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Chapter 5

Tapentadol potentiates Descending Pain Modulation in Chronic Pain Patients with Diabetic Polyneuropathy

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Introduction

Endogenous pain modulatory pathways are important regulators of human pain perception. Both inhibitory and facilitatory descending pathways, originating at higher centers, modulate the activity of nociceptive neurons at the level of the spinal dorsal horn, enhancing or inhibiting noxious signal propagation to the brain.[1] A shift in the balance between pain inhibition and facilitation has been suggested to underlie the development or maintenance of many chronic pain syndromes, such as fibromyalgia, irritable bowel syndrome, chronic pancreatitis and neuropathic pain syndromes.[2-5] Animal studies show that effective engagement of descending inhibition protects against chronic neuropathic pain development.[9] Various neurotransmitter systems are involved in the descending pain pathways including endogenous opioid peptides, noradrenaline (NA) and serotonin. Release of endogenous opioids and noradrenaline underlie pain inhibition, whereas the serotonergic pathway has both pain inhibitory and facilitatory properties.[7,8] The new analgesic tapentadol is a centrally acting drug with a dual mechanism of action. Tapentadol is a weak μ-opioid receptor (MOR) agonist (its affinity for the MOR is 50 times less than that of morphine) and inhibits neuronal reuptake of noradrenaline.[9,10] Both mechanisms act synergistically to produce analgesia.[11] Animal studies indicate that the opioidergic component is more important in the treatment of acute pain, whereas the noradrenergic component is largely involved in the treatment of chronic neuropathic pain.[8]

As tapentadol modulates opioidergic and noradrenergic pathways simultaneously, the analgesic effect of tapentadol is thought to rely on the enhancement of descending pain inhibitory activity.[12] However, up to know, no studies have been conducted to confirm the presence of such an effect in humans. In the current study the effects of tapentadol on two experimental paradigms, conditioned pain modulation (CPM) and offset analgesia (OA) were tested in chronic pain patients with diabetic polyneuropathy (DPN). CPM is an experimental measure of endogenous pain modulation that gates incoming pain signaling as consequence of a preceding or simultaneous tonic painful stimulation.[13-18] OA is a test in which a disproportionally large amount of analgesia becomes apparent upon a slight decrease in noxious heat stimulation.[19,20] Both tests have been used previously to evaluate the engagement of pain modulatory pathways.[4,15,20]

We performed a randomized, parallel-design, placebo-controlled study in chronic pain patients with diabetic polyneuropathy on the effect of a 4-week tapentadol treatment on CPM, OA and pain relief. We hypothesize that tapentadol's analgesic efficacy relies, in part, on the engagement of endogenous pain inhibitory pathways.

Methods

Chronic pain patients were recruited to participate in the study performed at Leiden University Medical Center over the period January 2012 to October 2012, after approval of the protocol was obtained from the local Medical Ethics Committee and the Central Committee on Research involving Human Subjects (CCMO, The Hague, The Netherlands). The study was registered at the Dutch trialregister under number NTR2716 and has EudraCT number 2010-012175-26. The study was registered as an addendum to an earlier trial on the effects of a single dose of tapentadol and morphine on CPM. All participants gave written informed consent and underwent a physical examination before enrollment in the study.

Patients were recruited via an advertisement in the journal of the national diabetic society. All recruited patients had diabetes and chronic pain in hands and/or legs and feet. They were included in the study when they were 18-75 years, had a body mass index below ≤ 40 kg/m^2 and had: (1) presence of at least two of the following symptoms in legs and/or arms (in a stocking-glove distribution): (i) symmetrical dysesthesias or paresthesias, (ii) burning or painful feet with nighttime worsening or (iii) peripheral tactile allodynia; and (2) an abnormal warm or cold detection threshold, an abnormal warm or cold pain threshold, or allodynia observed with quantitative sensory testing. Exclusion criteria included: indication of the presence of severe medical diseases (*e.g.* liver function elevation); allergy to opioids; current use of benzodiazepines and/or other sedatives; present or past use of illicit/recreational substances; present or past alcohol abuse; history of mental illness or epilepsy; pregnancy and/or lactation; current use of strong opioids; and inability to understand the purpose and instructions of the study. The patients were allowed to continue the following pain medications as long as they used a constant dose for the 8 weeks prior to the study and the dosage could be kept constant during the whole study period: acetaminophen, non-steroidal anti-inflammatory drugs, amitriptyline, gabapentin and pregabalin. Patients that had been using opioids previously (and terminated treatment due to absence of efficacy or side effects) were eligible for inclusion.

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Study design

This randomized, double blind, placebo-controlled study was performed in 24 DPN patients (see Consort flow chart, Fig. 1). Twelve patients were treated orally for 4 weeks with tapentadol slow release (SR), twelve others with placebo. The dose of tapentadol SR was titrated to effect starting with 100 mg twice daily in week 1, followed by 200 mg twice daily in week 2 and 250 mg twice daily in week 3 and 4. In case of the presence of side effects unacceptable to the patient, the tapentadol dose was decreased to a dose were side effects were absent or acceptable. All patients were tested twice, once 1 day before the treatment period and once on the last day of treatment. On each study day, the subjects were familiarized with the test procedures. Next the CPM and OA responses were obtained. Spontaneous pain scores (using a 11-point numerical rating scale (NRS) from 0

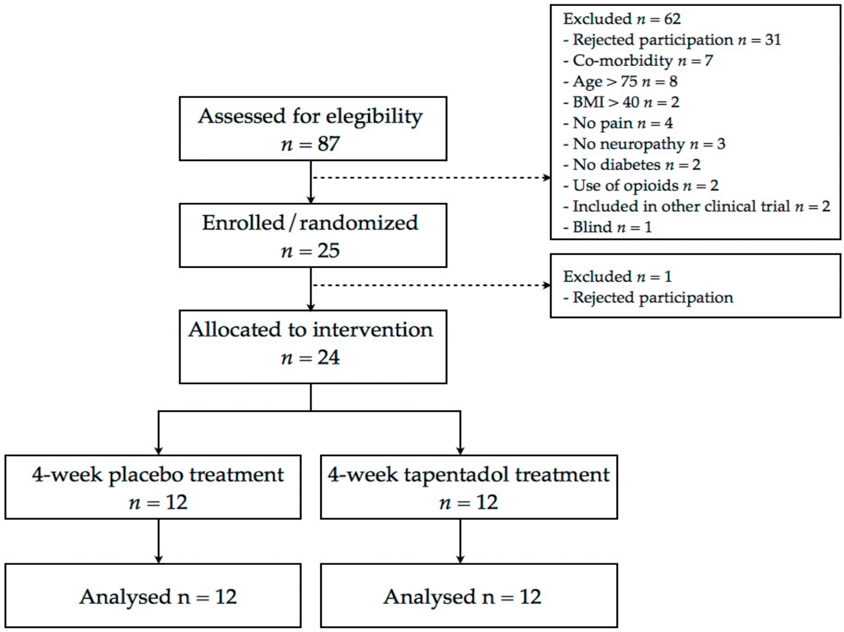

Figure 1. *Consort study flow chart.*

(corresponding with no pain) to 10 (corresponding with most imaginable pain)) and side effects (presence of nausea, vomiting, drowsiness, dizziness and dry mouth, using a dichotomous scale (yes/no)) were monitored on a weekly basis.

To get an indication of the nerve-fiber involvement in the patient population, quantitative sensory testing (QST) was performed according to the standardized protocol of the German Research Network on Neuropathic Pain.[21] In short, this protocol assesses cold, heat and mechanical detection and pain thresholds; paradoxical heat sensations; mechanical pain sensitivity; allodynia; wind-up and vibration and pressure pain thresholds. Sensory testing was performed on the hand and foot of all pain patients included in the study.

Application of nociceptive stimuli for CPM and OA testing

Heat pain was induced on the lower part of the non-dominant arm with a 3 x 3 cm thermal probe connected to the Pathway Neurosensory Analyzer (Medoc Ltd., Ramat Yishai, Israel). The probe was calibrated according to the specifications of the manufacturer. During the heat pain stimulation, 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). This allowed for continuous monitoring of the visual analogue scale (eVAS). To overcome sensitization, the thermode was moved between different zones on the forearm and ample time was incorporated between the different heat stimuli. On each of the two study days (that is before treatment and at 4-weeks of treatment), the individual test temperature was determined by applying a series of heat stimuli. First the temperature was increased from 32 °C (baseline temperature) by 1.5 °C/s to a target temperature of 42 °C and kept constant for 10 seconds. If the eVAS was less then 50 mm a next test was performed increasing the target temperature in steps of 1 °C. The cut-off temperature for these series was 49 °C. The temperature evoking an eVAS of at least 50 mm was used during the remainder of the study.

Cold pain was induced using a cold-water reservoir produced by a rapid water-cooling system (IcyDip, IcySolutions BV, Delft, The Netherlands). 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 remainder of the study. After the exposure to cold water, the subject's extremity was warmed to normal temperature using warm water collected from the counter-current outlet of the IcyDip system.

Conditioned pain modulation and offset analgesia

The method to induce CPM has been published previously.[2,4,15] In short, to measure CPM two series of three pain tests were performed. One series included stimulation of the forearm with the experimental stimulus (heat pain). For this, the temperature of the heat probe gradually increased from baseline temperature (32 °C) to the earlier set test temperature (at 1.5 °C/s) and remained constant for 30 seconds. Next, the temperature rapidly returned (at 6 °C/s) to baseline. The second series included stimulation with both the experimental stimulus and the conditioning stimulus (cold pain). The conditioning stimulus was applied 25 seconds before the start of the experimental stimulus and ended simultaneously with the end of the experimental stimulus. In both sessions the subject's only rated the pain intensity level of the experimental stimulus (heat pain on the arm). There were 3-minute intervals between single tests.

OA was studied by applying a three-temperature paradigm as described by Grill et al.[19] The temperature was ramped at 1.5 °C/s from baseline temperature to the previously set test temperature. The test temperature was kept constant for 5 seconds after which it was raised by 1 °C for 5 seconds and next decreased by 1 °C for 20 seconds. At the end of the test the temperature quickly returned (6 °C/s) to baseline. This temperature paradigm was applied three times with a 3-min interval between tests.

Randomization and blinding

Randomization and allocation was performed by the local pharmacy using a computer-generated randomization list. Placebo tablets were fabricated by the pharmacy and were identical to the tapentadol tablets in form, size and taste. The tablets were repackaged into unmarked containers and delivered to the research team and subsequently by the research team to the patients. The research team remained blinded to treatment until all CPM and OA responses had been analyzed.

Table 1. *Patient characteristics*

	Tapentadol	Placebo
Men/Women (*n*)	7/5	7/5
Age (years; median (range))	63 (54 - 75)	62 (53 - 71)
Weight (kg; median (range))	95 (56 - 140)	97 (71 - 125)
Height (cm; median (range))	177 (169 - 196)	178 (168 - 194)
Duration of disease		
Diabetes mellitus (years; median (range))	12 (3 - 35)	11 (2 - 45)
Neuropathic pain (years; median (range))	6 (1 - 10)	6.5 (2 - 25)
Affected limbs		
Legs (*n*)	8	8
Legs + arms (*n*)	4	4
Medication		
Insulin	8	6
Metformin	11	7
Pregabalin	3	2
Duloxetin	2	0
Amitriptyline	1	1
Steroids	0	2
Paracetamol	1	1

Data analyses

To quantify the magnitude of CPM, peak eVAS scores were used in the analyses. For each subject, the average peak eVAS without and with conditioning stimulus (CS) was calculated. Next, relative CPM responses were calculated to correct for variations in peak response between sessions and subjects using the formula: [(mean eVAS without CS stimulus – mean eVAS with CS)/(mean eVAS without CS)] × 100%.[2,26,27]

OA responses were quantified as previously described.[15,20] In short, the decrease in eVAS from the peak eVAS value to the eVAS nadir following the 1 °C decrease of the test stimulus was measured (ΔeVAS) and corrected for the value of the peak eVAS: ΔeVASc = [ΔeVAS/(peak eVAS)] x 100%.

Sample size and statistical analysis

A sample size of 24 (12 per treatment level) was calculated by assuming an increase in CPM of 20% (15%) (mean (SD)) with $\alpha = 0.05$ and $\beta > 0.95$. An effect of 20% was chosen as this constitutes the "average" value of CPM in healthy volunteers and is probably the maximum magnitude of CPM attainable in humans.[15]

The effect of the conditioning stimulus on the relative eVAS responses was tested by two-tailed paired-t-test. Treatment effects were assessed by two-way repeated measures analysis of variance (factors: time and treatment). For all analyses, the software package SigmaPlot version 12.5 for Windows (Systat Software Inc., San Jose, CA) was used. Data are presented as mean ± SEM unless otherwise stated and *p*-values < 0.05 were considered significant.

Results

Eighty-seven patients responded to the advertisement (Fig. 1). Thirty-one decided not to participate after they were informed on the nature of the study. Thirty-one others were excluded because of absence of pain, diabetes or neuropathy (as assessed by QST), not meeting age- or body mass index-related inclusion criteria, the use of strong opioids or their inclusion in another trial. Twenty five subjects were enrolled in the study and randomized. One patient retracted her consent after randomization; she was replaced by another subject. The demographics of the participating patients are given in table 1.

All patients completed the study without major side effects. QST measurements obtained from affected hands and feet are presented in figure 2. The patients presented with a mixed small- and large fiber neuropathy as evidenced by re-

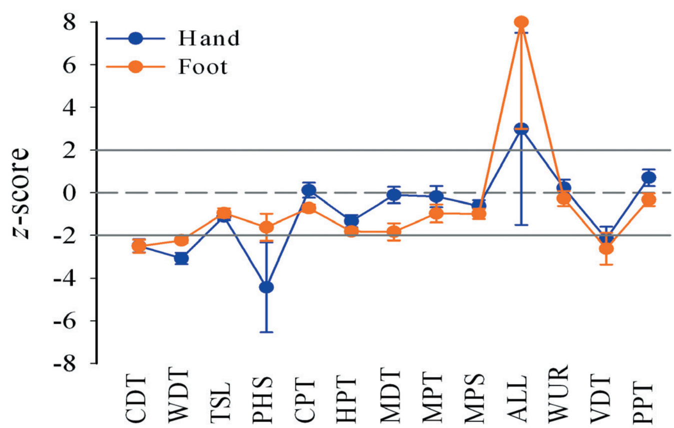

Figure 2. *Results of the quantitative sensory tests obtained on the affected skin areas (hand/feet). The data are the populations mean z-scores (SEM). Z-scores were calculated in relation to a population of healthy subjects as determined by Rolke et al.*[21] *Z-values above the broken line indicate a gain of function whereas values below this line are indicative for a loss of sensory function. CDT: cold detection threshold; WDT: warm detection threshold; TSL: thermal sensory limen; PHS: paradoxal heat sensations; 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.*

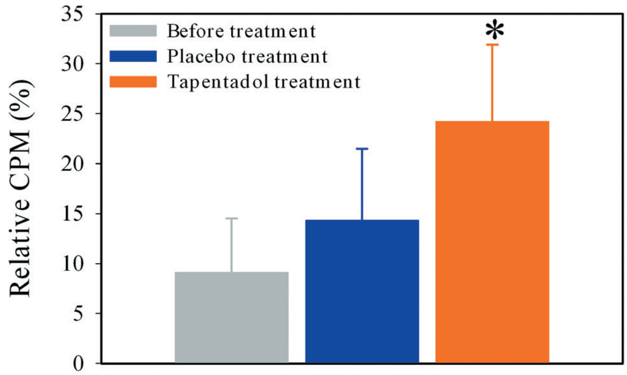

Figure 3. *Relative CPM responses at baseline (before treatment), in patients receiving a 4-week placebo treatment and in patients receiving a 4-week tapentadol treatment. At baseline the effect of the conditioning stimulus was not significant (p = 0.09). After placebo and tapentadol treatment the effect of the conditioning stimulus was significant (placebo p = 0.04, tapentadol p < 0.01). A treatment effect was present with greater increase in CPM responses during tapentadol treatment than during placebo treatment (* p < 0.001 vs. placebo).*

duced cold and warm detection thresholds and paradoxical heat sensation (signs of small fiber involvement) and a reduced vibration detection threshold (on the feet more than on the hands; a sign of large fiber involvement). Importantly, allodynia was observed in 7 (of 24) patients. During the study period the daily drug dose was titrated to a level with sufficient analgesic effect and acceptable side effects to the patients. In the placebo group the maximum daily dose of 500 mg per day was reached in all subjects compared to an average of 433 ± 31 mg per day in the tapentadol SR group. Reported side effects were nausea (placebo: n =

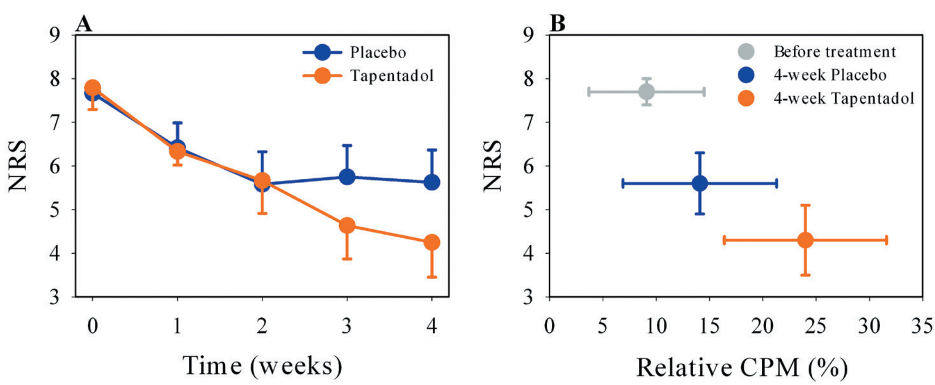

Figure 4. A. *Average spontaneous pain scores of patients with painful diabetic neuropathy during the 4-week treatment period. There was a significant treatment effect with greater pain relief during tapentadol treatment (p = 0.03).* ***B.*** *Relative CPM responses versus pain scores. Values are mean ± SEM.*

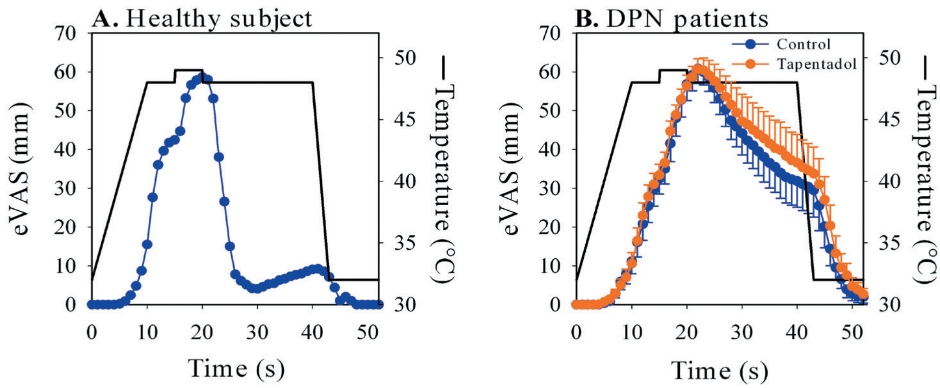

Figure 5. *Offset analgesia responses.* ***A.*** *An example of a healthy subject (female, 60 years). Data taken from ref. 20.* ***B.*** *Absence of tapentadol treatment on offset analgesia in painful diabetic neuropathy patients. DPN: diabetic polyneuropathy; eVAS: electronic visual analogue scale.*

4; tapentadol: n = 3), vomiting (placebo: n = 0; tapentadol: n = 2), sedation (placebo: n = 2; tapentadol: n = 6), dizziness (placebo: n = 2; tapentadol: n = 6) and dry mouth (placebo: n = 1; tapentadol: n = 5).

Prior to treatment significant CPM responses were not detectable as the effect of the conditioning stimulus was not significant (CPM = 9.1 ± 5.4%, p = 0.09, Fig. 3). Following both treatments CPM responses increased to significant levels (placebo: CPM = 14.3 ± 7.2%, p = 0.04; tapentadol SR: CPM = 24.2 ± 7.7%, $p < 0.01$). A clear treatment effect was present with tapentadol SR CPM responses being greater than placebo responses ($p < 0.001$, Fig. 3).

Weekly pain scores following tapentadol and placebo treatments are given in figure 4A. It shows a clear distinction in pain reduction in weeks 3 and 4 of treatment with greater analgesia in patients treated with tapentadol SR (pain scores at baseline 6.5 ± 0.6 reduced to 4.8 ± 0.7 following placebo and 3.9 ± 0.6 following tapentadol; 4-week treatment effect p = 0.03). Plotting pain relief *versus* CPM responses shows that greater pain relief from tapentadol SR coincided with enhanced CPM responses (Fig. 4B).

OA responses prior to tapentadol treatment and at week 4 of treatment are given in figure 5. As contrast, an example of an OA response in age and sex-matched healthy volunteer is added in figure 5A (data from ref. 20). ΔeVASc values in healthy volunteers in the age cohort 40-80 range between 90 and 100%, irrespective of sex.[20] Prior to treatment ΔeVASc was 40.7 ± 7.4%. Neither placebo (change from baseline +2.6 ± 11.6%) nor tapentadol SR treatment (change from baseline -0.8 ± 3.7%) had an effect in the magnitude of OA (treatment effect p = 0.78).

Discussion

Tapentadol is a new centrally acting analgesic agent for treatment of acute and chronic pain,[12,22-25] that acts through MOR agonism and neuronal noradrenaline reuptake inhibition (NRI).[8-10,26] Through this dual mechanism of action it is thought that tapentadol engages and potentiates descending pain inhibitory pathways,[12] although there are no human studies to substantiate this. We studied tapentadol's effect on two experimental paradigms of endogenous pain modulation (CPM and OA) in chronic pain patients with DPN. The main findings of our studies are that in DPN patients tapentadol SR caused significant pain relief that coincided with enhanced CPM responses. No effect of tapentadol was observed on OA responses. Taken these results we reason that relief of chronic pain in DPN patients by tapentadol is associated with engagement and potentiation of descending inhibitory pain pathways.

Conditioned pain modulation

Modulation of pain in humans involves activation of higher cortical centers (prefrontal cortex, anterior cingulate cortex, insula), brainstem (periaquaductal gray, rostral ventromedial medulla) and descending pathways projecting to the dorsal horn of the spinal cord.[1,27,28] These descending pathways may be inhibitory or excitatory. Consequently, nociceptive input that enters the spinal dorsal horn will undergo some form of modulation, either facilitation or inhibition, which results in an amplified or inhibited pain sensation at central sites. Various chronic pain syndromes show loss of descending pain inhibition, including fibromyalgia, irritable bowel syndrome, chronic tension headache, temperomandibular disorder, complex regional pain syndrome and chronic pancreatitis.[2-5] Of importance is the finding by De Felice *et al.* who showed in rodents that a genetic predisposition to activate descending inhibition protects against the development of chronic pain following peripheral nerve damage.[6] In humans, examples of efficacious engagement of descending inhibitory pain modulation include placebo analgesia, stress-induced analgesia and CPM.[16-18,29,30] CPM is an experimental and consequently surrogate tool used to quantify descending pain inhibition in humans. Central inhibition of a focal noxious stimulus is induced by the administration of a noxious stimulus at a remote area (conditioning stimulus), thereby reducing the perception of the focal or test pain stimulus ("pain inhibits pain").[13,16] The central nature of CPM has been ascertained by the observation that specific brain regions involved in descending inhibition are activated during CPM-tests in volunteers.[31,32]

Volunteer studies show that CPM engagement is less effective in women relative to men and that CPM efficacy is reduced in elderly people (starting at middle-age).[33,35] Indeed in our middle-aged DPN patient population (mean age 59 years) CPM was not present prior to the intake of study medication. Whether this is related to the underlying disease or an age-effect is unknown. Irrespective, individuals that are less able to activate CPM may have a higher probability of chronic pain development following a specific insult such as peripheral nerve damage from diabetes (cf. De Felice *et al*.[6]) or surgery. Yarnitsky *et al.* showed that patients with less efficient CPM responses were at risk for development of chronic post-thoracotomy pain.[17] The method of induction of CPM has been validated previously by us in healthy volunteers and is applied and others in chronic pain patients.[15,17]

Taken its mechanisms of action, tapentadol will interact within the descending modulatory system by activation of MORs and inhibition of neuronal noradrenaline reuptake.[7,8] Both neurotransmitter systems play an important role in the activation of descending inhibitory pain pathways at supraspinal sites as well as in the spinal dorsal horn (at pre- and postsynaptic sites). See for an excellent review on this topic ref. 1. For example, animal studies show that activation of MORs on brainstem nociceptive "on-cells" will release the inhibition of brainstem nociceptive "off-cells" that project to the spinal dorsal horn where nociceptive signal propagation is subsequently inhibited.[1] Activation of spinal dorsal horn pre- and postsynaptic α_2-adrenergic receptors will cause potent analgesic responses by inhibiting nociceptive afferent input. Such analgesic effects are observed after the intrathecal administration of the postsynaptic α_2-adrenergic receptor agonist clonidine.[36] Although tapentadol displays weak MOP-receptor affinity, animal studies show that its synergistic effect at MOP- and adrenergic-receptor systems will cause potent analgesic responses.[9,10,26] Indeed, animal studies and clinical trials show that tapentadol is an effective analgesic in a variety of chronic pain syndromes (for example osteoarthritis pain, low back pain, neuropathic pain).[8,12,25,37,38]

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We observed that the analgesic efficacy of analgesic treatment (tapentadol/placebo) was coupled to its effect on CPM (Fig. 4). A 4-week treatment with placebo caused small analgesic effects (ΔNRS = 1.7 cm) coupled to a modest increase in CPM (+14.3%), while tapentadol treatment caused a larger analgesic response (ΔNRS = 3.9) coupled to a large CPM response (+24.2%). This latter CPM value is similar to those observed in young healthy volunteers.[14] These findings support a mechanistic role for the endogenous analgesia system in producing effective pain relief by tapentadol, possibly by its synergistic effect at MOP and α_2-adrenergic receptors (see above). Yarnitsky *et al.*[18] showed a coupling between drug efficacy and magnitude of CPM responses for duloxetine, a serotonin-noradrenaline reuptake inhibitor (SNRI) in DPN patients with initially less effective CPM responses. While our small patient population, with initially minor or absent CPM responses benefited from the 4-week tapentadol SR treatment, we remain uninformed on the efficacy of tapentadol in chronic pain patients with "normal" CPM responses (*i.e.* responses of similar magnitude to those observed in young and healthy volunteers). Extrapolating the duloxetine data from Yarnitsky *et al.* would suggest that tapentadol is less effective in these patients. There is now ample evidence to argue that in painful neuropathy patients with absent or reduced CPM, CPM responses may be reactivated or potentiated by analgesic treatment that targets one or more components of the endogenous pain modulatory system.[4,18]

In chronic pain patients, the effect of tapentadol SR requires several weeks to develop (Fig. 3). Similar observations have been made for other S(N)RI-type of analgesics and tricyclic antidepressants.[39] Hence, it is recommended to evaluate the start of pain therapy with these agents not earlier than after 2 weeks of treatment.[40] Taken the similarities of mechanisms of action among these analgesics, we argue that the slow accumulation of noradrenaline at its putative effector sites may be held responsible for its slow onset of action. Our findings stress the importance of the noradrenergic component in inducing tapentadol analgesia in chronic pain as was earlier observed in animal studies.[8]

Two patients in the tapentadol group used duloxetine (duration of treatment > 1 year), a serotonin and noradrenaline reuptake inhibitor without opioidergic activity. Theoretically, the use of this drug may have enhanced the CPM responses induced by tapentadol. However, prior to tapentadol treatment these patients had no detectable CPM response and the magnitude of their CPM response after the 4-week tapentadol treatment was well within the range observed in patients not on duloxetine. We argue that these two patients did not confound the results of our study.

Offset analgesia
OA is a relatively novel model of endogenous analgesia that produces temporal alterations in pain processing. The phenomenon occurs when a small decrease (1 °C) in temperature during noxious stimulation evokes a disproportionately large decrease in pain perception.[19,20] We previously assessed OA responses in a large population of volunteers aged 6-88 years and observed response values ranging from 92-99%. It has been suggested that OA is of central origin as functional imaging studies show that OA activation coincides with activation of brain regions involved in the central modulation of pain.[41] However, it cannot be excluded that OA is initiated by dynamic responses of primary afferents or spinal processes. For example, Darian-Smith *et al.*[42] reported that in monkeys the discharge of heat-sensitive nerve fibers innervating the skin was nearly completely suppressed during a 10 second 1 °C cooling pulse from a baseline temperature of 39 °C. A similar mechanism may occur during OA activation. A peripheral origin of OA is further supported by the observation that central acting drugs such as opioids (tapentadol, morphine, remifentanil), opioid antagonists (naloxone) and NMDA receptor antagonists (ketamine) are unable to affect OA responses in volunteers and neuropathic pain patients.[15,20,43] Finally, a recent observation that while offset analgesia is present on the forearm of healthy volunteers, it is absent on the palm of the hand further suggests that peripheral mechanisms are important in the development of offset analgesia.[44]

We reproduce our earlier observation that OA responses are absent or reduced in patients with peripheral neuropathy.[20] The ΔeVASc values observed in the DPN patients were about 40% of those previously observed by us in healthy volunteers of the same age and sex.[20] No improvement or alteration of OA responses was observed after the 4-week tapentadol treatment, which indicates that this phenomenon of endogenous analgesia is without opioidergic or noradrenergic involvement. However, it may well be that the large and small nerve fiber damage that was present in our current population prevented their ability to discern small changes in skin temperature and consequently prevented peripheral activation of OA.

Conclusions

In conclusion, our results show that patients with DPN that display absent CPM responses benefit from tapentadol causing pain relief coupled to (re)-activation of descending inhibitory pain pathways.

References

1. Ossipov MH, Dussor GO, Porreca F. Central modulation of pain. *J Clin Invest* 2010; 120: 3779-87
2. King CD, Wong F, Currie T et al. Deficiency in endogenous modulation of prolonged heat pain in patients with Irritable Bowel Syndrome and Temporomandibular Disorder. *Pain* 2009; 143: 172-8
3. Lautenbacher S, Rollman GB. Possible deficiencies of pain modulation in fibromyalgia. *Clin J Pain* 1997; 13: 189-96
4. Olesen SS, Brock C, Krarup AL et al. Descending Inhibitory Pain Modulation is Impaired in Patients with Chronic Pancreatitis. *Clin Gastroenterol Hepatol* 2010; 8: 724-30.
5. Seifert F, Kiefer G, DeCol R et al. Differential endogenous pain modulation in complex-regional pain syndrome. *Brain* 2009; 132: 788-800
6. De Felice M, Sanoja R, Wang R et al. Engagement of descending inhibition from the rostral ventromedial medulla protects against chronic neuropathic pain. *Pain* 2011; 152: 2701-9
7. Kress HG. Tapentadol and its two mechanisms of action: is there a new pharmacological class of centrally-acting analgesics on the horizon? *Eur J Pain* 2010; 14: 781-3
8. Schröder W, Vry JD, Tzschentke TM et al. Differential contribution of opioid and noradrenergic mechanisms of tapentadol in rat models of nociceptive and neuropathic pain. *Eur J Pain* 2010; 14: 814-21
9. Tzschentke TM, Christoph T, Kogel B et al. (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol hydrochloride (tapentadol HCl): a novel mu-opioid receptor agonist/norepinephrine reuptake inhibitor with broad-spectrum analgesic properties. *J Pharmacol Exp Ther* 2007; 323: 265-76
10. Tzschentke TM, De Vry J, Terlinden R et al. Tapentadol HCl, analgesic, mu-opioid receptor agonist, noradrenaline reuptake inhibitor. *Drugs Future* 2006; 31: 1053–61
11. Suzan E, Midbari A, Treister R et al. Oxycodone alters temporal summation but not coniditioned pain modulation: preclinical findings and possible ralations to mechanisms of opioid analgesia. *Pain* 2013; 154: 1413-8
12. Steigerwald I, Muller M, Kujawa J et al. Effectiveness and safety of tapentadol prolonged release with tapentadol immediate release on-demand for the management of severe, chronic osteoarthritis-related knee pain: results of an open-label, phase 3b study. *J Pain Res* 2012; 5: 121-38
13. Arendt-Nielsen L, Andresen T, Malver LP et al. A double-blind, placebo-controlled study on the effect of buprenorphine and fentanyl on descending pain modulation: a human experimental study. *Clin J Pain* 2012; 28: 623-7
14. Niesters M, Aarts L, Sarton E et al. Influence of ketamine and morphine on descending pain modulation in chronic pain patients: a randomized placebo-controlled cross-over proof-of-concept study. *Br J Anaesth* 2013; 110: 1010-6
15. Niesters M, Dahan A, Swartjes M et al. Effect of ketamine on endogenous pain modulation in healthy volunteers. *Pain* 2011; 152: 656-63
16. Yarnitsky D, Arendt-Nielsen L, Bouhassira D et al. Recommendations on terminology and practice of psychophysical DNIC testing. *Eur J Pain* 2010; 14: 339

17. Yarnitsky D, Crispel Y, Eisenberg E et al. Prediction of post-operative pain: Pre-operative DNIC testing identifies patients at risk. *Pain* 2008; 138: 22-8
18. Yarnitsky D, Granot M, Nahman-Averbuch H et al. Conditioned pain modulation predicts duloxetine efficacy in painful diabetic neuropathy. *Pain* 2012; 153: 1193-8
19. Grill JD, Coghill RC. Transient analgesia evoked by noxious stimulus offset. *J Neurophysiol* 2002; 87: 2205-8
20. Niesters M, Hoitsma E, Sarton E et al. Offset analgesia in neuropathic pain patients and effect of treatment with morphine and ketamine. *Anesthesiology* 2011; 115: 1063-71
21. Rolke R, Baron R, Maier C et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. *Pain* 2006; 123: 231-43
22. Frampton JE. Tapentadol immediate release: a review of its use in the treatment of moderate to severe acute pain. *Drugs* 2010; 70: 1719-43
23. Hoy SM. Tapentadol extended release in adults with chronic pain. *Drugs* 2012; 72: 375-93
24. Schwartz S, Etropolski M, Shapiro DY et al. Safety and efficacy of tapentadol ER in patients with painful diabetic peripheral neuropathy: results of a randomized-withdrawal, placebo-controlled trial. *Curr Med Res Opin* 2011; 27: 151-62
25. Steigerwald I, Muller M, Davies A et al. Effectiveness and safety of tapentadol prolonged release for severe, chronic low back pain with or without a neuropathic pain component: results of an open-label, phase 3b study. *Curr Med Res Opin* 2012; 28: 911-36
26. Tzschentke TM, Folgering JH, Flik G et al. Tapentadol increases levels of noradrenaline in the rat spinal cord as measured by in vivo microdialysis. *Neurosci Lett* 2012; 507: 151-5
27. Bingel U, Tracey I. Imaging CNS modulation of pain in humans. *Physiology* (Bethesda) 2008; 23: 371-80
28. Millan MJ. Descending control of pain. *Prog Neurobiol* 2002; 66: 355-474
29. Eippert F, Bingel U, Schoell ED et al. Activation of the opioidergic descending pain control system underlies placebo analgesia. *Neuron* 2009; 63: 533-43
30. Yilmaz P, Diers M, Diener S et al. Brain correlates of stress-induced analgesia. *Pain* 2010; 151: 522-9
31. Brock C, Olesen SS, Valeriani M et al. Brain activity in rectosigmoid pain: unraveling conditioning pain modulatory pathways. *Clin Neurophysiol* 2012; 123: 829-37
32. Moont R, Crispel Y, Lev R et al. Temporal changes in cortical activation during conditioned pain modulation (CPM), a LORETA study. *Pain* 2011; 152: 1469-77
33. Edwards RR, Fillingim RB, Ness TJ. Age-related differences in endogenous pain modulation: a comparison of diffuse noxious inhibitory controls in healthy older and younger adults. *Pain* 2003; 101: 155-65
34. Larivière M, Goffaux P, Marchand S et al. Changes in pain perception and descending inhibitory controls starts at middle age in healthy adults. *Clin J Pain* 2007; 23: 506-10
35. Lautenbacher S, Kunz M, Burkhardt S. The effects of DNIC-type inhibition on temporal summation compared to single pulse processing: does sex matter? *Pain* 2008; 140: 429–35
36. Ginosar Y, Riley ET, Angst MS. Analgesic and sympathicolytic effects of low-dose intrathecal clonidine compared with bupivacaine: a dose-response study in female volunteers. *Br J Anaesth* 2013; 111: 256-63
37. Afilalo M, Etropolski MS, Kuperwasser B et al. Efficacy and safety of tapentadol extended release compared with oxycodone controlled release for the management of moderate to severe chronic pain related to osteoarthritis of the knee: a randomized, double-blind, placebo- and active-controlled phase III study. *Clin Drug Investig* 2010; 30: 489–50.
38. Bunyak R, Shapiro DY, Okamoto A et al. Efficacy and safety of tapentadol extended release for the management of chronic low back pain: results of a prospective, randomized, double-blind, placebo- and active-controlled Phase III study. *Exp Opin Pharmacother* 2010; 11: 1787-1804
39. Chappell AS, Desaiah D, Liu-Seifert H et al. A double-blind, randomized, placebo-controlled study of the efficacy and safety of duloxetine treatment of chronic pain due to osteoarthritis of the knee. *Pain Practice* 2011; 11: 33-41
40. O'Conner AB, Dworkin RH. Treatment of neuropathic pain: an overview of recent guidelines. *Am J Med* 2009; 122: S22-32
41. Derbyshire SW, Osborn J. Offset analgesia is mediated by activation in the region of the periaqueductal grey and rostral ventromedial medulla. *Neuroimage* 2009; 47: 1002-6

42. Darian-Smith J, Johnson KO, LaMotte C et al. Warm fibers innervating palmar and digital skin of the monkey: responses to thermal stimuli. *J Neurophysiol* 1979; 42: 1297-315
43. Martucci KT, Eisenach JC, Tong C et al. Opioid-independent mechanisms supporting offset analgesia and temporal sharpening of nociceptive information. *Pain* 2012; 153: 1232-43
44. Naugle KM, Cruz-Almeida Y, Fillingim RB et al. Offset analgesia is reduced in older adults. *Pain* 2013; 154: 2381-7