

UC Irvine

UC Irvine Previously Published Works

Title

Changes in morphine reward in a model of neuropathic pain

Permalink

<https://escholarship.org/uc/item/4jt435mk>

Journal

Behavioural Pharmacology, 24(3)

ISSN

0955-8810

Authors

Cahill, Catherine M
Xue, Lihua
Grenier, Patrick
et al.

Publication Date

2013-06-01

DOI

10.1097/fbp.0b013e3283618ac8

Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, available at <https://creativecommons.org/licenses/by/4.0/>

Peer reviewed

Changes in morphine reward in a model of neuropathic pain

Catherine M. Cahill^{a,d}, Lihua Xue^a, Patrick Grenier^a, Claire Magnussen^a, Samantha Lecour^a and Mary C. Olmstead^{b,c}

In addition to sensory disturbances, neuropathic pain is associated with an ongoing and persistent negative affective state. This condition may be reflected as altered sensitivity to rewarding stimuli. We examined this hypothesis by testing whether the rewarding properties of morphine are altered in a rat model of neuropathic pain. Neuropathic pain was induced by chronic constriction of the common sciatic nerve. Drug reward was assessed using an unbiased, three-compartment conditioned place preference (CPP) paradigm. The rats underwent two habituation sessions beginning 6 days after surgery. Over the next 8 days, they were injected with drug or vehicle and were confined to one CPP compartment for 30 min. On the following test day, the rats had access to all three compartments for 30 min. Consistent with the literature, systemic administration of morphine dose-dependently increased the CPP in pain-naïve animals. In rats with neuropathic pain, however, the dose-dependent effects of morphine were in a bell-shaped curve, with a low dose of morphine (2 mg/kg) producing a greater CPP than a higher dose of morphine (8 mg/kg). In a separate group

of animals, acute administration of morphine reversed mechanical allodynia in animals with neuropathic pain at the same doses that produced a CPP. The increased potency of systemic morphine to produce a CPP in animals with neuropathic pain suggests that the motivation for opioid-induced reward is different in the two states. *Behavioural Pharmacology* 24:207–213 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Behavioural Pharmacology 2013, 24:207–213

Keywords: chronic pain, conditioned place preference, neuropathic pain, opioid, reward

Departments of ^aBiomedical and Molecular Science, ^bPsychology, ^cCentre for Neuroscience Studies, Queen's University, Kingston, Ontario, Canada and ^dDepartment of Anesthesiology and Perioperative Care, University of California, Irvine, California, USA

Correspondence to Catherine M. Cahill, PhD, Department of Anesthesiology and Perioperative Care, University of California, 2125, Gillespie Neuroscience, 837 Health Science Road, Irvine, CA 92697, USA
E-mail: cmcahill@uci.edu

Received 5 November 2012 Accepted as revised 15 March 2013

Introduction

Neuropathic pain, caused by various central and peripheral nerve disorders, results in chronic and intractable pain. Treatment of this condition is particularly challenging as it is typically refractory to both conventional (opioids) and nonconventional (antidepressants and antiepileptics) analgesics; the use of these medications is limited, further, by intolerable side-effects (Gilron *et al.*, 2006; Dworkin *et al.*, 2010). In addition to the marked sensory disturbances that result in pain hypersensitivity (allodynia and hyperalgesia), neuropathic pain is associated with tonic ongoing pain and adverse affective and emotional states. The negative affect, or how much the pain is 'bothersome', significantly impacts the quality of life of the sufferer and leads to the common comorbidities of psychiatric disorders such as depression. Comorbidity between chronic pain and axis I disorders of the DSM-IV has been well documented, where depression is the most common comorbidity, with some studies finding a prevalence rate approaching 100% among clinical chronic pain samples (reviewed by Nicholson and Verma, 2004). In fact, chronic pain is second only to bipolar disease as the major cause of suicide among all medical illnesses, further highlighting the importance of negative affect in this condition (Juurink *et al.*, 2004).

Although it can be argued that treating the affective aspect of pain has as much clinical relevance as alleviating

the sensory aspects of pain, much less is known about pain affect compared with the vast knowledge of mechanisms underlying sensory disturbances in pain transmission. Drug reward is frequently assessed in animals using the conditioned place preference (CPP) paradigm, which measures time spent in an environment previously associated with motivationally salient stimuli (e.g. drugs or food). In recent years, this test has also been used to measure the tonic aversive component of ongoing pain (King *et al.*, 2009). Using this paradigm, spinal administration of a local anesthetic or the $\alpha 2$ adrenergic agonist clonidine, a drug used clinically to alleviate pain, elicited a CPP in neuropathic pain, but not sham, animals (King *et al.*, 2009). This suggests that neural circuitry engaged by analgesic drugs is distinct in neuropathic and pain-naïve states. In contrast, opioids, including morphine, a strong analgesic and drug of abuse that activates hedonic reward circuits, are reported to be less rewarding in animals with neuropathic pain (Ozaki *et al.*, 2002, 2003; Oe *et al.*, 2004; Martin *et al.*, 2007; Petraschka *et al.*, 2007; Niikura *et al.*, 2008). In addition, neuropathic pain suppresses the opioid-induced potentiation of electrical self-stimulation in the ventral tegmental area (Ewan and Martin, 2011). One interpretation of these findings is that the blunted analgesic effect of opioids in chronic pain is because of alterations in neural systems responsible for reward as their analgesic

effects are strongly linked to their rewarding capacity (Franklin, 1989).

Although our understanding of the neural circuitry in reward states has advanced significantly (Wise, 2008; Volkow *et al.*, 2012), how motivation is modified by pain remains relatively unexplored. Such studies would be informative not only in understanding the neural mechanisms of affective states in chronic pain but also in helping to understand why analgesics have limited efficacy in treating neuropathic pain. In this study, we used a CPP paradigm in neuropathic pain and surgery control animals to determine the effectiveness of systemic morphine in eliciting a reinforcing effect. This involved determining the dose-dependent effects of morphine in neuropathic pain states.

Methods

Subjects

Adult male Long–Evans rats (220–250 g at the beginning of experimentation; Charles River, St Constant, Quebec, Canada) were maintained on a reverse 12-h light/dark cycle and allowed free access to food and water. Experiments were conducted during the dark phase and in accordance with protocols approved by the Queen's University Animal Care Committee and according to the guidelines set forth by the Canadian Council on Animal Care and the International Association for the Study of Pain Committee for Research and Ethical Issues. After arrival within the housing facility, animals were allowed to acclimatize for 3–4 days before any handling. The experimenter performed all handling processes including cage changing, food and water replacement, surgery, and drug injections.

Surgery

Rats were assigned randomly to either surgery to induce neuropathic pain, sham, or naive (no surgery) groups. Rats undergoing sham or peripheral nerve injury received an analgesic preoperatively (acetaminophen 32 mg/ml, 0.25 ml/100 g orally) and were anesthetized with gaseous isoflurane (induction at 5% and maintenance at 2.0–2.5% in oxygen). Rats received 5 ml lactated ringers saline and 0.04 ml/100 g tribriksen 24% subcutaneously perioperatively. The lateral left thigh was shaved, and surgery was performed under aseptic conditions. A skin incision was made, followed by blunt dissection to expose the sciatic nerve. Peripheral nerve injury was performed as described previously (Bennett and Xie, 1988). Briefly, four ligatures (4.0 chromic gut) were tied loosely around the nerve so that the total length of the nerve affected was 3–5 mm. Care was taken to ensure that the nerve was not pinched by the ligatures and that these were not too tight to prevent the occlusion of perineural blood flow. The separated muscle was stitched and the incision was closed with 3-0 monocryl. The sham animals received similar surgery, but without manipulation of the nerve. After surgery and recovery from anesthesia, rats were returned

to their cage with food and water freely available (soft food or Jello was provided to any rat that did not appear to be eating well). Rats also received a Jello cube containing 50 mg of acetaminophen the evening of surgery and on day 1 postoperatively. Because of the nature of the study, no opioid analgesic was administered postoperatively as these may affect the outcome of the results.

Conditioned place preference apparatus

CPP experiments were conducted in a three-compartment apparatus consisting of two large compartments of equal size (45 × 45 × 30 cm) joined by a gray tunnel (18 × 18 × 30 cm). The two large compartments were distinguished by visual cues (black and white stripes or unpainted wood). Different floor textures (e.g. grid versus sawdust) could evoke more pain in animals with neuropathic pain; therefore, tactile cues in the large compartments were distinguished by different patterns of wire-grid flooring. Beam breaks were recorded when animals entered and left each compartment. This information was sent to a PC computer with software written in-house.

Conditioned place preference paradigm

The CPP protocol included habituation, conditioning, and testing phases. The first was initiated 6 days after surgery (or not, in naive animals): on 2 consecutive days, rats were placed in the tunnel and allowed to explore the entire apparatus for 30 min. None of the rats showed a significant preference for one of the large compartments, indicating that the boxes were unbiased (Table 1). During the subsequent eight daily conditioning sessions, rats in each group (neuropathic pain, sham, and naive) were injected with either drug or vehicle and confined to one of the large compartments for 30 min. The order of injection (drug vs. vehicle) as well as the drug-paired compartment were counterbalanced within groups. Drug-free testing occurred on the day immediately after conditioning when animals were placed in the tunnel and allowed free access to the entire compartment. The amount of time spent in each compartment was assessed over a 30-min session.

Pain-naive (no surgery), sham, or animals with neuropathic pain were assigned randomly to one of the four doses of morphine (1, 2, 4, and 8 mg/kg, subcutaneously), administered during conditioning sessions. A dose–response curve was generated by conducting multiple experiments, where at least one animal from each group [surgery or not (3) × morphine dose (4)] was included. This helped to minimize the impact of extraneous variables such as time of the year, shipping incident, etc. Animals were used only once and were not retested with a different dose of morphine.

Mechanical withdrawal thresholds

Mechanical withdrawal responses to von Frey filament stimulation were assessed in rats with peripheral nerve

Table 1 Preconditioning times before drug and compartment assignment for all groups

Group to which animals were assigned (dose of morphine) (mg/kg, subcutaneously)	Naïve		Sham		NP pain	
	Left	Right	Left	Right	Left	Right
1	657 (578–736)	659 (582–737)	659 (611–707)	658 (597–720)	672 (557–787)	696 (602–790)
2	643 (579–707)	658 (574–741)	681 (590–773)	667 (604–730)	727 (637–817)	664 (576–752)
4	648 (581–716)	618 (562–674)	685 (611–761)	626 (543–709)	672 (588–757)	681 (601–761)
8	660 (603–718)	653 (581–724)	701 (624–778)	644 (554–733)	675 (572–777)	648 (534–762)

Before drug administration, all animals received one habituation session, where they were placed in the tunnel (neutral compartment) and had free access to the entire apparatus for 30 min. The following day, animals were again placed in the tunnel and the time spent in the left and right compartment was recorded over 30 min to assess any side bias. None of the groups showed a significant preference for one of the large compartments, confirming that this procedure is unbiased.

Data are expressed as mean with lower and upper 95% confidence intervals.

NP, neuropathic.

injury as described previously by Chaplan *et al.* (1994). Rats were placed under opaque Plexiglas boxes positioned on a wire-grid platform (5 × 5 mm mesh), through which von Frey filaments were applied to the plantar surface of the hindpaw in an up-down manner. In brief, filaments were applied in either ascending or descending force as necessary to most accurately determine the threshold of response. The intensity of stimuli ranged from 0.25 to 15 g. From the resulting response patterns, the 50% response thresholds (g) were calculated. Paw withdrawal thresholds were assessed before and on days 4, 7, and 10 after nerve injury in addition to testing 30, 60, and 90 min following systemic morphine injection on day 10 after nerve injury.

Statistical analysis

Data are expressed as the mean (\pm SEM) amount of time (s) spent in the drug-paired and vehicle-paired compartments on the test day for place-preference experiments. A paired student *t*-test was used to compare the amount of time spent in the drug-paired versus the vehicle-paired compartment for each group. In addition, a two-way analysis of variance (ANOVA), with drug dose and group as between-subjects factors, was used to examine differences in the magnitude of preference for the morphine-paired compartment across neuropathic pain, sham, and naive groups. A two-way ANOVA was also used to determine the effects of morphine (1, 2, and 4 mg/kg subcutaneously) on mechanical withdrawal thresholds in animals with neuropathic pain.

Results

The conditioning apparatus was deemed unbiased as there was no significant difference between the times spent in each of the large compartments during the habituation and preconditioning phase (Table 1). Preference for the drug-paired compartment after conditioning to systemic morphine administration is presented in Fig. 1. In sham animals (Fig. 1a), the only dose that produced a significant place preference was the highest dose of morphine tested (i.e. 8 mg/kg) ($t_7 = 5.66$, $P < 0.001$; all other P values > 0.05). In contrast, morphine produced a CPP in animals with

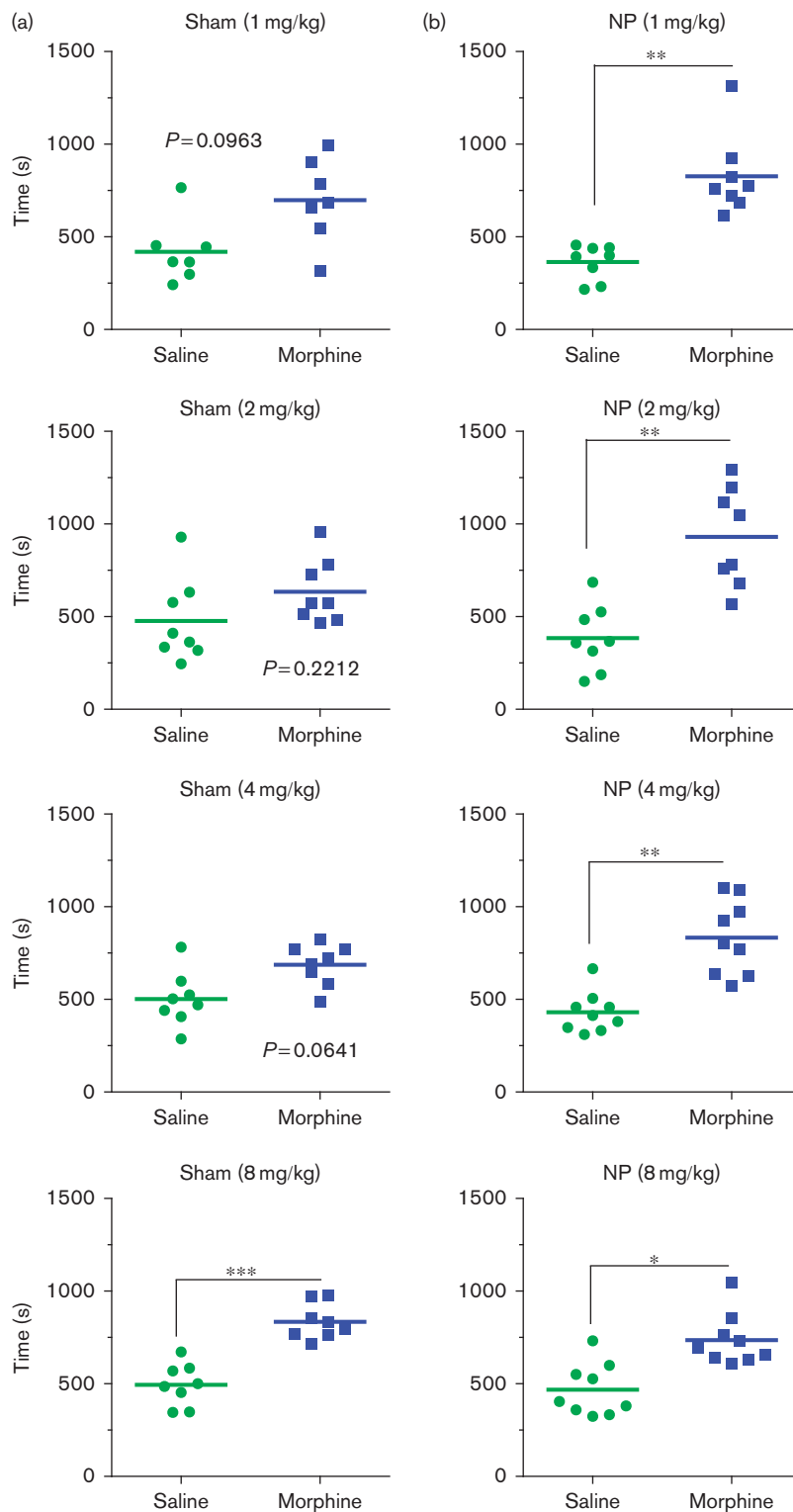
neuropathic pain (Fig. 1b) at all four doses tested: 1 mg/kg ($t_7 = 4.56$, $P < 0.0035$), 2 mg/kg ($t_7 = 4.54$, $P < 0.0035$), 4 mg/kg ($t_8 = 4.55$, $P < 0.002$), and 8 mg/kg ($t_8 = 3.12$, $P < 0.02$). Data from Fig. 1 were transformed into dose-response curves by plotting the time spent in the drug-paired compartment for each dose of morphine in sham and neuropathic pain animals. A naive (nonsurgical) group was also included in this data set to determine any effect of sham surgery on the place preference. Figure 2 shows the dose-dependent effect of morphine in all three groups. A two-way ANOVA showed a significant effect of group [$F_{(2,114)} = 9.49$, $P < 0.001$] and dose [$F_{(3,114)} = 2.73$, $P < 0.05$]. A significant interaction was also present [$F_{(6,114)} = 3.29$, $P < 0.01$].

In a separate group of animals, the ability of systemic administration of morphine to attenuate pain hypersensitivity associated with peripheral nerve injury was evaluated. Mechanical withdrawal thresholds were significantly lower 7 and 10 days after nerve injury as determined by a two-way ANOVA [time: $F_{(3,20)} = 51.36$, $P < 0.001$, Fig. 3a], but there was no significant difference between groups [treatment assignment: $F_{(3,20)} = 0.74$]. Acute administration of all three doses of morphine tested attenuated mechanical allodynia in neuropathic animals, as assessed by stimulation with von Frey filaments [treatment assignment: $F_{(3,20)} = 17.91$, $P < 0.001$, Fig. 3b]. Post-hoc analysis showed that the antiallodynic effects produced by the two lowest doses of morphine were only significant at the 30-min timepoint, whereas 4 mg/kg morphine attenuated mechanical pain hypersensitivity at 60 and 90 min after the morphine injection.

Discussion

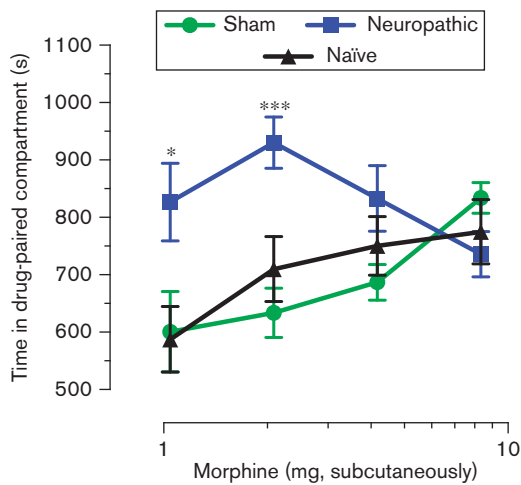
The principal findings of this study are that morphine can elicit a rewarding effect in neuropathic pain, but the dose dependency of this effect was bell shaped, where low doses that did not produce a CPP in naive or sham animals produced a CPP in chronic pain animals. In addition, preference for the drug-paired compartment was greater with lower, rather than higher, doses of morphine in animals with neuropathic pain. These effects correlate with the ability of morphine to alleviate

Fig. 1



Dose-dependent effects of morphine (1, 2, 4, and 8 mg/kg, subcutaneously)-induced conditioned place preference in (a) sham and (b) neuropathic (NP) animals. Data are expressed as a scatter plot with mean and SEM of the time spent in the morphine-paired and vehicle-paired compartment. Statistical analysis showed a significant effect of only the highest dose of morphine (8 mg/kg) in sham animals (** $P<0.001$). However, statistical analysis showed that all doses of morphine tested were significantly different compared with the time spent in the vehicle-paired compartment in the neuropathic animals (1 mg/kg, ** $P<0.005$; 2 mg/kg, ** $P<0.005$; 4 mg/kg, ** $P<0.002$; 8 mg/kg, * $P<0.02$). $n=8-15$ /group.

Fig. 2

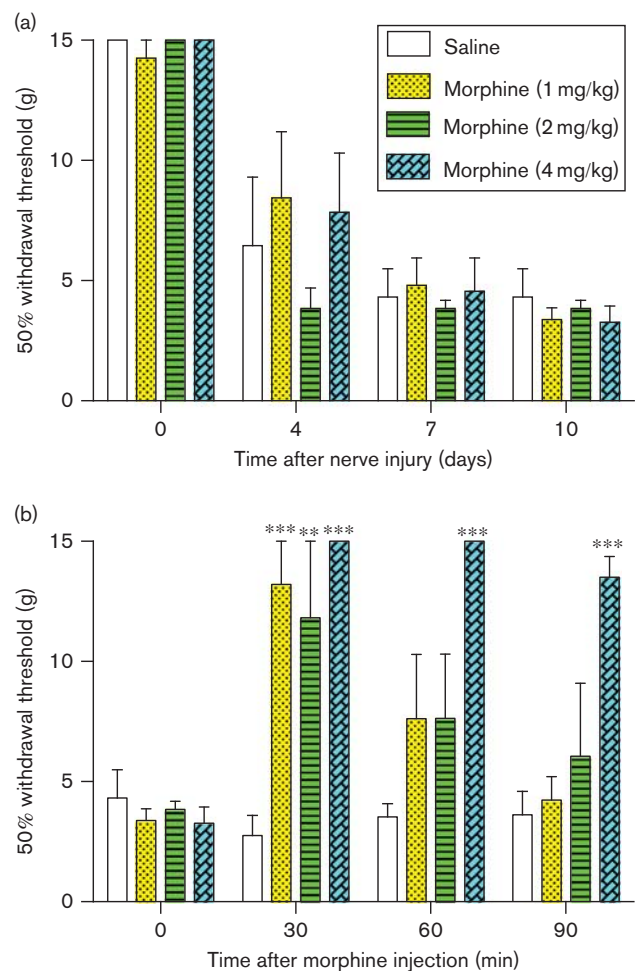


Dose-dependent morphine-induced conditioned place preference in pain-naïve, sham, and neuropathic animals. A two-way analysis of variance showed a significant effect of group [$F_{(2,114)}=9.45$, $P<0.001$] and dose [$F_{(3,114)}=2.73$, $P<0.05$]. A significant interaction was also present [$F_{(6,114)}=3.291$, $P<0.01$]. A Bonferroni multiple comparison post-hoc analysis showed a significant difference between neuropathic and sham or naïve groups at the 1 and 2 mg/kg doses. Data are expressed as mean \pm SEM ($n=8-15$ /group, * $P<0.05$, *** $P<0.001$).

mechanical allodynia, as evidenced by an increase in mechanical withdrawal thresholds.

The primary finding that low doses of opioids produced a CPP in neuropathic pain, but not in pain-naïve, animals was unexpected. This finding is not consistent with the reports showing a reduced place preference to opioid analgesics compared with sham animals. Specifically, a CPP to morphine (4 and 8 mg/kg, subcutaneously) was attenuated in neuropathic pain, compared with sham, rats (Ozaki *et al.*, 2002). The methodological differences between the present study and that of Ozaki and colleagues are that their study was on a normal light-dark cycle, used Sprague-Dawley rats, nerve injury was a spared nerve injury rather than chronic constriction, conditioning was for 1 h rather than 30 min, conditioning occurred for 6 days rather than 8 days, and commenced 4 days after surgery. They did not report the time spent in the nondrug-paired compartment, only the difference between morphine and saline compartments in sham and neuropathic pain animals. In addition, the same research group reported that the time spent in the drug-paired compartment was significantly reduced after sciatic nerve ligation when mice were conditioned to tramadol or its active metabolite (Nakamura *et al.*, 2008). A reduction in morphine CPP was also reported in mice with peripheral nerve injury (Petraschka *et al.*, 2007). However, this latter study exposed animals to morphine daily (conditioning twice a day) and implicated desensitization of opioid receptors because of the release of endogenous opioids in

Fig. 3



The acute antiallodynic effects of morphine in peripheral nerve-injured animals were evaluated using the von Frey test. Mechanical withdrawal thresholds before and on days 4, 7, and 10 after nerve injury (a). Differences in bar appearance are only for assignment of drug group in (b). No drugs were administered to animals for data presented in (a). On day 10, mechanical withdrawal thresholds were assessed 30, 60, and 90 min after morphine administration (1, 2, and 4 mg/kg subcutaneously) in separate groups of animals (b). Data represent mean \pm SEM for $n=4-6$ /group. Statistical analyses using a two-way analysis of variance showed a significant effect of time and treatment (** $P<0.01$, *** $P<0.001$).

the attenuated place preference in animals with neuropathic pain. As no previous study examined more than two doses of morphine to examine opioid preference in neuropathic pain and pain-naïve states, we constructed a dose-response curve to compare the sensitivity of morphine in these two states. Contrary to expectations, our data showed that animals with neuropathic pain spent more time in the drug-paired compartment with low doses of morphine (≤ 2 mg/kg) compared with the pain-naïve animals, but this effect was not observed with higher doses. Interestingly, Woller *et al.* (2012) also reported greater morphine reward in animals with central neuropathic pain resulting from spinal cord injury.

This latter study used doses similar to the present study, where low doses between 1 and 2 mg/kg produced a CPP in chronic pain, but not in sham or naive groups.

It remains unknown why our results differ from those of other previously published studies. However, a few methodological differences are worth reflecting on. First, a potential explanation for the reduced CPP observed by others is the occurrence of opioid receptor desensitization (Ozaki *et al.*, 2002, 2003; Oe *et al.*, 2004) or that the protocols used for conditioning to morphine exposed animals to opioids daily rather than every other day (Petraschka *et al.*, 2007). In addition, endogenous opioid release in the brain of animals with neuropathic pain may facilitate exogenous opioid-induced desensitization of μ -opioid receptors. In support of this hypothesis, there is a reduction in opioid-induced GTP γ S activation in the ventral tegmental area (Ozaki *et al.*, 2002) and an increase in μ -opioid receptor phosphorylation in the striatum of animals with neuropathic pain (Petraschka *et al.*, 2007). Moreover, it has been proposed that the release of endogenous opioids partially mediates this decreased effect, as animals with neuropathic pain lacking the opioid peptide β endorphin show similar reinforcing effects to morphine as pain-naive animals (Petraschka *et al.*, 2007; Niikura *et al.*, 2008). Second, another possible explanation for the discrepancies between the present study and the previous literature may involve circadian rhythms, as our studies were carried out in the active (dark) phase, whereas previous studies were carried out on rodents in the light phase. Pain because of several pathological conditions shows temporal variations in intensity throughout the circadian cycle. This diurnal variation is multifactorial and may be affected by endogenous fluctuations in neuroendocrine or other factors, as well as external influences, which affect touch-induced pain and levels of physical activity. Clinical impressions suggest that neuropathic pain is often worse at night (Belgrade, 1999; Odrich *et al.*, 2006). Indeed, a clinical study identified that neuropathic pain intensity increases progressively throughout the day and this temporal profile appears to be unaffected by treatment with gabapentin and/or morphine (Odrich *et al.*, 2006). To our knowledge, no study has directly compared pain hypersensitivities associated with neuropathic pain in the light and dark phases; however, it is well established that opioid-induced analgesia is shifted to the left in the active (dark) phase (Bornschein *et al.*, 1977). Nevertheless, these results suggest that the motivation for opioid-induced reward is different in animals with neuropathic pain compared with pain-naive groups, and this warrants further research on how chronic pain alters reward circuitry.

Conclusion

It remains unknown why low doses of opioids produce a place preference in animals with neuropathic pain; however, two possibilities prevail. The presence of

morphine-induced CPP could be because of the association of a positive affective state of the drug with contextual cues in the drug-paired compartment. Positive affect is equated with hedonic pleasure but it seems unlikely that lower doses of morphine would induce mechanisms that enhance this state. Rather, we propose that μ -opioid activation induces a CPP because it alleviates pain associated with neuropathy. In this conceptualization, the rewarding effect of the conditioned stimuli is pain relief that most likely encompasses the negative affective (subjective), cognitive, and sensory discriminative components of the pain experience.

Acknowledgements

This work was supported by the Canadian Institutes of Health Research (C.M.C.), the Canada Research Chairs Program (C.M.C.), and the Natural Sciences and Engineering Research Council of Canada (M.C.O. and P.G.). The authors thank Stephanie Metcalfe for her contribution to preliminary data in this study.

Conflicts of interest

There are no conflicts of interest.

References

- Belgrade MJ (1999). Following the clues to neuropathic pain. Distribution and other leads reveal the cause and the treatment approach. *Postgrad Med* **106**:127–132, 135–140.
- Bennett GJ, Xie YK (1988). A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man. *Pain* **33**:87–107.
- Bornschein RL, Crockett RS, Smith RP (1977). Diurnal variations in the analgesic effectiveness of morphine in mice. *Pharmacol Biochem Behav* **6**:621–626.
- Chaplan S, Bach FW, Pogrel JW, Chung JM, Yaksh TL (1994). Quantitative assessment of tactile allodynia in the rat paw. *J Neurosci Methods* **53**:55–63.
- Dworkin RH, O'Connor AB, Audette J, Baron R, Gourlay GK, Haanpää ML, *et al.* (2010). Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. *Mayo Clin Proc* **85** (Suppl):S3–S14.
- Ewan EE, Martin TJ (2011). Rewarding electrical brain stimulation in rats after peripheral nerve injury: decreased facilitation by commonly abused prescription opioids. *Anesthesiology* **115**:1271–1280.
- Franklin KB (1989). Analgesia and the neural substrate of reward. *Neurosci Biobehav Rev* **13**:149–154.
- Gilron I, Watson CP, Cahill CM, Moulin DE (2006). Neuropathic pain: a practical guide for the clinician. *CMAJ* **175**:265–275.
- Juurlink DN, Herrmann N, Szalai JP, Kopp A, Redelmeier DA (2004). Medical illness and the risk of suicide in the elderly. *Arch Intern Med* **164**: 1179–1184.
- King T, Vera-Portocarrero L, Gutierrez T, Vanderah TW, Dussor G, Lai J, *et al.* (2009). Unmasking the tonic-aversive state in neuropathic pain. *Nat Neurosci* **12**:1364–1366.
- Martin TJ, Kim SA, Buechler NL, Porreca F, Eisenach JC (2007). Opioid self-administration in the nerve-injured rat: relevance of antiallodynic effects to drug consumption and effects of intrathecal analgesics. *Anesthesiology* **106**:312–322.
- Nakamura A, Narita M, Miyoshi K, Shindo K, Okutsu D, Suzuki M, *et al.* (2008). Changes in the rewarding effects induced by tramadol and its active metabolite M1 after sciatic nerve injury in mice. *Psychopharmacology (Berl)* **200**:307–316.
- Nicholson B, Verma S (2004). Comorbidities in chronic neuropathic pain. *Pain Med* **5** (Suppl 1):S9–S27.
- Niikura K, Narita M, Narita M, Nakamura A, Okutsu D, Ozeki A, *et al.* (2008). Direct evidence for the involvement of endogenous beta-endorphin in the suppression of the morphine-induced rewarding effect under a neuropathic pain-like state. *Neurosci Lett* **435**:257–262.

- Odrzich M, Bailey JM, Cahill CM, Gilron I (2006). Chronobiological characteristics of painful diabetic neuropathy and postherpetic neuralgia: diurnal pain variation and effects of analgesic therapy. *Pain* **120**:207–212.
- Oe K, Narita M, Imai S, Shibasaki M, Kubota C, Kasukawa A, *et al.* (2004). Inhibition of the morphine-induced rewarding effect by direct activation of spinal protein kinase C in mice. *Psychopharmacology (Berl)* **177**:55–60.
- Ozaki S, Narita M, Narita M, Iino M, Sugita J, Matsumura Y, Suzuki T (2002). Suppression of the morphine-induced rewarding effect in the rat with neuropathic pain: implication of the reduction in mu-opioid receptor functions in the ventral tegmental area. *J Neurochem* **82**:1192–1198.
- Ozaki S, Narita M, Narita M, Iino M, Miyoshi K, Suzuki T (2003). Suppression of the morphine-induced rewarding effect and G-protein activation in the lower midbrain following nerve injury in the mouse: involvement of G-protein-coupled receptor kinase 2. *Neuroscience* **116**:89–97.
- Petraschka M, Li S, Gilbert TL, Westenbroek RE, Bruchas MR, Schreiber S, *et al.* (2007). The absence of endogenous beta-endorphin selectively blocks phosphorylation and desensitization of mu opioid receptors following partial sciatic nerve ligation. *Neuroscience* **146**:1795–1807.
- Volkow ND, Wang GJ, Fowler JS, Tomasi D (2012). Addiction circuitry in the human brain. *Annu Rev Pharmacol Toxicol* **52**:321–336.
- Wise RA (2008). Dopamine and reward: the anhedonia hypothesis 30 years on. *Neurotox Res* **14**:169–183.
- Woller SA, Moreno GL, Hart N, Wellman PJ, Grau JW, Hook MA (2012). Analgesia or addiction?: implications for morphine use after spinal cord injury. *J Neurotrauma* **29**:1650–1662.