

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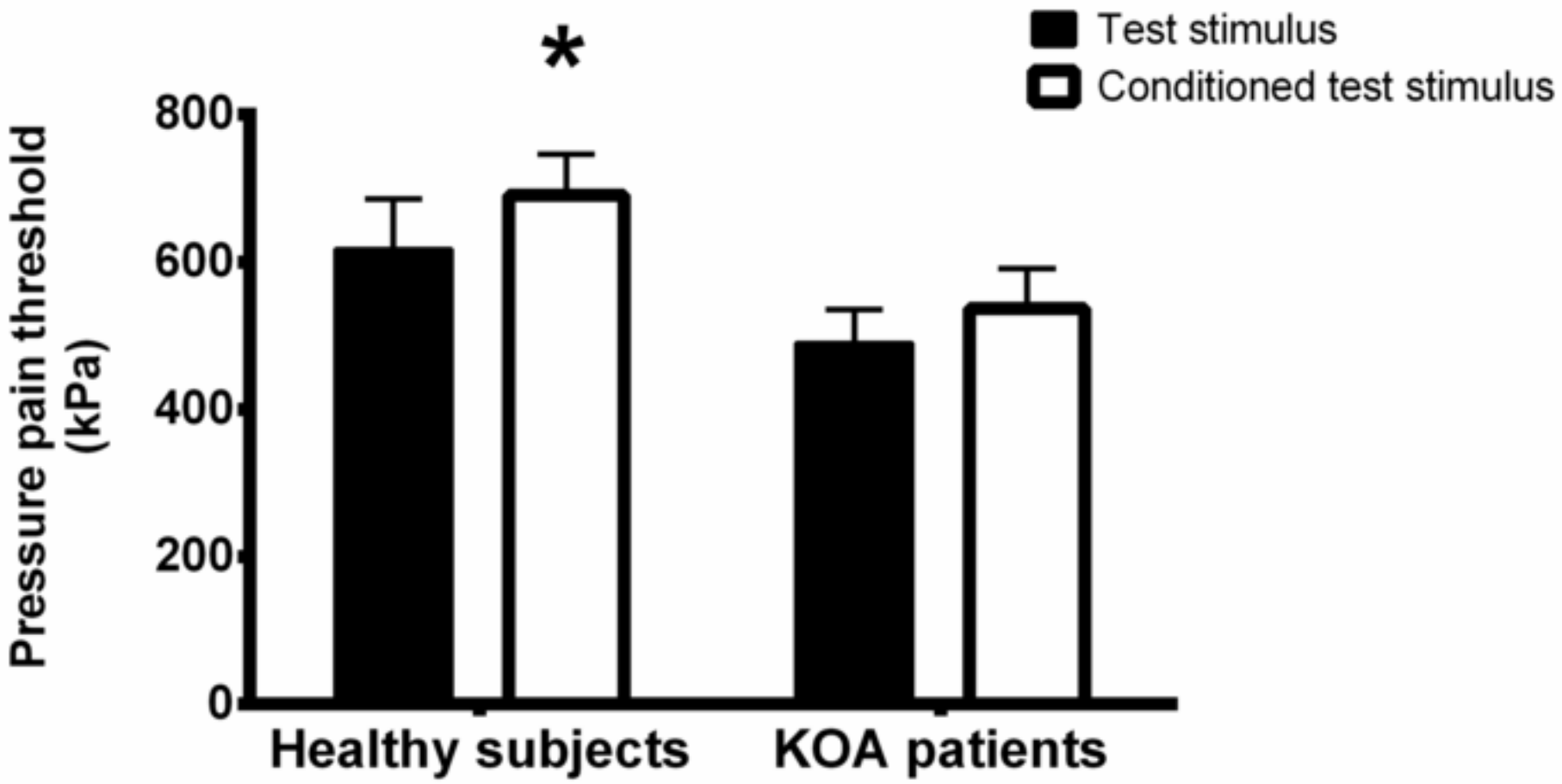
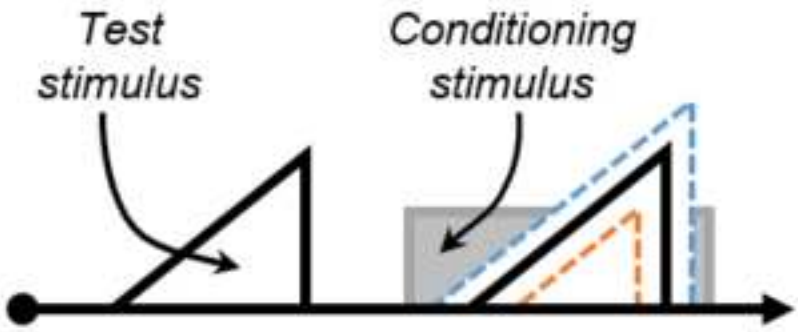
SPC130202 Graven-Nielsen Figure 1 Final



A Methodological Considerations

Good test-retest reliability
Repeatable without carry-over effects
Might be influenced by psychological factors



B Probing the Descending Inhibitory Pathways

Advantageous Plasticity
Acute pharmacological modulation
Non-invasive brain stimulation
Exercise programs

Maladaptive Plasticity
Prolonged opioid use
Ongoing pain
Increasing age

C Clinical Utility of Conditioned Pain Modulation

CPM is improved when a painful condition is resolved

Impaired CPM may predict pharmaceutical efficacy and chronic post-operative pain