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Pain inhibitory mechanisms and response to weak analgesics in patients with knee osteoarthritis

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Significance: This study demonstrated that conditioned pain modulation is correlated with the response to a standard pharmaceutical interventions treating osteoarthritis pain. Further, we demonstrated that a decrease in clinical pain intensity is not associated with a normalization of conditioned pain modulation or offset analgesia, which questions if restoring these descending pain inhibitory mechanisms are pain intensity driven.

Keywords: osteoarthritis, conditioned pain modulation, offset analgesia, non-steroidal anti-inflammatory drug, acetaminophen

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Abstract

Background: Conditioned pain modulation (CPM) and offset analgesia are different features of descending pain inhibition. This study investigated CPM, offset analgesia and clinical pain measures in patients with knee osteoarthritis (KOA) before and after treatment with the combination of a non-steroidal anti-inflammatory drug (NSAIDs) plus acetaminophen.

Methods: Forty-two patients with KOA received Ibuprofen 1.2 g/daily and acetaminophen 3.0 g/daily for three weeks. Before administration, CPM magnitude was assessed as the difference between cuff pain detection (cPDT) with and without a conditioning stimulus (evoked by tourniquet pain). Offset analgesia was assessed as the pain intensities evoked by a constant 46ºC for 30-seconds stimulus compared to an offset analgesia paradigm of 46ºC for 5-seconds, 47ºC for 5-seconds, and 46ºC for 20-seconds. The worst pain within the last 24-hours and pain during activity were assessed before and after treatment.

Results: Clinical pain significantly decreased after treatment ($P<0.001$) and less efficient CPM before treatment was associated with weaker analgesic effect ($R=0.354$, $P=0.043$). No significant modulation of CPM or offset analgesia were found for the treatment.

Conclusion: This study found that less efficient CPM is associated with reduced analgesic effect of NSAIDs plus acetaminophen in patients with KOA whereas the treatment did not modulate CPM nor offset analgesia magnitude.

Introduction

Pain inhibitory pathways have been studied for decades, and the first studies on animals showed that a painful stimulus could be inhibited by another concurrent extra-segmental pain stimulus (Le Bars et al., 1979a, 1979b). In humans, this assessment is called conditioned pain modulation (CPM) (Yarnitsky et al., 2010) and is found to be impaired in patients with chronic pain (Arendt-Nielsen et al., 2018). Impaired CPM has been associated with poor outcome after e.g. surgery (Vaegter et al., 2017; Wilder-Smith et al., 2010; Yarnitsky et al., 2008) and associated with the effect of duloxetine (a serotonin–noradrenalin reuptake inhibitor) in painful diabetic neuropathy (Yarnitsky et al., 2012). More recently, efficient CPM has been associated with improved analgesic effect of topical diclofenac in patients with osteoarthritis (Edwards et al., 2016) and patients with osteoarthritis with central sensitization gain less pain relief from total joint replacements (Izumi et al., 2017; Kurien et al., 2018; Petersen et al., 2015, 2016, 2018), indicating that measure of central sensitization might hold prognostic value for standard treatments of osteoarthritis.

Offset analgesia has been suggested as another manifestation of descending pain inhibition (Hermans et al., 2016) and is observed as a disproportionally reduction in perceived pain following a slight decrease in a tonic painful stimulus intensity (Grill & Coghill, 2002). Offset analgesia has been suggested to act via different pain pathways than CPM (Honigman et al., 2013; Niesters et al., 2011),

but the specific pathways of offset analgesia are still largely unknown (Hermans et al., 2016). Furthermore, differences in brain activity have been recorded during an offset analgesia and CPM paradigm (Nahman-Averbuch et al., 2014), which further suggests that the underlying mechanisms are different. Patients with neuropathic pain, however, display impairments in both offset analgesia (Niesters et al., 2011) and CPM (Niesters et al., 2014). More evidence is needed in clinical populations to investigate the underlying mechanisms of these two assessments and to investigate if these mechanisms can be associated with analgesic effects following pharmaceutical and non-pharmaceutical interventions.

The prevalence of osteoarthritis is increasing worldwide and international guidelines for treatment of osteoarthritis (Hochberg et al., 2012; Jordan et al., 2003) recommend a combination of non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen as the first line of treatment. The analgesic effect of NSAIDs and acetaminophen is widely documented by the underlying mechanisms are not completely understood (Graham et al., 2013). Both NSAIDs and acetaminophen inhibits the prostaglandin synthesis through the cyclooxygenase (COX) enzymes. Preclinical studies have shown that non-selective NSAIDs and acetaminophen enhances the activity of the cannabinoid system (Ahn et al., 2007) and that the analgesic effect of selective COX-2 inhibitors is depending on a intact serotonin system (Graham et al., 2013). Serotonin is important for descending inhibitory pain control (Bannister et al., 2017) and administration of COX-2 inhibitors can modulate widespread hyperalgesia (Malfait & Schnitzer, 2013; Reinold et al., 2005), which has been suggested to be associated with impaired descending pain inhibitory control (Graven-Nielsen & Arendt-Nielsen, 2010).

In this study, NSAIDs and acetaminophen were utilized as a standard pain treatment for osteoarthritis patients and the hypothesis was that CPM and offset analgesia prior to treatment would be associated with the analgesic effect of this treatment as seen previously (Edwards et al., 2016). Further, we hypothesized that, endogenous pain inhibition would improve with reduced clinical pain and have been observed in when assessing total joint arthroplasties in knee osteoarthritis (Graven-Nielsen et al., 2012; Kosek & Ordeberg, 2000). Based on this rationale, the current study aimed to investigate: 1) the possible role of CPM and offset analgesia to predict clinical treatment effects, and: 2) the relationship between endogenous pain inhibition and clinical pain modulation in patients with knee osteoarthritis.

Method

Protocol

Patients were recruited, and data were collected at the Orthopedic Outpatient Clinic, Aalborg University
Hospital, Aalborg, Denmark in the time period between January 2016 and February 2018. The study was approved by The North Denmark Region Committee on Health Research Ethics (N-20140077) and registered at ClinicalTrials.gov (NCT02967744). The data presented here are from an amendment protocol to N-20140077, which was added after the first 100 patients were enrolled for the main protocol. The presented work is from a subsample of the original protocol with 62 patients being enrolled specifically for the offset analgesia and CPM paradigms. Written informed consent was obtained before patient inclusion. Clinical osteoarthritis was defined following the American

College of Rheumatology criteria (Wolfe et al., 2010). The pain during activity, the worst pain during the last 24 hours, CPM, and offset analgesia were assessed before treatment. The pain intensity during activity and the worst pain during the last 24 hours were reassessed three weeks after NSAID plus acetaminophen treatment. Analgesic effect was calculated as the absolute differences in pain intensities before and after treatment. In addition, the Knee Injury and Osteoarthritis Score (KOOS) questionnaire(Roos & Toksvig-Larsen, 2003) was evaluated before treatment. A percentage KOOS score from 0% to 100% was calculated for each dimension; 100% representing the best possible score.

Exclusion criteria included the presence of other pain problems (e.g. hip osteoarthritis), sensory dysfunction (e.g. fibromyalgia, neuropathic pain), or mental impairment.

Treatment

Patients were treated with ibuprofen 400 mg (three times per day), acetaminophen 1g (three times per day), and pantoprazole 20 mg (once per day) for three weeks, which have previously been recommended for managing osteoarthritis pain(Doherty et al., 2011). Pantoprazole was administrated to prevent ulcers. Patients were instructed to report any adverse and severely adverse events.

Conditioned Pain Modulation

CPM magnitude was assessed as the changes in cuff pain detection threshold (cPDT) sensitivity with and without a conditioning stimulus (cuff pressure stimulation). The cPDT was applied to the lower leg ipsilaterally to the osteoarthritic affected knee, and the conditioning stimulus was applied to the contralateral lower leg. This combination has proven reliable (Graven-Nielsen et al., 2017; Imai et al., 2016). The pressure stimuli were applied using a computer-controlled cuff algometer (Cortex Technology and Aalborg University, Denmark) including two 13-cm wide tourniquet cuff (VBM, Sulz, Germany) and an electronic VAS (Aalborg University, Denmark) for recording of the pain intensity. The cuffs were placed at the level of the head of the gastrocnemius leg muscle mostly affected by osteoarthritis. The electronic continuous VAS (sliding resistor) was 10 cm long and sampled at 10 Hz; 0 cm indicated “no pain”, and 10 cm indicated “maximum pain”.

For the cPDT, the pressure (in kPa) was increased by 1 kPa/s, and the patient was instructed to rate the pain intensity continuously on the electronic VAS until the tolerance level was reached. Further, the patient was asked to press a stop button after which the pressure was released immediately. The cPDT was defined as the pressure at which the VAS score exceeded 1 cm as previously used(Thomas Graven-Nielsen et al., 2015; Imai et al., 2016; Kurien et al., 2018; Rathleff et al., 2015; Vaegter & Graven-Nielsen, 2016). The conditioning stimulus was applied as a constant stimulus with the intensity of 70% of the pain tolerance level (Graven-Nielsen et al., 2017). This CPM protocol has previously been utilized when studying patients with chronic pain (Heredia-Rizo et al., 2019; Holden et al., 2018; Izumi et al., 2017; Kurien et al., 2018). The CPM-effect was calculated as the absolute difference in cPDT with and without a conditioned stimulus and the unconditioned cPDT was always assessed before the conditioned cPDT.

Offset Analgesia

Heat stimuli (rise and fall rate: 6°C/s) were applied using the Medoc Pathway system (Medoc ltd., Ramat Yishai, Israel) with a 30×30mm squared probe to the volar forearm.

Initially, the offset analgesia paradigm was conducted, and the patients were asked to continuously rate the pain intensity to the heat provocations. The stimuli were delivered in three coherent time intervals of 5 seconds (T1), 5 seconds (T2), and 20 seconds (T3. The baseline temperature was 35°C, and temperatures during the different time intervals were T1=46°C, T2=47°C, and T3=46°C. Secondly, a control paradigm was conducted with a constant heat provocation of 46°C for 30 seconds. It is well known that a pain reduction due to prolonged pain heat stimuli can be caused by the adaptation of primary afferents known to occur during prolonged stimulation (LaMotte et al., 1983) , and this control paradigm was conducted to account for the adaptation.

The offset analgesia effect was calculated as the difference in average pain rating in T2 in the offset analgesia and the same period in the control paradigm as previously described (Ligato et al., 2018).

Statistics

The data are presented as means and standard error of the mean (SEM) if not otherwise stated. Paired-sample t-tests were used to compare pain intensities before and after treatment. For CPM, the pain inhibition was assess by paired-sample t-test comparing cPDT with and without a conditioned stimulus. The differences between the constant heat control paradigm and the offset analgesia paradigm were investigated using paired-sample t-test. Pearson correlations were used to investigate correlations between pain inhibitory magnitude and analgesic effect to the treatment and a linear regression using backwards selection was used to identified independent factors for the prediction of the analgesic effect. The analgesic effect on CPM and offset analgesia were investigated using the differences between the CPM and offset analgesia magnitude before and after treatment and assessed by paired-sample t-tests. The statistical analyses were performed using SPSS (version 23, IBM Corporation, New York, USA). P-values < 0.05 were considered significant.

Results

Sixteen patients (26%) were excluded from the data analysis due to technical issues with the Medoc Pathway system (incomplete data), and four subjects (6%) were excluded due to misunderstanding of the experimental procedure or incomplete clinical pain rating data (missing data). Forty-two patients had complete data set of offset analgesia, CPM, and pain rating before and after treatment and were therefore included in the data analysis. The patients included in the present analysis were not significantly different compared with the patients excluded with regards to age ($P = 0.516$), BMI ($P = 0.654$), worst pain during the last 24 hour, and pain during activity before treatment ($P > 0.6$) or CPM ($P = 0.574$). Demographics of included patients at baseline are listed in table 1.

Predicting Analgesic Effect

Both pain during activity (paired-sample t-test: $P < 0.001$) and the worst pain during the last 24 hours (paired-sample t-test: $P < 0.001$) were significantly decreased by the treatment. A significantly

positive correlation was found between the CPM before treatment and the analgesic effect using pain during activity (R = 0.394, P = 0.021, figure 1) indicating that less efficient CPM is associated with reduced analgesic effect. In addition, pain during activity before treatment significantly correlated with CPM before treatment (R = -0.432, P = 0.011) and the analgesic effect of the treatment (R = -0.436, P = 0.003). A linear regression aiming to predict the analgesic effect for pain during activity using pain during activity and CPM before treatment demonstrated a predictive value of 18.6% (adjusted R-squared) and applying backwards selection demonstrated that pain during activity before treatment was the only independent factor (P = 0.012).

No significant interaction was observed for CPM and worst pain within the last 24 hours ($R < 0.3$, $P > 0.1$) or for offset analgesia ($R < 0.1$, $P > 0.6$).

Pain Inhibition before Treatment

To investigate the CPM-effect before treatment, a conditioned and unconditioned cPDT was investigated and no significant difference was found for cPDT with and without the conditioning stimulus (paired-sample t-test: P = 0.158, figure 2A). To investigate the offset analgesia effect before treatment, the pain intensity to the offset analgesia and a constant control paradigm were investigate and a significant lowered pain response was found for the offset analgesia paradigm (paired-sample t-test: P = 0.075, figure 2B) during the first five seconds of T3 compared to the constant control paradigm.

Analgesic effect and Pain Inhibitory Mechanisms

The combined treatment with NSAID plus acetaminophen did not modulate CPM magnitude (paired-sample t-test: P = 0.654) nor offset analgesia magnitude (paired-sample t-test: P = 0.185) in patients with knee osteoarthritis (figure 3).

Discussion

A significant clinical analgesic effect was demonstrated after three weeks of treatment with NSAID plus acetaminophen. CPM magnitude before treatment was correlated with the clinical analgesic effect. The current study is the first to investigate and compare two different pain inhibitory mechanisms (CPM and offset analgesia) in patients with osteoarthritis before and after pharmacological treatment. No changes were found when comparing CPM and the offset analgesia magnitude before and after treatment.

Using Pain Inhibitory Mechanisms as Predictors for Analgesic Effect

Increasing evidence suggests that pain mechanistic profiling can identify patients who will respond to analgesic treatments (Grosen et al., 2013; Sangesland et al., 2017). Specifically, impaired CPM have been found associated to improved analgesic effect to duloxetine (a serotonin–noradrenalin reuptake) (Yarnitsky et al., 2012), indicating that serotonin and noradrenalin might play a crucial role in functional pain inhibition. In the present study, we found that CPM magnitude associates to the clinical response to treatment with weak analgesics, which is similar to a recent study on topical diclofenac sodium gel (Edwards et al., 2016). In relation to surgery, studies have found associations between impaired preoperative CPM and increased chronic postoperative pain following

thoracotomy (Yarnitsky et al., 2008), abdominal surgery (Wilder-Smith et al., 2010), and total knee replacement (Vaegter et al., 2017). In combination, these studies might hold information, which can direct the future of personalized pain medicine but future studies targeting the pain mechanisms are needed to further improve the research area.

Currently, no studies have investigated the association between offset analgesia magnitude and association to response to pharmaceutical treatments (Hermans et al., 2016) and the current study could not demonstrate a correlation between offset analgesia and the analgesic effect.

Pain Inhibition and Modulation of Chronic Pain

For CPM, a functioning inhibitory system is commonly reported in healthy subjects corresponding to a significant increase in the perceived intensity of a test stimulus during the delivery of a conditioning stimulus (Yarnitsky et al., 2010), and this is often impaired when assessed in chronic pain patients (Arendt-Nielsen et al., 2018). Offset analgesia has been reported to be impaired in clinical pain populations (Kobinata et al., 2017). Therefore, one could assume that offset analgesia and CPM would act via the same pain pathways, and/or that these assessments were associated, but recent studies have indicated differences between the two phenomena (Hermans et al., 2016).

The analgesic effect from offset analgesia and CPM appears to add to each other in healthy subjects suggesting that the pathways are different (Honigman et al., 2013). This is further supported by studies showing that the administration of ketamine (a N-methyl-D-aspartate (NMDA) antagonist) influences CPM, but not offset analgesia (Niesters et al., 2011) suggesting that CPM is NMDA-dependent, and offset analgesia is NMDA-independent. Administration of hydromorphone (an opioid) does not have an effect on CPM or offset analgesia in pain patients(Suzan et al., 2015). Administration of remifentanil (an opioid agonist) and naloxone (an opioid antagonist) to healthy subjects does not alter offset analgesia (Martucci et al., 2012), suggesting that offset analgesia is opioid-independent whereas administration of morphine impairs the CPM in healthy subjects (Martini et al., 2015), which suggests that CPM is opioid-dependent. Offset analgesia as an opioid-independent measure is further supported by a recent study (Olesen et al., 2018), which found that administration of oxycodone to healthy male subjects did decrease the heat pain sensitivity, but did not change the offset analgesia effect compared with placebo. In the present study, no modulation of either CPM nor offset analgesia was seen after treatment with weak analgesics. The lack of descending pain inhibitory modulation reported in the current study in spite of a decrease in clinical pain intensity, questions if impairment of CPM and offset analgesia is pain intensity driven or if the pain should abolished for a longer period of time before pain inhibitory mechanisms are reestablished.

MRI recordings have shown differences in brain activity during an offset analgesia and CPM paradigm (Nahman-Averbuch et al., 2014), which further suggests that the mechanisms underlying CPM and offset analgesia are different. A recent study found that increased heart rate variability (HRV) was associated with lower pain ratings during an offset analgesia paradigm (Van Den Houte et al., 2018), suggesting an association between offset analgesia and the autonomic nervous system (ANS). Nahman-Averbuch et al., (Nahman-Averbuch et al., 2016) found that increased ANS activity in men was associated with an increased CPM-effect and modulatory capacity to offset analgesia, which was not present for women, indicating sex-dependent effects, which should be investigated in

future studies. It could be assumed that measures of the ANS activity are associated with CPM since afferent baroreceptor signals have been implicated in the modulation of pain perception via medullary and mesencephalic neural circuitry, which influences the descending pain inhibition (Ghione, 1996; Thurston & Randich, 1992) and medullary transections, reducing diffuse noxious inhibitory control (the preclinical counterpart to CPM) in rats (Bouhassira et al., 1992). In contrast to this, Petersen et al., 2018 (Petersen et al., 2018) found that administration of propranolol (a beta-blocker, increasing ANS activity) did not affect offset analgesia or CPM in healthy subjects, which could indicate that the ANS does not influence the pain inhibitory pathways. In addition, the current study found that the CPM was associated with analgesic effect to NSAID plus acetaminophen treatment whereas no correlation was found with the offset analgesia paradigm, which could indicate that these two measures represent two different pain inhibitory pathways but further studies are needed to investigate this.

Limitations

The current explorative study is limited by the lowered sample size due to technical errors associated with the heat stimulation, and unfortunately, our group has encountered these technical errors before in similar set-ups (Petersen et al., 2018). In general, the findings from the current study should be interpreted with care, and larger studies should confirm these findings. However, a clear analgesic effect was observed despite the lowered sample size.

Patients with musculoskeletal pain are often pain sensitive to pressure stimuli and not necessarily to heat stimuli (Neziri et al., 2012; Kristian Kjær Petersen et al., 2017). Offset analgesia can be evoked by heat (Grill et al., 2002; Ligato et al., 2018; Kristian Kjær Petersen et al., 2018) and electrical stimuli (K K Petersen et al., 2018), but currently no study has demonstrated an offset analgesia effect using pressure stimuli. Therefore, the results from the current study using heat evoked offset analgesia should be interpreted with care.

The current study is not placebo controlled, since the analgesic effect of NSAID plus acetaminophen is well documented (Hochberg et al., 2012; Jordan et al., 2003). Despite this, these preliminary results should be interpreted with care.

Conclusion

Three weeks treatment with NSAID plus acetaminophen decreased clinical pain scores in patients with osteoarthritis. Less efficient CPM before treatment was correlated of the analgesic effect. No changes were observed when comparing offset analgesia and CPM magnitudes before and after the treatment. These findings should be replicated in larger studies than this to confirm the validity.

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Author Contributions

Kristian Kjær Petersen (KKP), Ole Simonsen (OS), Anne Estrup Olesen (AEO) and Lars Arendt-Nielsen (LAN) designed the study. OS collected the data and KKP and Carsten Dahl Mørch conducted the statistical analysis. KKP wrote the first draft of the manuscript and KKP, OS, AEO, CDM and LAN discussed the results and commented on the manuscript.

Table

	Mean (SD)
Age (years)	63.09 (8.60)
BMI (kg/m^2)	29.84 (5.15)
Gender (percentage female)	54.8 %
Pain intensity [cm]	
- worst pain within the last 24 hours	6.93 (2.63)
- During activity	6.25 (2.37)
KOOS subscales	
- Pain	53.53 (17.67)
- Symptoms	60.79 (19.46)
- ADL	58.11 (18.78)
- Sport/Rec	28.08 (20.09)
- QoL	34.88 (19.92)

Table 1: Demographics (means and standard deviation, SD) of 42 patients with osteoarthritis before three weeks treatment with NSAID plus acetaminophen. Abbreviations: Body mass index, BMI; Knee Injury and Osteoarthritis Score, KOOS; Activities of daily living, ADL; Sport and recreation function, Sport/Rec; Knee-related quality of life, QOL.

Figure legends

Figure 1: Pearson correlation between CPM-effect before treatment and analgesic effect of treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen for three weeks.

Figure 2: Assessments of pain inhibition of patients with knee osteoarthritis before treatment assessed as the differences in **(A)** cuff pain detection threshold (cPDT) with and without a conditioning stimulus and **(B)** the difference between pain intensities to a 30-seconds constant control paradigm and an offset analgesia paradigm.

Figure 3: (A) Conditioned pain modulation magnitude and **(B)** offset analgesia effect before and after three weeks of treatment with NSAIDs plus acetaminophen in patients with moderate-to-severe knee osteoarthritis. Offset analgesia magnitude are calculated as the difference in average and minimum pain intensities to a constant heat stimuli and an offset analgesia paradigm.

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