Evolution of endogenous analgesia

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Chapter 4

Influence of Ketamine and Morphine on Descending Pain Modulation in Chronic Pain Patients

A randomized placebo-controlled proof-of-concept study

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Introduction

Normal pain processing involves the modulation of pain signals in the central nervous system by activation of endogenous inhibitory (analgesic) or facilitatory (algesic) mechanisms.[1-3] These modulatory mechanisms allow optimal functionality in response to an acute painful insult.[4] For example, activation of endogenous inhibition of pain allows for an evolutionary well-preserved fight or flight response;[5,6] facilitation of pain responses puts the emphasis on tissue damage and forces an individual to seek rest and/or medical attention.[6] In recent years, various experimental (surrogate) expressions of endogenous modulation of pain gained increasing interest in chronic pain research. Conditioned pain modulation (CPM, formerly known as diffuse noxious inhibitory controls or DNIC) has been investigated most intensively and induces central inhibition of a focal pain stimulus by administering a second noxious stimulus at a remote area.[7,8] In contrast to animals, where endogenous inhibition involves activation of a spinal-medullary-spinal feedback loops (*i.e.* DNIC),[9] in humans more complex supraspinal mechanisms also plays an important role (*i.e.* CPM).[7,10] Absent or impaired CPM responses have been observed in several chronic pain states.[8,11-13] Defects in CPM possibly reflect the inability to engage descending inhibition, either causing the perseverance of pain symptoms or possibly even leading to the development of chronic pain. For example, recent animal data show that less efficient descending inhibition is associated with a high probability of chronic pain development following peripheral nerve injury.[14,15]

Few studies address the effect of analgesic medication on CPM responses in chronic pain patients. It can be hypothesized that chronic pain patients may benefit from analgesics that enhance descending inhibition as measured by CPM.[14,16] A recent study showed that duloxetine-induced improvement of CPM responses correlated with drug efficacy in patients with painful diabetic neuropathy.[16] Hence, the positive effect of analgesics on CPM might have a predictive effect on their ability to cause (long-term) analgesia. In the current study, we assessed the effect of morphine and ketamine on CPM responses in a group of patients with chronic painful peripheral neuropathy. Both treatments are effective in chronic pain patients, but their effects on CPM responses have only been tested in volunteers but not in chronic pain patients. We hypothesized that both drugs enhance CPM responses and that the magnitude of these responses correlates positively with the magnitude and duration of spontaneous pain relief.

Methods

Approval of the study was obtained from the local human ethics committee, and written informed consent was obtained from all subjects. The study was registered in the Dutch trial register (www.trialregister.nl) under trial number NTR2005.

Subjects

Ten patients with chronic pain were recruited to participate in the study. They were diagnosed with chronic peripheral neuropathic pain and included on the basis of their symptoms, the results of quantitative sensory testing (QST) and a neurological examination.[17-19] Subjects were required to have at least two of the following symptoms in legs, arms or both (in a stocking-glove distribution): (i) symmetrical dysesthesias or paresthesias; (ii) burning or painful feet with night-time worsening; or (iii) peripheral tactile allodynia. With respect to the QST the patients were included if they had an abnormal warm and cold detection threshold, an abnormal warm and cold pain threshold, or allodynia.

Before participation, all subjects underwent a physical examination. Exclusion criteria for the study were: age < 18 years or > 80 years; presence or history of a medical disease such as renal, cardiac, vascular (including hypertension) or infectious disease; presence or history of a neurological and psychiatric disease such as increased cranial pressure, epilepsy or psychosis; glaucoma; pregnancy; obesity (body mass index > 30 kg/m^2); or the use of strong opioid medication. Subjects were allowed to continue the following pain medications as long as they used a constant dose for at least 3 months before the start of the study and could be kept constant during the whole study period: acetaminophen, non-steroidal anti-inflammatory drugs, amitriptyline, gabapentin and pregabalin.

Pain assessment and CPM

As examined by Pud and collegues,[7] noxious cold water is the most used pain modality as a conditioning stimulus combined with different pain modalities as test stimulus. We applied a heat pain stimulus as test stimulus and cold water as conditioning stimulus, in agreement with earlier studies from our laboratory and from King and colleagues.[8,20] The test stimulus was a noxious thermal stimulus applied to clinically normal skin of the volar side of the non-dominant forearm (with normal warm and cold thresholds). The skin was stimulated with a 3 × 3 cm thermal probe of the Pathway Neurosensory Analyzer (Medoc Ltd., Ramat Yishai, Israel). During the heat pain stimulus, subjects continuously quantified the pain intensity level of the stimulus using a slider on a computerized potentiometer that ranged from 0 (no pain) to 100 (worst pain imaginable), which allowed continuous, electronic monitoring of the visual analogue scale (eVAS). To overcome sensitization, a 3-minute interval was incorporated between tests and the volar side of the arm was divided into three zones.[8] The thermode was moved from zone to zone between stimuli. The test stimulus was obtained by gradually increasing the thermode temperature from baseline (32 °C) to the test temperature (at 1.5 °C/s). When the test temperature was reached it remained constant for 30 seconds. Next, the temperature rapidly decreased (at 6 °C/s) to baseline.

Before the test, individual test and conditioning temperatures were determined. For the test stimulus, a series of heat stimuli was applied. Baseline temperature was set at 32 °C after which the temperature increased by 1.5 °C/s to tempera-

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tures ranging from 42 °C to 49 °C for 10 seconds. The temperature evoking an eVAS of at least 50 mm was set as test temperature and used during the remainder of the study for the experimental stimulus. Before testing, the thermode was calibrated using a surface thermometer (K-Thermocouple thermometer, Hanna Instruments, Woonsocket, RI).

The conditioning stimulus was cold water immersion in a cold-water bath which was filled and temperature adjusted using a rapid-water cooling system (IcyDip, IcySolutions BV, Delft, The Netherlands).[20] The subject's foot and lower leg was immersed into the cold water reservoir, which could be set at different temperatures ranging from 6 °C to 18 °C. The temperature that produced an eVAS of at least 30 mm was used in the study for the conditioning stimulus. After exposure to cold water, the subject's extremity was immediately warmed to normal temperature using the warm water reservoir of the IcyDip system.

To measure CPM, eVAS responses to the test stimulus were obtained without (n = 3) and with the conditioning stimulus (n = 3).[8,20] The conditioning stimulus was applied 25 seconds before the start of the test stimulus and ended simultaneously with the end of the test stimulus. The subject was instructed to only rate the pain intensity level of the test stimulus with the eVAS slider.

Study design
Each subject visited the laboratory on three days, at least 2 weeks apart, in which placebo, morphine and ketamine were tested using a double-blind, randomized cross-over study design. Initially, CPM was measured without treatment (baseline values). After a break, intravenous treatment was given (infusion duration 1 hour), and 20 minutes later, the CPM responses were repeated. Treatments were as follows: (A) a 1-hour intravenous infusion of 0.57 mg/kg S(+)-ketamine (Ketanest-S, Pfizer BV, Capelle a/d IJssel, The Netherlands); (B) morphine bolus of 0.05 mg/kg followed by 0.015 mg/kg per hour for 1 hour (Morphine HCl, Pharmachemie BV, Haarlem, The Netherlands); and (C) a 1-hour placebo (0.9% NaCl) infusion.

Disease-related pain
The effect of treatment on disease-related pain or spontaneous pain scores was measured after treatment on a 0 – 10 numerical rating scale (NRS). Subjects were contacted after their treatment to determine the duration of pain relief. An arbitrary distinction was made between pain relief lasting 0 – 6 hours post treatment, 6 – 12 hours post treatment and 12 – 24 hours post treatment.

Data and statistical analyses
The difference between the eVAS response to the test stimulus without and with conditioning stimulus is the generated CPM. The eVAS data were averaged over 1-second periods. To quantify CPM, the area under the curve (AUC) of each eVAS response was calculated. For analysis of the relative amount of CPM, the mean of the three AUC responses per condition was calculated (*i.e.* the mean of

the 3 AUCs without conditioning stimulus and the 3 AUCs with the conditioning stimulus). The percentage of CPM (CPM%) was calculated as: CPM% = [(mean AUC without CS stimulus – mean AUC with CS)/(mean AUC without CS)] × 100 (*i.e.* corrected for the variation in the magnitude of the peak response between sessions and between subjects). The drug study was powered to detect a significant difference between treatment effects on CPM%. Assuming a difference between groups of 20% (derived from previous data)[20] with SD 10%, $\alpha = 0.05$ and power = 0.9, we estimated a groups size of 10 (SigmaPlot v12, Systat Software Inc., Chicago IL, USA). A linear mixed model was used to compare the AUCs of the eVAS responses with and without conditioning stimulus within each experimental session. The effect of treatment on CPM% and spontaneous pain scores was tested by one-way analysis of variance with post-hoc Bonferroni correction. Statistical analysis was performed in SigmaPlot version 12.0 for Windows (Systat Software Inc., Chicago IL). *p*-values < 0.05 were considered significant. Data are presented as mean ± SEM unless otherwise stated.

Results

Subjects
All 10 subjects completed the protocol without major side effects. The study population included two men, eight women, and had a mean age of 54.4 ± 4.2 years
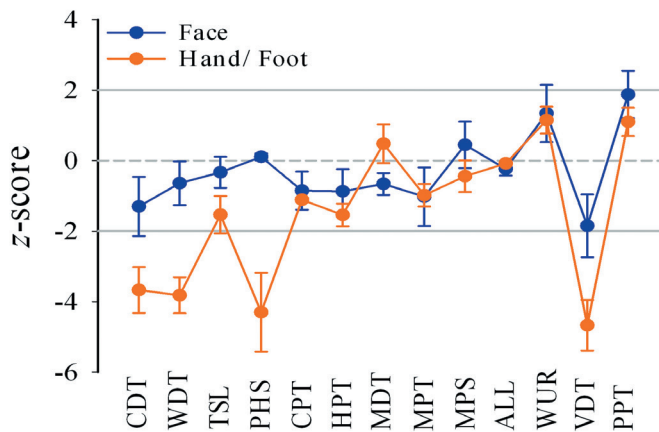

Figure 1. Quantitative sensory testing. The test site was the site most affected by pain (either hand or foot; orange symbols), the control site was the face (blue symbols). Data are the population mean z-scores ± SEM. Z-scores were calculated in relation to a population of healthy subjects as determined by Rolke and collegues.[39] The horizontal broken lines indicate the +2 and -2 z-score boundaries. A specific QST test is considered abnormal if the test value lies above the upper or below the lower boundary. CDT: cold detection threshold; WDT: warm detection threshold; TSL: thermal sensory limen; PHS: paradoxal heat sensation; CPT: cold pain threshold; HPT: heat pain threshold; MDT: mechanical detection threshold; MPT: mechanical pain threshold; MPS: mechanical pain sensitivity; ALL: dynamic mechanical allodynia; WUR: windup ratio; VDT: vibration detection threshold; PPT: pressure pain threshold.

and mean weight of 83.6 ± 7.6 kg. All suffered from chronic neuropathy with signs of mixed small and large fiber neuropathy on the QST (significant abnormalities in cold detection threshold, warm detection threshold, paradoxal heat sensation and vibration detection threshold (Fig. 1). The patients were diagnosed with diabetes mellitus (n = 4), sarcoidosis (n = 2) and Sjögren's syndrome (n = 1). In three subjects the origin of the pain was unknown. Feet were affected in all subjects; in four subjects the hands were affected as well. Subjects used the following medication during the study: acetaminophen, non-steroidal anti-inflammatory drugs, gabapentin, pregabalin and amitriptyline.
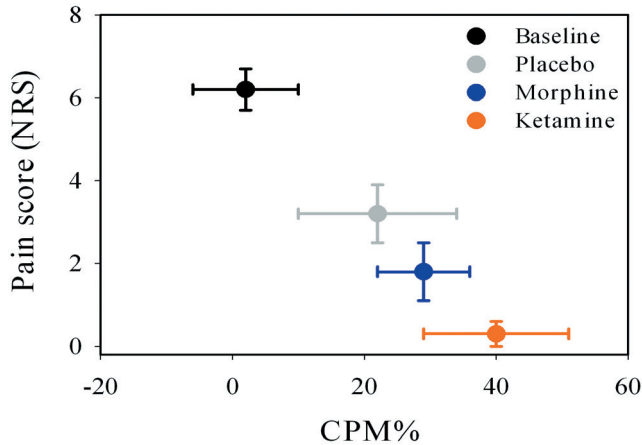
CPM responses

Average test and conditioning stimulus temperatures were 45.1 ± 0.1 °C and 9.8 ± 1.0 °C, respectively. At baseline, the average eVAS scores were 43.0 ± 2.4 mm and after treatment 49.0 ± 3.4 mm, 50.1 ± 2.9 mm and 51.1 ± 2.9 mm for ketamine, morphine and placebo, respectively. No significant CPM responses were detected before treatment: AUC without conditioning stimulus 1180 ± 71 mm·sec compared with AUC with conditioning stimulus 1080 ± 79 mm·sec ($p > 0.05$). After all three treatments, significant CPM was detected indicating an inhibitory effect of the cold water conditioning stimulus on the experimental heat pain stimulus. Placebo AUCs were reduced by the conditioning stimulus from 1241 ± 209 to 862 ± 135 mm·sec ($p = 0.001$); morphine AUCs were reduced from 1503 ± 224 to 1049 ± 185 mm·sec ($p < 0.001$); ketamine reduced the AUCs from 1352 ± 118 to 809 ± 159 mm·sec ($p = 0.000$) (Fig. 2A). Ketamine caused the largest increase in CPM: mean CPM% after placebo 22.1 ± 12.0% (95% confidence interval (95% CI): -5.1 –
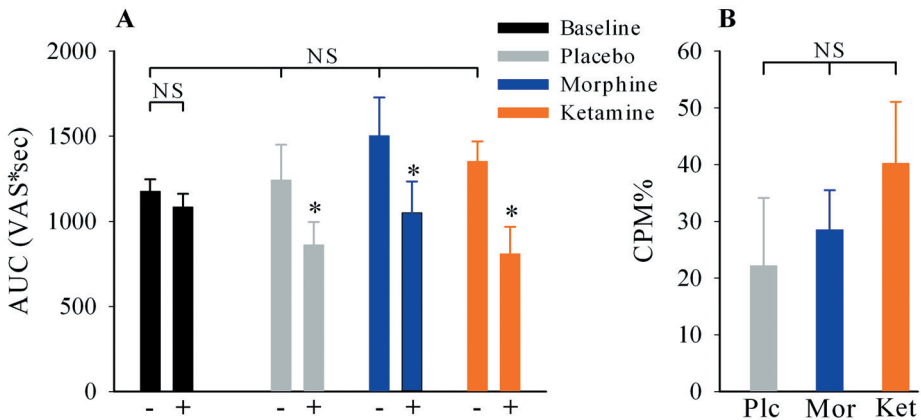
Figure 2. A. *AUC values of the eVAS-time responses without conditioning stimulus (–) and with conditioning stimulus (+). The conditioning stimulus had no effect on baseline responses, but decreased eVAS responses after treatment with placebo, morphine and ketamine. * p < 0.001 vs AUC of eVAS-time responses without conditioning stimulus. AUCs of responses without the conditioning stimulus were similar for baseline, placebo, morphine and ketamine. NS = not significant.* ***B.*** *Magnitude of conditioned pain modulation (CPM%) responses after treatment with placebo (Plc), morphine (Mor) and ketamine (Ket). The magnitude of CPM% responses did not differ among treatments.*

Figure 3. Conditioned pain modulation (CPM% responses) versus spontaneous pain ratings in chronic pain patients. Data are mean ± SEM.

49.3), after morphine 28.5 ± 7.0% (95% CI: 12.8 – 44.3) and after ketamine 40.2 ± 10.9% (95% CI: 15.6 – 64.6); however no difference in CPM enhancement could be detected between the three treatment groups ($p > 0.05$, see also Fig. 2B).

Pain relief and magnitude of CPM
The mean NRS at baseline was 6.2 ± 0.5. In terms of magnitude, pain relief was greatest after ketamine (mean NRS after treatment: 0.3 ± 0.3, $p < 0.01$ *vs*. baseline), followed by morphine (1.8 ± 0.7) and placebo (3.2 ± 0.7). In terms of duration of effect, ketamine had effects lasting > 12 hours in eight of 10 subjects and > 6 hours in the remaining two subjects. Morphine had effects lasting > 12 hours in zero of 10 subjects, > 6 hours in eight of 10 subjects and < 6 hours in the remaining two subjects. After placebo treatment all analgesic effects had dissipated within 6 hours of treatment. The magnitude of CPM correlated positively with the magnitude of pain relief (Fig. 3) and duration of spontaneous pain relief.

Side effects after analgesic treatment
Minor side effects occurred with nausea in four subjects (two of whom vomited) during ketamine infusion and in seven patients (four of whom vomited) during morphine infusion. No nausea or vomiting was observed during placebo infusion. At the end of the infusion, the mean drug high scores were 7.2 ± 0.6 for ketamine, 2.4 ± 0.5 for morphine and 0.4 ± 0.2 for placebo.

Discussion

We tested CPM responses in a relatively homogenous population (in terms of QST abnormalities) of subjects with chronic pain related to peripheral neuropathy. The main findings of our explorative studies are that CPM responses were not detectable in this patient population, but that treatment with ketamine, morphine and placebo caused activation of CPM responses ($p < 0.001$). The magni-

tude of CPM responses correlated positively with the magnitude and duration of spontaneous pain relief.

Descending inhibitory and facilitatory pathways involved in the modulation of pain originate at higher sites in the CNS including the prefrontal cortex, rostral anterior cingulate cortex (rACC) and insula, which project to the periaquaductal gray and rostral ventromedial medulla (RVM) and modulate nociceptive input at the level of the dorsal horn.[1-4,6] Activation of inhibitory pathways will reduce trafficking of nociceptive input to supraspinal sites involved in pain processing and perception. Activation of facilitatory pathways will have the reverse effect. A shift in the balance between inhibition and facilitation has been suggested as an underlying mechanism in the development or maintenance of pain.[20] There are various expressions of descending inhibitory pain modulation, including place-bo and stress-induced analgesia and CPM.[3,21,22] CPM is considered to be a central mechanism with activation of specific brain regions involved in descending in-hibition.[23,24]

Dysfunctional endogenous pain modulation (as tested by CPM or CPM-like par-adigms) has been observed in several chronic pain states.[8,11-13,25] In our current study we included patients with chronic (poly)neuropathic pain (from mixed small and large fiber neuropathy who all displayed abnormal CPM responses. Previous studies in healthy volunteers showed that females have less efficient CPM responses compared to males and that CPM efficiency decreases with in-creasing age (starting at middle-age).[26-29] Indeed, in a separate set of healthy peo-ple of similar age and sex as our current study population, we did not observe significant CPM responses (M. Niesters, unpublished observation). Since the pa-tient population in this study was predominantly middle-aged and female, CPM responses were a priori not expected or were at least assumed to be small. Our data and those of others indicate that patients of 40 years and older (especially females) have absent of less activated pain modulation mechanisms (compared to younger patients) and are therefore at a disadvantage in situations where a functional descending inhibitory mechanism is necessary for normal pain per-ception. Consequently, in response to a noxious insult, pain may be more severe and persistence of pain may occur, which possibly is one of the factors involved in the development of chronic pain. There is indeed evidence from animal stud-ies for a link between chronic pain development and efficacy of descending in-hibitory pain pathways. Animals with more efficient engagement of descending inhibition show a reduced probability of peripheral nerve injury-induced chron-ic allodynia compared with animals with less efficient descending inhibition.[14,15]

A novel observation in our study is that CPM responses in neuropathic pain pa-tients could be re(activated) after pharmacological treatment and that ketamine, morphine and placebo were equally effective in this respect. The large effect of a 1-hour intravenous treatment with placebo was not unexpected. There is ample evidence that activation of descending pain control underlies placebo-analge-sia, via central opioidergic mechanisms.[22,30] For example Levine and collegues[30]

showed that placebo analgesia is abolished by the opioid receptor antagonist naloxone. Furthermore, animal research demonstrated that remifentanil and placebo analgesia both activate brain areas involved in descending inhibition including the rACC.[31]

An important finding in our study is that there was a significant correlation between the magnitude of CPM responses and the magnitude (and duration) of spontaneous pain relief (Fig. 3). As stated by De Felice and colleagues,[14] such findings provide a mechanistic explanation for medications that engage descending inhibitory control or mimic its consequences and cause efficient and long-term pain relief, such as we observed after treatment with ketamine. To the best of our knowledge our study is the first to show that morphine enhances CPM responses in chronic neuropathic pain patients. Recently, Arendt-Nielsen and colleagues[32] tested the effect of two opioid analgesics (fentanyl and buprenorphine transdermal patches) on CPM in healthy volunteers and showed enhanced responses after treatment. In contrast to these and our data, others observed that morphine reduces rather than increases CPM responses in healthy volunteers (after an intravenous infusion of 0.05 mg/kg) and non-neuropathic chronic pain patients (after prolonged opioid treatment).[33,34] We have no conclusive explanation for these differences in the effect of opioid treatment on CPM engagement. Involvement of endogenous opioids in CPM engagement is inferred from studies showing that naloxone reduces CPM.[35] Furthermore, opioid receptors are expressed on neurons involved in pathways of descending pain modulation both at spinal and supraspinal sites.[1-3]

Similar to morphine, ketamine enhanced CPM responses in our patient population. Ketamine has gained a position in the treatment of chronic pain, especially of therapy-resistant neuropathic pain.[36] Ketamine treatment results in prolonged analgesia, with persistence of effect beyond the treatment period. For example, we showed previously that a 100-hour ketamine infusion (20-30 mg/h) results in pain relief up to 3 months after intravenous treatment in patients with complex regional pain syndrome type 1.[37] The mechanisms through which ketamine exerts these prolonged effects remain unknown. Possibly one of the factors that contribute to ketamine's prolonged analgesic effect is desensitization of upregulated N-methyl-D-aspartate receptors within the spinal cord.[37] Another mechanism might be that ketamine activates endogenous pain modulatory pathways. The observation that ketamine produced greater analgesia than morphine (or placebo) in our patient population correlated with a greater ability to engage descending inhibition as tested by CPM (Fig. 3). Recently, we assessed the effect of ketamine on brain function using the technique of resting-state functional magnetic resonance imaging. Ketamine altered connectivity in brain regions responsible for pain sensing and the affective processing of pain, and also in regions involved in activation of descending inhibitory pain pathways, including the rACC, insula, orbitofrontal cortex and brain stem.[38] These findings corroborate our observation of ketamine's effect on CPM in neuropathic pain patients.

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The effects of ketamine on CPM responses in chronic patients differ from results in volunteers.[20] In a population of healthy young volunteers, ketamine shifted the balance between pain inhibition and pain facilitation towards pain facilitation. Major differences between study populations (*i.e.* age and underlying disease) could be responsible for the difference in study outcomes. For example, in healthy volunteers, CPM responses may be at maximum strength such that treatment leads to activation of interfering pathways (facilitatory pathways). This may also explain the effect of morphine on CPM in healthy volunteers and possibly also in chronic non-neuropathic pain patients.[33,34] We can also not exclude that treatment at maximum CPM activates noise sources resulting in inconsistencies in the data.

Critique of methods
One might contend that no population of healthy age- and sex-matched controls was included to make a comparison of treatment effects between groups possible. However, as discussed above, healthy volunteers lack underlying disease, that is a primary hit (*i.e.* peripheral nerve damage) and possibly also secondary damage (*i.e.* a defect in the descending inhibitory control system) of their pain pathways. Although we believe that knowledge on the effect of treatment on CPM responses in volunteers is valuable on its own, we argue that a direct comparison between populations is of limited value, as treatment induced changes in CPM responses in volunteers may differ mechanistically from those in patients.

Subjects were allowed to continue their pain medication as long as they had used these drugs for at least 3 months and dosages were constant during the study period. Subjects that used pain medication did not have a larger (or smaller) enhancement of CPM responses compared with those that did not. Therefore, we do not believe that continuation of analgesics during the study period affected our outcome.

Finally, we tested a small group of predominant middle-aged female pain patients. While this reflects the majority of chronic pain patients in clinical practice, our study needs replication in younger patients (including males) with neuropathic pain. This will further clarify the link between sex, age, defective CPM responses and chronic pain.

Conclusions
In chronic neuropathic pain patients with similar QST abnormalities, treatment with placebo, morphine and ketamine activated prior absent CPM responses, suggesting a role of engagement of descending pain inhibition in their analgesic efficacy. We suggest that in clinical practice, drugs that cause enlargement of re-engagement of CPM should be the first drugs of choice in the treatment of chronic (neuropathic) pain.

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