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The Effect of Hydromorphone Therapy on Psychophysical Measurements of the Descending Inhibitory Pain Systems in Patients with Chronic Radicular Pain

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Abstract

Objective. Conditioned pain modulation (CPM) and offset analgesia (OA) are considered to represent paradigms of descending inhibitory pain modulation in humans. This study tested the effects of hydromorphone therapy on descending inhibitory pain modulation, as measured by changes from baseline in the magnitudes of CPM and OA.

Design. Prospective evaluation.

Setting. Institute of Pain Medicine, Rambam Health Care Campus.

Subjects. Patients with chronic radicular pain.

Methods. Thirty patients received 4 weeks of oral hydromorphone treatment at an individually titrated dose (mean ± standard deviation dose of 11.6 ± 4.8 mg/day). CPM and OA were assessed before and after hydromorphone treatment. CPM was assessed by subtracting the response to a painful phasic heat stimulus administered simultaneously with a conditioning cold pain stimulus, from the response to the same heat stimulus administered alone. The OA paradigm consisted of a three-temperature stimuli train (T1 = 49°C [5 seconds], T2 = 50°C [5 seconds], and T3 = 49°C [20 seconds]). The magnitude of OA was quantified by subtracting minimal pain scores obtained during T3 from the maximal pain scores obtained during T2.

Results. CPM scores changed from a baseline of 17.7 ± 20.6 to 21 ± 20.4 following treatment, and OA scores changed from 7.8 ± 20.5 to 9.7 ± 14.6. Wilcoxon signed rank test indicated that these changes were not significant (CPM: $P = 0.22$; OA: $P = 0.44$). McNemar test revealed that the percentage of patients who exhibited a change in the direction of CPM or OA in response to hydromorphone treatment was not significant (CPM: $P = 0.37$; OA: $P = 0.48$).

Conclusions. These results suggest that the descending inhibitory pain modulation, as manifested in humans by CPM and OA, is unlikely to be mediated by hydromorphone therapy.

Key Words. Conditioned Pain Modulation (CPM); Offset Analgesia (OA); Hydromorphone; Pain Pathways; Opioids; Neuropathic Pain

Introduction

Conditioned pain modulation (CPM), formerly referred to as diffuse noxious inhibitory control [1], and offset

analgesia (OA) are considered as two manifestations of the descending inhibitory pain system in humans [2–8]. CPM describes a phenomenon whereby the response to a given noxious test stimulus is attenuated by another conditioning noxious stimulus that is simultaneously administered to a remote area of the body [3]. OA, first described by Grill and Coghil in 2002, is defined by a disproportionately large decrease in the perceived pain intensity following an incremental decrease in the intensity of a painful heat stimulus [5,8]. Studies suggest that both CPM and OA coincide with the activation of areas related to the descending inhibition of pain (i.e., periaquaductal gray [PAG], rostraventral medulla, and locus coeruleus) [7–9]. Although both phenomena describe temporal sharpening mechanisms, OA is distinct from CPM in that the former is time-locked to the *offset* of a noxious stimulus, whereas the latter is activated by the *onset* of a noxious stimulus administrated remotely from an ongoing noxious stimulus [3,10–12].

Despite the debate regarding opioids' use for chronic nonmalignant pain, they remain a cornerstone therapy for the treatment of moderate to severe acute and cancer pain [13]. Animal studies have fairly consistently shown that one supraspinal mechanism by which opioids exhibit their analgesic effect is by enhancing pain modulation via activation of the descending inhibitory pathways [11,14,15]. Based on that, it is reasonable to expect that opioids will display an effect both on CPM and OA in translational studies in both healthy humans and patients with various painful conditions. Yet, with regard to CPM, human studies conducted in both populations yielded inconclusive results, whereas some studies demonstrated a decline in the magnitude of CPM following opioid administration [3,16], others showed an opposing incline [17,18], or even no effect at all [19–21]. The effect of opioids on OA has had very little investigation. The few existing studies point to opioids lacking any effect on OA [22,23]. The inconsistency of the outcomes of these studies may result from various methodological shortcomings of the existing studies, which limits our ability to draw unequivocal conclusions about the effect of opioids on psychophysical measurements of descending analgesia in humans. Thus, the aim of the current prospective study was to learn about the effects of a 4-week hydromorphone therapy regimen on the descending inhibitory system, as measured by CPM and OA, in a single population of patients with chronic neuropathic (radicular) pain.

Methods

Subjects

The study population consisted of 30 patients diagnosed with chronic lumbosacral radicular (neuropathic) pain, rated as moderate to severe, who were recruited for a larger study on opioid-induced hyperalgesia (OIH). The results relating to OIH and clinical pain intensity have already been published elsewhere [24].

Patients were recruited either from the Institute of Pain Medicine at Rambam Health Care Campus or in response to an advertisement in the local newspaper. The diagnosis of radicular pain was made by pain specialists and met the new International Association for the Study of Pain suggested criteria for the diagnosis of neuropathic pain [25]. Patients were enrolled in the study after meeting the following inclusion criteria: 1) pain projecting from the lower back to one lower limb, at a distribution of one specific dermatome, for a duration of at least 3 months; 2) pain intensity above 40/100 on a visual analog scale (VAS) at rest; 3) positive straight leg raising/femoral stretch test in patients with lower/upper lumbar disc herniation (below/above L4), respectively; 4) positive/negative sensory findings on neurological examination; 5) pain attributed to lumbar disc herniation, meaning that magnetic resonance imaging and/or computed tomography scan findings were consistent with clinical symptoms in terms of the side and level of the herniated disc; 6) willingness to discontinue all previous analgesic medications (with the exception of acetaminophen) for a washout period of 7 days and subsequently to consume opioids for at least 1 month; and 7) ability to understand the purpose and instructions of the study and to sign an informed consent form. Exclusion criteria were: 1) presence of peripheral neuropathy of any etiology (with the exception of lumbar radiculopathy); 2) presence of any other type of pain in another body region; 3) use of antidepressants and/or anticonvulsants; 4) pregnancy; 5) allergy, history of substance abuse, or any other contraindication for the use of opioids; or 6) a diagnosis of Raynaud's syndrome.

Clinical Pain Assessment

Patients were instructed to record their average daily pain intensity at baseline and during the 4 weeks of the study. Pain was rated each day from 0 to 100 on a VAS, where 0 represented "no pain" and 100 represented the "worst pain one can imagine."

CPM

In order to induce CPM, phasic heat stimulation was given and considered as the "test pain," whereas cold stimulation was used as a "conditioning stimulation."

Test Pain

TSA 2001-II thermal sensory testing device (contact area 30×30 mm; Medoc, Ramat Yishai, Israel) was attached to the skin above the left thenar eminence. Two heat pain stimuli of 47°C (starting from 37°C in an increasing and decreasing rate of 10°C/sec) were delivered at an interstimulus interval of 30 seconds, each lasting 4 seconds. After each stimulus, subjects were asked to report verbally the pain intensity experienced, using a 0–100 numeric pain scale (NPS).

Conditioning Stimulation

The right hand was immersed into a cold bath (12°C) for 30 seconds.

CPM Test Paradigm

First heat stimulation was delivered, and the subjects were asked to verbally report the level of pain intensity (NPS, 0–100) at the point when the temperature reached 47.0°C. This was considered as "baseline pain." Then subjects were instructed to immerse their right hand into the cold bath. Following 30 seconds of immersion, while the hand was still in the bath, the second test stimulation was delivered, and pain intensity was recorded again (test pain). CPM was calculated by subtracting "test pain" intensity from "baseline pain" intensity. Thus, positive values represent effective CPM. This paradigm is based on multiple previous studies conducted in our laboratory using a similar design that has produced CPM consistently [21,26,27].

OA

As previously described [5], OA was induced by using a TSA 2001-II device (contact area 16 × 16 mm) attached to the ventral surface of the dominant forearm of the subject by a Velcro strap and maintained at a baseline of 32°C. This paradigm was used to quantify the magnitude and time-course of OA and consisted of a three-temperature stimulus train (T1 = 49°C [5 seconds], T2 = 50°C [5 seconds], and T3 = 49°C [20 seconds]).

First, the temperature was ramped from a baseline temperature (32°C) to 49°C and maintained constant for 5 seconds after which it was raised by 1°C for 5 seconds and next decreased by 1°C to the test temperature and kept constant for 20 seconds. Next, the temperature quickly returned (6°C/s) to baseline. Subjects rated the intensity of the heat stimulus using the co-VAS (computerized visual analog scale, 0–100). The magnitude of OA was quantified by subtracting minimal co-VAS values obtained during T3 (following the 1°C decrease from 50°C to 49°C) from the maximal co-VAS values obtained during T2. Hence, positive values represent efficient OA.

Study Medication

Patients were treated with escalating doses of once-daily, sustained-release oral hydromorphone hydrochloride tablets (Jurnista®, Janssen-Cilag, developed by ALZA Corporation, Vacaville, CA, USA). The initial daily dose for all patients was 4 mg, and the maximal dose allowed was 24 mg, administered as a single dose at bedtime. Dose increments were allowed every fifth day and were based on clinical judgment while taking into account the following considerations: 1) whether adequate analgesia had been achieved (as determined by the patient); 2) whether side effects precluded further titration; and 3) whether a total of 24 mg per day had been reached. In the case of intolerable side effects, patients were instructed to return to the previous dosage. Patients were requested not to change the hydromorphone dosage for at least 3 days prior to the second study session.

Patients who reported constipation following hydromorphone administration were instructed to use lactulose (maximal dose 30 cc/day) or bisacodyl (maximal dose 5 mg/day). No additional mediations or treatments for pain control were allowed with the exception of rescue doses of acetaminophen (500 mg) tablets. Patients were instructed not to use acetaminophen for at least 6 hours prior to initiation of study sessions.

Study Design

This single-center, open-labeled, prospective study was approved by the Ethics Committee of Rambam Health Care Campus in Haifa, Israel (IRB number 143-10 RMB). Patients who responded to the advertisement in the newspaper underwent initial telephone screening, and eligible patients were subsequently seen for a clinical evaluation. All patients received a detailed explanation about the study medication and procedures. Those who had previously been taking opioids or other analgesics were required to undergo a washout period in order to ensure that they were not consuming any pain medications, apart from rescue doses of acetaminophen (up to 3 gr/day), for at least 72 hours prior to the first study session. Patients attended two different study sessions: 1) before and 2) 4 weeks following initiation of hydromorphone therapy. CPM and OA were tested at both sessions. At the beginning of each session, patients received brief training in order to familiarize them with the tasks, the devices, and the perceived sensations. The training tests were not used in the statistical analyses. Ten minutes later, a second round of tests was conducted and counted as the test measurements.

Statistical Analyses

All analyses were conducted using the SPSS for Windows Version 17 statistical package (SPSS, Inc., Chicago, IL, USA). The change in CPM and OA was calculated by subtracting the values obtained after treatment from those obtained before treatment initiation. A Shapiro-Wilk *W* test of normality (Analyse-it, version 2.20, Analyse-it Software Ltd., Leeds, UK) revealed that both measures were not normally distributed; hence, all analyses were based on nonparametric tests. Wilcoxon signed rank test was employed to assess the differences in CPM and OA between sessions. As two main outcome parameters (CPM and OA) were measured, Bonferroni correction was applied in order to manage type I statistical error. The results were considered significant at the $P < 0.025$ level (0.05/2). McNemar test was used to assess if the percentage of patients who exhibited a change in the direction of their CPM or their OA in response to the treatment was statistically significant (e.g., percentage of patients who changed from positive to either negative CPM or no CPM, etc.), whereas Spearman's correlations were utilized to assess the correlations

between the change in the tested measures (CPM and OA) and patients' age, hydromorphone dosage and the effect of hydromorphone on the clinical pain. Values are presented as means ± standard deviation (SD) and median unless otherwise specified.

Results

Subjects

One hundred and sixty-two patients were initially screened, and 37 of them were found eligible for the study. Of those 37 patients, seven were unable to complete the study (four patients lacked improvement in their clinical pain and three patients had transient side effects). Thus, complete data were available from a total of 30 patients (21 men and nine women), ranging in age from 22 to 68 years old (mean age ± SD 47.5 ± 13.1). Their mean pain duration was 70 ± 107 months. The L5 and S1 were the most commonly affected dermatomes (57% and 27%, respectively, followed by L4 and L2 (13% and 3%, respectively). Only three patients (10%) consumed low doses of opioids (equivalent to 30 mg of oral morphine or less) for pain control, but none of them on a regular basis or during the 14 days prior to entering the study. An a priori power analysis revealed that the required calculated sample size for demonstrating significant effects of hydromorphone on CPM and OA should consist of 28 patients (power [1-β] = 0.8; α error = 0.05; effect size = 0.5). The mean hydromorphone dosage at the end of the 4-week treatment period was 11.6 ± 4.8 mg/day, ranging from 4 to 20 mg with a median of 12 mg/day.

The Effects of Hydromorphone on Clinical Pain

The mean daily pain intensity reports dropped from 64 ± 15.2 VAS units at baseline to 38.6 ± 26 following treatment ($P < 0.001$).

The Effects of Hydromorphone on CPM

CPM Before Hydromorphone Treatment

The average CPM magnitude for the entire group before treatment initiation was 17.7 ± 20.6 (Figure 1), with a median of 20. As shown in Figure 2, CPM magnitude ranged from 88 to −10. In 21 patients, the conditioning stimulus reduced the intensity of the heat pain stimulus from baseline (positive CPM): in seven patients, the intensity of heat pain remained unchanged (CPM was not produced), whereas in two patients, heat pain intensity increased from baseline when coadministrated with the conditioning stimulus (negative CPM).

CPM after Hydromorphone Treatment

The average CPM magnitude for the entire group 4 weeks following treatment increased to 21 ± 20.4 with a median of 20 (Figure 1). In that session CPM magnitude ranged from 75 to −10 (Figure 2). Twenty-four patients exhibited positive CPM, five patients exhibited no CPM, and one patient showed a negative CPM.

In the comparison of the average magnitude of CPM for the entire group between both sessions (before vs after treatment), Wilcoxon signed rank test revealed no statistically significant difference ($P = 0.22$; Figure 2). Additionally, McNemar test showed that the percentage of patients who exhibited a change in the direction of their CPM was not statistically significant (83.3%; $P = 0.37$; Figure 2).

The Effects of Hydromorphone on OA

OA Before Hydromorphone Treatment

The average magnitude of OA for the entire group before treatment initiation was 7.8 ± 20.5 with a

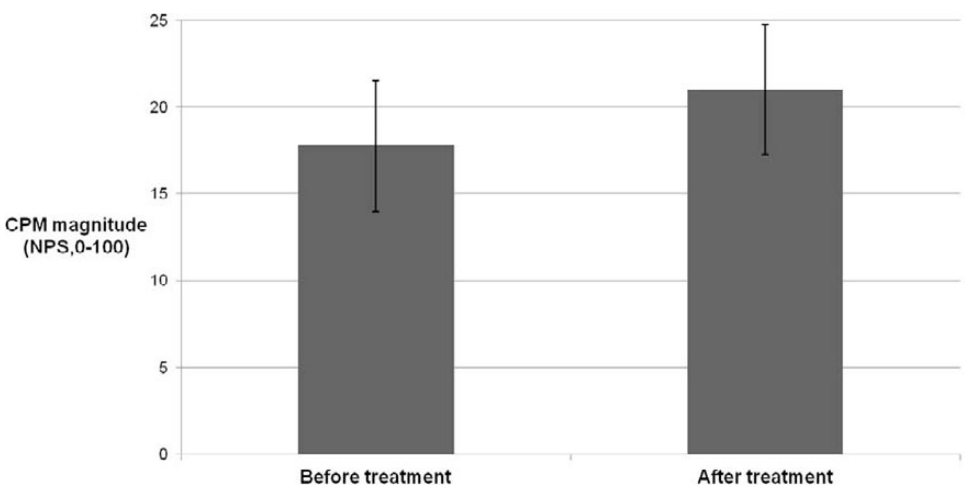

Figure 1 The effect of hydromorphone treatment on CPM magnitude (mean ± standard error of the mean; N = 30).

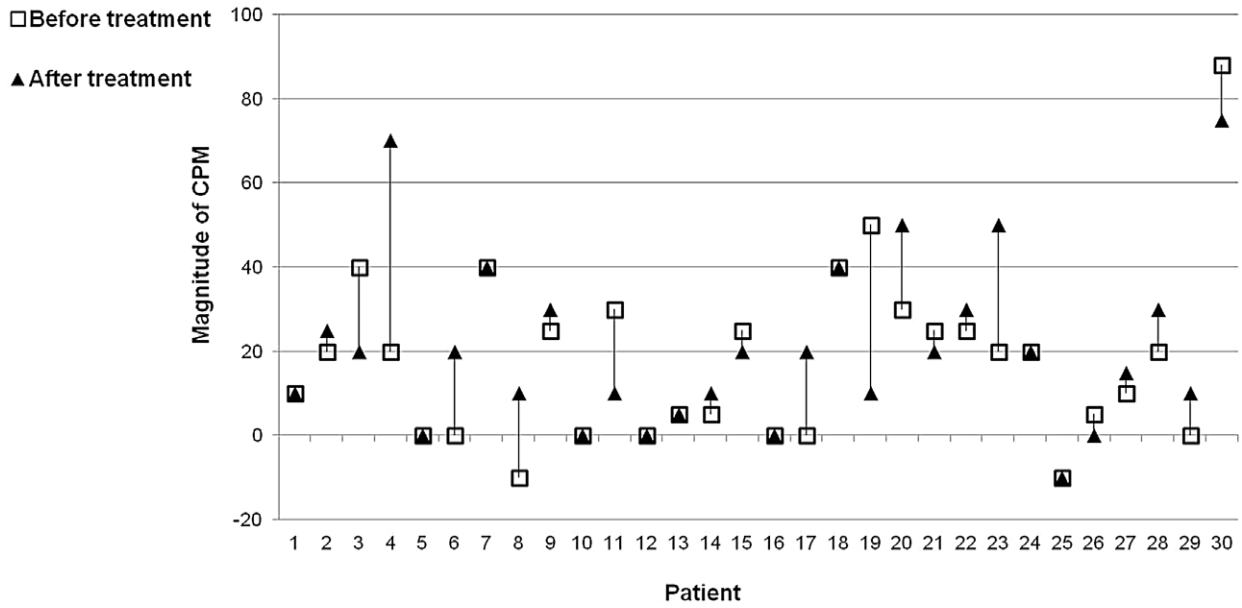

Figure 2 CPM magnitudes prior to and following 4 weeks of hydromorphone treatment in each of the 30 patients. The empty squares represent CPM magnitude before treatment and the blackened triangle represent CPM magnitude 4 weeks following treatment initiation.

median of 1 (Figure 3). As can be seen in Figure 4, OA magnitude ranged from 66 to −26. In 15 patients, there was an increase in the magnitude of pain (positive OA), in five patients the magnitude of pain intensity remained unchanged (OA was not produced), and in 10 patients the intensity of the pain magnitude decreased (negative OA).

OA Following Hydromorphone Treatment

The average magnitude of OA for the entire group 4 weeks following treatment initiation was 9.7 ± 14.6 with a median of 6.5 (Figure 3). The magnitude of OA following treatment ranged from 55 to −10 (Figure 4). In 20 patients, there was an increase in the magnitude of pain (positive OA), in three patients the magnitude of

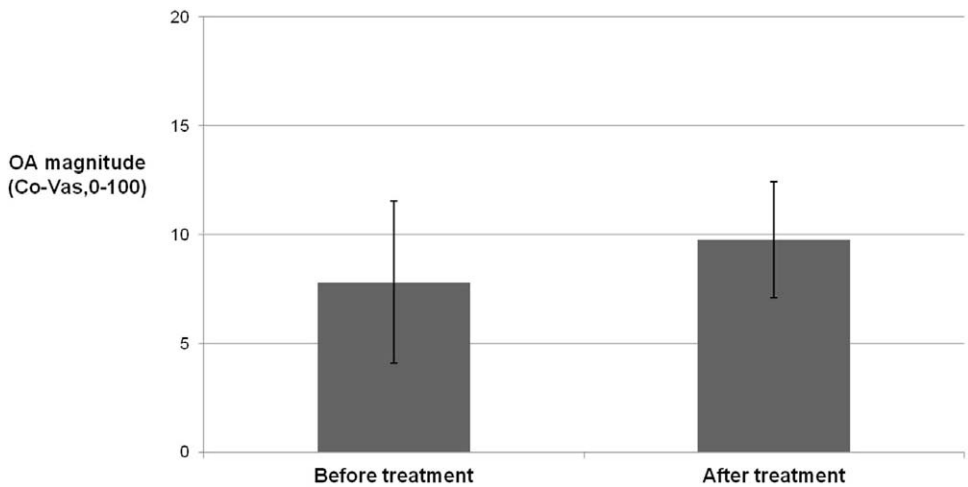

Figure 3 The effect of hydromorphone treatment on OA magnitude (mean ± standard error of the mean; N = 30).

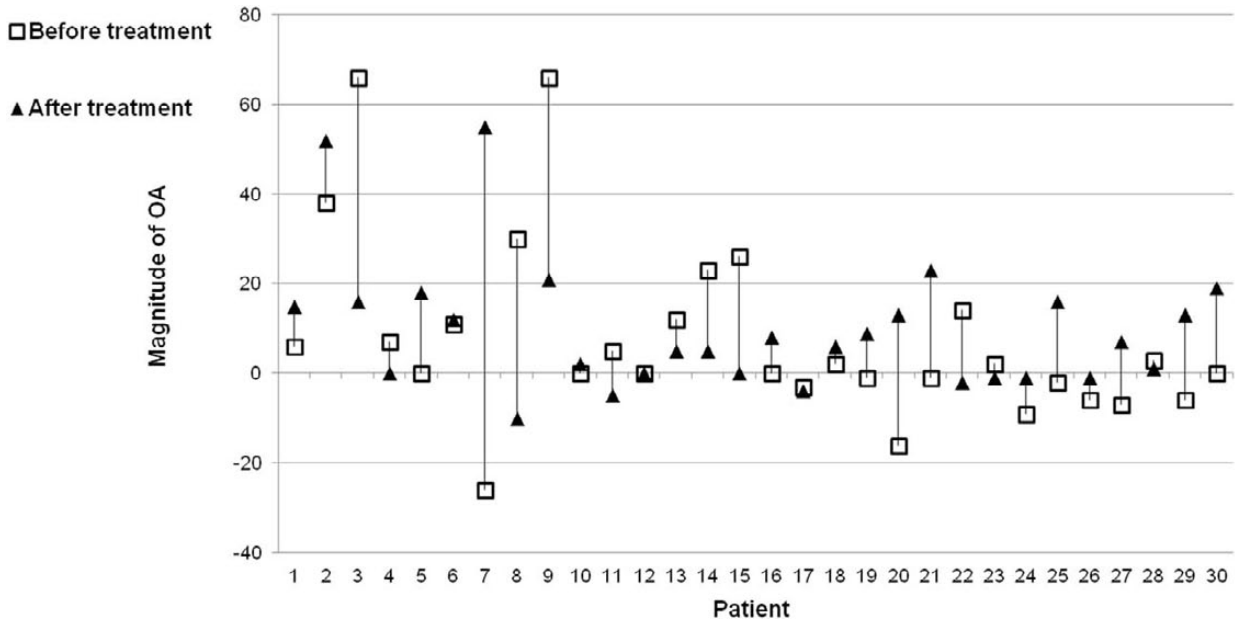

Figure 4 OA magnitudes prior to and following 4 weeks of hydromorphone treatment in each of the 30 patients. The empty squares represent OA magnitude before treatment and the blackened triangle represent OA magnitude 4 weeks following treatment initiation.

pain intensity remained unchanged (OA was not produced), and in seven patients the intensity of the pain magnitude decreased (negative OA).

There was no significant difference in the average magnitude of OA for the entire group between both sessions (before vs after treatment) (Wilcoxon signed rank test, $P = 0.44$; Figure 3). McNemar test revealed that even though the percentage of patients who exhibited a change in the direction of their OA was larger than of CPM, it was still not statistically significant (43.3%; $P = 0.48$; Figure 4).

Correlations

No significant correlations between the changes from baseline (Δ) in the magnitude of CPM or OA and patients' age (ΔCPM: $r = -0.285$, $P = 0.127$; ΔOA: $r = -0.023$, $P = 0.904$), hydromorphone dosage (ΔCPM: $r = 0.008$, $P = 0.967$; ΔOA: $r = -0.247$, $P = 0.188$) and change in pain intensity from baseline (ΔCPM: $r = 0.234$, $P = 0.214$; ΔOA: $r = -0.147$, $P = 0.439$) were found.

Discussion

The main finding of the current prospective study was that in patients with chronic neuropathic pain, a 4-week regimen of individually titrated dose of hydromorphone therapy did not change the magnitudes of both CPM and OA from baseline.

Neither the average magnitude of CPM nor the percentage of patients who exhibited positive, negative, or no CPM at baseline changed in response to hydromorphone therapy to a statistically significant level. These results are in line with several additional studies in humans, which showed no relationship between CPM and the opioidergic system [19–21]. In two of those studies, the administration of the opioid antagonist naloxone yielded no effect on CPM either in healthy subjects or in patients with acute or chronic pain [19,20]. A third study showed no effect of a single dose of oxycodone on the magnitude of CPM in healthy subjects [21]. The lack of effect of opioids on CPM is supported by an animal study that showed that microinjection of morphine into the PAG of rats did not enhance descending inhibition on the dorsal horn in rats. The authors concluded that "there is little evidence that the supraspinal action of morphine includes increased descending controls and depression of dorsal horn neurons" [28]. In contrast, other human studies demonstrated that opioids do have effects on CPM but in contradicting directions: In one such report, Le Bars et al. demonstrated a blocking effect on CPM by intravenous morphine administration in a small group (N = 9) of healthy subjects, which was reversed by naloxone [3]. In agreement with Le Bars' findings, another study on patients with chronic pain by Ram et al. (2008) found a lower average magnitude of CPM in the opioid treated patients as compared with non-opioid–treated patients [16]. Yet, a conclusion regarding the effect of opioids on CPM could not be drawn from that report because it was a "snapshot" rather than a randomized, prospective study. An opposing (potentiating) effect of opioids on CPM has been demonstrated in at least three other

studies. Willer et al. (1990) showed in a small (N = 9), double-blind, cross-over study that naloxone, but not saline, blocked CPM in healthy subjects [17]. This was supported by a later study, showing CPM enhancement in response to buprenorphine and fentanyl administration in healthy volunteers [18]. Finally, another "snapshot" study [29] demonstrated higher magnitude of CPM in opioid-treated patients as compared with opioid-naive patients with chronic pain.

Thus far, there is no clear explanation for this inconsistency except for the possibility that it emerges from methodological differences between the various studies in terms of their design, the conditioning and test stimuli applied for inducing CPM, the agents used (different opioid agonists and antagonists), the small sample size in many trials, and the populations studied (healthy subjects vs patients with pain). Unfortunately, this wide methodological variability precludes the possibility of drawing firm conclusions regarding the effects of opioids on CPM at this time point.

Regardless of that, the present study's findings, as well as several others [19–21,28], suggest that CPM might not be mediated by opioid-related mechanisms but rather point to the involvement of other, non-opioid mechanisms in CPM. The results of a recent study, which demonstrated CPM attenuation by the serotonin and neurepinephrine reuptake inhibitor deloxutine in patients with painful diabetic neuropathy [30], support this possibility. However, additional prospective studies are needed for its verification.

The results of the few existing studies regarding the effect of opioids on OA, both in healthy volunteers and patients with neuropathic pain, are in line with the results of the current study. Martucci et al. showed that the magnitude of OA in 19 healthy volunteers was not altered by naloxone administration, during or following the termination of remifentanil infusion [22]. Niesters et al. found a reduced or absent OA in 10 patients with neuropathic pain and showed in a randomized, placebo-controlled design that intravenous treatment with ketamine, morphine, and placebo had no effect on OA in these patients [23]. Together, these studies indicate that opioids are unlikely involved in mechanisms underlying OA. It is notable that unlike the studies on the effect of opioids on CPM, all studies on OA and opioids, including the present one, utilized similar testing paradigms (although different opioid agonists and antagonists). This may explain the consistency of the findings among these studies, indicating that OA is not affected by opioids.

Two limitations of the present study should be noted: first, this in an uncontrolled study and therefore its results should be interpreted cautiously. Second, the average daily dose of hydromorphone was less than 12 mg, the equivalent of about 60 mg/day of oral morphine, which is a moderate opioid dose. Thus, the results of the present study should be regarded as relevant only in that dose-range.

In summary, the results of the current study point to the possibility that the descending inhibitory system, as manifested by both CPM and OA, is mediated by non-opioid mechanisms. Alternatively, it raises a possibility that CPM and OA are not suitable paradigms for studying the mechanisms of opioid analgesia in humans. One way or another, the question of how to properly evaluate opioid-mediated central descending analgesic pathways remains open.

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