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Analgesics as Reinforcers with Chronic Pain: Evidence from Operant Studies

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Abstract

Previously preclinical pain research has focused on simple behavioral endpoints to assess the efficacy of analgesics in acute and chronic pain models, primarily reflexive withdrawal from an applied mechanical or thermal stimulus. However recent research has been aimed at investigating other behavioral states in the presence of pain, including spontaneous, non-elicited pain. One approach is to investigate the reinforcing effects of analgesics in animals with experimental pain, which should serve as reinforcers by virtue of their ability to alleviate the relevant subjective states induced by pain. The gold standard for assessing drug reinforcement is generally accepted to be drug self-administration, and this review highlights the ability of drugs to serve as reinforcers in animals with experimental neuropathic pain, and the extent to which this behavior is altered in chronic pain states. Additionally, intracranial self-stimulation is an operant procedure that has been used extensively to study drug reinforcement mechanisms and the manner in which neuropathic pain alters the ability of drugs to serve as reinforcers in this paradigm will also be discussed. Drug self-administration and intracranial self-stimulation have promise as tools to investigate behavioral effects of analgesics in animals with chronic pain, particularly regarding the mechanisms through which these drugs motivate consumption in a chronic pain state.

Overview

Numerous preclinical models for chronic neuropathic pain have been developed in rodents including models of surgical nerve injury, diabetic neuropathy, chemotherapeutic induced neuropathy, and bone cancer pain models [4, 29]. Of these, surgical nerve injury has been studied most extensively due to the reproducibility of the extent of nerve injury and reproducibility between laboratories. Most surgical nerve injury models involve the sciatic nerve in one way or the other, with ligation by suture and/or nerve section of one or more spinal dorsal roots, the sciatic nerve itself, or collateral branches of the sciatic nerve that innervate discrete hindpaw regions of rodents. Due to the wealth of physiological and pharmacological data that have been generated with these models, our laboratory chose to explore drug reinforcement mechanisms in the L5/L6 spinal nerve ligation model originally

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described by Kim and Chung in 1992 and most of the discussion on the effects of chronic pain on drug reinforcement will be centered around the use of this model [22].

For the purpose of assessing the reinforcing mechanisms of drugs, several laboratory protocols have been developed since the early 1960's and continue to evolve even now [37]. These procedures include intravenous and oral drug self-administration in which the animal is allowed to determine its own rate of drug consumption, either spontaneously as is typical with oral self-administration, or through operant responding more often used with the intravenous route. Laboratory animals typically self-administer drugs that humans abuse or misuse including opiates and psychostimulants. Another technique that has been developed in the conditioned-place preference paradigm, considered an indirect assessment of the rewarding effects of drugs in which animals are conditioned to associate a novel environment with the subjective state induced by drug administration [3]. Intra-cranial self-stimulation is a procedure that is a variant of drug self-stimulation, in that operant behavior is maintained by electrical stimulation of limbic brain sites, a behavior that is potentiated by administration of drugs that typically maintain intravenous self-administration [44]. Although anecdotally it has been suggested that the presence of pain alters the reinforcing effects of some drugs, such as opiates, relatively few studies exist that directly ask the question of how the presence of chronic pain alters opioid reinforcement mechanisms, and if other analgesic drugs that reverse elicited reflexive withdrawal will serve as opioid-sparing drugs in such animals or serve as unique reinforcers by virtue of their analgesic properties. Additionally, the use of intracranial self-stimulation permits one to ask questions regarding the effects of drugs specifically on reinforcement by activation of discrete limbic structures. This review focuses on the use of these techniques typically employed in the drug abuse field to address some of these questions.

Drug Self-Administration in Rats with Neuropathic Pain

Several key questions have been addressed by examining how the presence of neuropathic pain alters drug self-administration. These questions generally fall under two main categories: one being the effects of neuropathic pain on the abuse potential of drugs, and the other being the ability of analgesics to serve as reinforcers selectively in animals with a chronic pain state. Both questions raise key issues in the mechanistic study of neuropathic pain and provide the means to test hypotheses regarding the efficacy and therapeutic potential of novel targets for pain therapy.

Opioid self-administration in rats with neuropathic pain

Early work examining the ability of opioids to serve as reinforcers in rats with persistent pain utilized the Freund's adjuvant model of inflammatory pain. These studies demonstrated that opioid intake was increased during the time period in which inflammatory pain was present, and that administration of anti-inflammatory drugs would diminish opioid consumption [9, 10, 25, 27]. In our laboratory we sought to determine if chronic neuropathic pain would alter opioid self-administration. The overall goal was to determine if rats could be trained to self-administer opioids principally for pain relief rather than for the positive reinforcing effects that underlie the abuse liability of these drugs in the absence of a pain state.

While there is some disagreement regarding the ability of opioids given intrathecally to reverse mechanical hypersensitivity in animals with neuropathic pain, most investigators find at least a modest reversal with systemic opioid administration [6, 30]. A variety of opioids given intravenously dose-dependently reverse mechanical allodynia, with heroin and methadone being relatively more efficacious than morphine or fentanyl, and hydromorphone somewhere in between [31]. Rats with neuropathic pain resulting from L5/L6 spinal nerve

ligation reliably self-administered only doses of these opioids that significantly reversed mechanical hypersensitivity, and the rate of consumption through self-administration was consistent with the duration of the antiallodynic effect of each drug. Fentanyl however, did not maintain reliable self-administration at any dose, suggesting that the duration of reversal of allodynia was insufficient to maintain responding in animals with neuropathic pain, since fentanyl's antiallodynic effects were relatively modest and dissipated rapidly compared to the other opioids studied. All of these opioids maintained self-administration over a much broader range of doses in normal rats, suggesting that nerve injury either diminished the potency of these drugs in producing positive reinforcement, or that rats with neuropathic pain were self-administering opioids for a different subjective effect than normal rats, possibly reversal of allodynia.

Theoretically, if reversal of allodynia were the sole subjective effect responsible for self-administration of opioids in animals with neuropathic pain, then alleviation of allodynia through some other means should decrease or eliminate opioid consumption selectively in these animals. Numerous compounds from a host of different drug classes diminish mechanical hypersensitivity in rats following peripheral nerve injury and several of these drugs have been examined in humans with intrathecal administration. Two such compounds are clonidine and adenosine. Interestingly, only clonidine diminished opioid self-administration when given intrathecally and did so only in rats with neuropathic pain [31]. Adenosine had no effect on opioid self-administration in either normal or nerve injured rats. In humans, clonidine and adenosine do not differ appreciably in their ability to alleviate hypersensitivity but only clonidine alleviates non-elicited pain at rest, often referred to as spontaneous pain [14, 15]. Modeling spontaneous pain in a nonverbal species has proven to be quite difficult with neuropathic pain models, despite a number of attempts to validate behavioral endpoints including facial grimacing, weight bearing, exploratory locomotor activity, and a variety of normal home cage rodent behaviors [34]. Spontaneous pain is more prevalent and more difficult to treat in patients with neuropathic pain however, and reversal of spontaneous or ongoing pain is particularly relevant to the therapeutic utility of opioids in this population [2, 8, 40]. Therefore, these data collectively support the idea that alleviation of ongoing pain is a major subjective state that motivates opioid self-administration in rats with neuropathic pain.

Given the data suggesting that the pharmacology of opioid self-administration differs significantly between rats with neuropathic pain and normal animals, it is reasonable to ask how the neurobiology of opioids differs in the presence of pain and how this altered neurobiology translates into differential mediation of drug consumption. Nociceptive input occurs through two basic systems originating in the periphery, notably the spinothalamic tract that encodes location and stimulus type, and the spinomesencephalic tract that is thought to be more relevant to affective dimensions of pain [21]. Drug reinforcement mechanisms however are generally ascribed to activity within limbic structures, primarily in forebrain [24]. However there are several key regions that provide input from classical nociceptive pathways to limbic regions, and vice versa. The amygdala is one such region. The amygdala receives direct nociceptive input from the parabrachial nucleus [5]. Activation of the amygdala occurs during a number of pain states and correlates with pain behaviors in rats, and pharmacological inhibition of the amygdala suppresses many of these pain related behaviors[36]. The amygdala can also indirectly modulate spinal pain transmission via descending projections to the PAG, and focal administration of the mu opioid receptor agonist DAMGO into the lateral amygdala increases tail flick latency to noxious heat that is blocked by pharmacological inhibition of the PAG or RVM [20]. As the amygdala is a key region that modulates activity in both reinforcement and pain circuits in the brain and contains a dense population of mu opioid receptors, we postulated that this region might be central to the differential pharmacology of opioids in maintaining self-

administration between normal rats and rats with neuropathic pain. Indeed, administration of the irreversible mu opioid antagonist β -funaltrexamine into the lateral amygdala inhibited the anti-allodynic effects of opioids in SNL rats [28]. More importantly, tonic inhibition of mu opioid receptors significantly reduced the potency of heroin in maintaining self-administration in SNL rats selectively. The subjective state motivating opioid consumption through self-administration in the presence of neuropathic pain therefore appears to require mu opioid receptor activation to a greater extent than in animal models of recreational opioid abuse.

Intrathecal self-administration of analgesics in rats with neuropathic pain

Early work suggested that rats could be trained to self-administer morphine intrathecally during an acute pain stimulus [13]. Above evidence suggests that in the presence of neuropathic pain, rats experience a subjective state of ongoing pain that can be alleviated through either intrathecal clonidine administration or opioid consumption through self-administration. Additional support for the idea that clonidine produces relevant subjective effects beyond reversal of mechanical hypersensitivity comes from conditioned place preference studies [23]. These investigators demonstrated that clonidine, but not adenosine, would selectively provide a place conditioning stimulus in rats with peripheral nerve injury, but not in normal animals. If this were true, then one would also expect that intrathecal administration of clonidine would maintain self-administration selectively in rats with neuropathic pain.

Establishment of drug self-administration in non-verbal species relies heavily upon the ability of subjects to associate the subjective state produced by the drug under study with the performance of the task or behavior being reinforced [1]. The establishment of such associations typically requires close temporal correlation between the performance of the target behavior, such as a lever press, and the production of the subjective state. This necessitates that the salient subjective effect occur rapidly after drug administration and dissipate within a sufficient time such that a measurable and reliable amount of behavior can be obtained and manipulated. For example, if infusion of a drug produces the intended subjective state for 6 hours, then only one infusion would be expected through self-administration every 6 hours. This is particularly relevant for intrathecal self-administration. The effects of clonidine on mechanical allodynia for example reach a maximum about 30 min after intrathecal administration and gradually decline over 2 hours [32]. For this reason, studies on intrathecal clonidine self-administration require continual 24 h access, unlike typical intravenous drug self-administration studies that permit drug access for a few hours only.

Despite these limitations, rats with neuropathic pain can be successfully trained to self-administer clonidine intrathecally [32]. While increased rate of lever pressing reinforced by intrathecal clonidine infusion in rats with neuropathic pain relative to normal animals was demonstrated, that finding alone is insufficient to demonstrate that the subjective state of clonidine per se is responsible for maintaining operant behavior. Further support for this idea includes dose-responsiveness of the ability of clonidine to maintain behavior and extinction of lever pressing when infusions of saline are substituted for clonidine. Addition of idazoxan, an α_2 adrenergic antagonist, to the infusion with clonidine likewise results in extinction of lever pressing. These data again collectively suggest that rats with neuropathic pain following L5/L6 spinal nerve ligation experience a subjective state following intrathecal clonidine infusion that is selectively reinforcing compared to normal rats. Given what is known regarding the effects of clonidine following intrathecal delivery in humans, it seems most reasonable to suggest that this subjective state is alleviation of ongoing spontaneous pain.

While intrathecal delivery of drugs results in a relatively greater concentration at spinal sites of action, most drugs given by this route achieve pharmacological concentrations in both the periphery and in brain. The major side effects of clonidine include hypotension and sedation with either systemic or intrathecal administration [7, 14]. Indeed, we have found that local inactivation of α_2 adrenergic receptors in the lateral amygdala with the nonselective alkylating agent EEDQ inhibits acquisition of intrathecal clonidine self-administration in rats with SNL (unpublished observations). Additionally, intra-amygdala EEDQ partially inhibits the anti-allodynic effects of intrathecal clonidine administration. These data indicate that while spinal sites undoubtedly contribute to the behavioral effects of clonidine given intrathecally in SNL rats, activation of supraspinal sites within the extended limbic system is also important.

Intracranial self-stimulation and stimulation-induced analgesia

Examining mechanisms that mediate drug consumption by either the intravenous or intrathecal route in the presence of pain has numerous strengths, however there are limitations to the techniques and the interpretation of the data as noted above. Drugs when given by either route produce a number of pharmacological effects in many different brain regions, some of which may be relevant for pain, some relevant for addiction, and some irrelevant for either but interfere with behavior (e.g. sedation and hypotension). It is therefore beneficial to evaluate drug effects using reinforcers other than the drugs themselves, such as electrical stimulation of specific brain sites or intracranial self-stimulation (ICSS). ICSS can be considered self-administration of electricity. As with drug self-administration, this technique was developed largely by researchers interested in understanding drug abuse mechanisms (see Wise, 1996 for review) [44]. The same general principles apply when evaluating ICSS as drug self-administration, with “dose” of electricity being either the intensity (in μA) or frequency (in Hz) of stimulation. Rate of operant behavior is dependent on either one of these parameters and displays a typical sigmoidal dose-response relationship. For examining abuse relevant mechanisms, drugs that are typically abused in humans and self-administered in rodents shift the rate-frequency curves to the left (i.e. potentiating ICSS) and manipulations that inhibit these mechanisms shift the curves to the right. By combining ICSS with analgesic administration in rats with neuropathic pain, one can specifically ask questions related to the ability of pain states to inhibit limbic system activation or the effects of analgesic drugs on this system in animals with pain. This method therefore provides a nice complementary tool with drug self-administration to ask pain-related questions.

Historically, investigators have found that most brain regions will maintain some measurable rate of self-stimulation in a percentage of animals, with the success rate of training ICSS varying widely between brain sites [44]. However it should be noted that for the vast majority of these early studies the rate-frequency relationships were not established and very little pharmacology was performed, underscoring the importance of measuring these parameters in future studies. However, for studying drug abuse mechanisms most investigators utilize ICSS with electrical stimulation of either the ventral tegmental area (VTA) or the medial forebrain bundle (MFB), and stimulation of either of these sites is thought to ultimately mediate operant responding through dopaminergic modulation of the nucleus accumbens (NAc). Administration of dilute lactic acid i.p. inhibits MFB ICSS by shifting the rate-frequency curve downward and to the right, and this effect is reversed by a number of analgesics including NSAIDs, opioids, and monoamine reuptake inhibitors [35, 39, 42]. One important feature of this paradigm is that behavior is increased with analgesic administration like drug self-administration, unlike inhibition of reflexive withdrawal responses. We have found that, unlike with i.p. lactic acid administration, that neuropathic pain through SNL surgery does not alter the rate-frequency relationship for either MFB or

VTA ICSS in rats [16, 18]. As mentioned above, opioids and other drugs of abuse shift the rate-frequency curve for MFB or VTA ICSS in normal animals to the left, potentiating the rewarding effects of electrical stimulation. However in SNL rats this effect of opioids was significantly diminished, and there was little to no potentiation of VTA or MFB ICSS [16, 19]. These data are consistent with the findings of drug self-administration studies in SNL rats using many of the same compounds cited above. Examining the drug self-administration data alone, it is not clear if the shift in dose-response curves in the presence of neuropathic pain is due to a diminished ability of the drugs to produce positive reinforcement through activation of limbic areas, or if the animals are titrating an analgesic effect for which these opioids possess diminished potency and efficacy. In concert with the VTA or MFB ICSS data however, it is clear that following SNL surgery opioids display diminished ability to activate these limbic regions and therefore likely have diminished ability to produce subjective states related to abuse through this system. Further evidence to support this conclusion is that neither VTA nor MFB electrical stimulation reverse allodynia in SNL rats, and that intrathecal administration of analgesics such as clonidine do not potentiate MFB ICSS in either normal or SNL rats [16, 18].

There is an abundant literature suggesting that electrical stimulation of various brain regions will produce analgesia in rodents including the PAG and thalamus and this behavioral effect is typically referred to as stimulation-induced analgesia (SIA) [33, 41]. More recently, a few investigators have found that some brain regions will support SIA in animals with neuropathic pain, including the paraventricular nucleus of the hypothalamus (PVN), lateral thalamus, and the motor cortex [11, 12, 26]. In our laboratory, we found that SNL rats would perform PVN ICSS over a range of frequencies that reversed allodynia, and that both the anti-allodynic effects and PVN ICSS could be partially inhibited by intrathecal administration of the oxytocin/vasopressin receptor antagonist atosiban [17]. For this reason we postulated that PVN ICSS might be a means of assessing SIA in SNL rats and examining novel analgesic mechanisms in the absence of positive reinforcement. However surprisingly rats were easily trained to perform PVN ICSS in the absence of SNL [17]. When potentiation of PVN ICSS by opioids and psychostimulants was examined, two novel findings were discovered. One is that opioids were capable of potentiating PVN ICSS to a much greater extent than cocaine, and that SNL did not reduce this potentiation unlike ICSS in the MFB or VTA. These data indicate that systems emanating from the PVN may be more important for the reinforcing effects of opioids than previously identified dopaminergic neurons, both in the presence and absence of neuropathic pain. Further studies on the reinforcing mechanisms of PVN ICSS and the potentiation by opioids are warranted. Additionally, many other brain areas support SIA however electrical stimulation of most of these regions is accompanied by dysesthesias or rapid loss of analgesic efficacy [38, 43]. The use of ICSS as a means to determine if any of these brain areas are uniquely reinforcing in a pain state as well as the effects of novel drug targets to potentiate ICSS of these areas could provide a novel preclinical means to explore novel regions for SIA in humans as well as a way to screen for novel druggable targets for chronic pain therapy. The motor cortex, a region that is being explored for SIA in humans, has been shown to support electrical stimulation induced conditioned place preference in rats with neuropathic pain [12].

Concluding remarks and future directions

This review provides a brief synopsis of pain research using operant conditioning studies to explore the effects of acute and chronic pain on the reinforcing effects of analgesics, including electrical stimulation of discrete brain areas. It is clear that the presence of neuropathic pain produces significant alterations in the reinforcing effects of opioids, and that these effects are brain region dependent. Pain is appreciated to be primarily a subjective state in humans, rather than solely a physiological condition consisting primarily of

hypersensitivity to various peripheral stimuli. While historically preclinical pain studies have relied heavily on reflexive withdrawal behaviors as behavioral endpoints, the drug abuse research community by necessity has developed a number of validated models to access subjective states in laboratory animals. These models have been used extensively to address neurobiological mechanisms of genetics, environment, and drugs on complex behavior. Two such models, drug self-administration and intracranial self-stimulation, have proven useful in addressing the influence of pain on both pharmacology and behavior and should prove useful in the future for developing novel pain therapies that have less abuse potential than those current employed.

References

1. Ator NA, Griffiths RR. Principles of drug abuse liability assessment in laboratory animals. *Drug Alcohol Depend.* 2003; 70:S55–S72. [PubMed: 12759197]
2. Backonja MM, Stacey B. Neuropathic pain symptoms relative to overall pain rating. *J Pain.* 2004; 5:491–497. [PubMed: 15556827]
3. Bardo MT, Bevins RA. Conditioned place preference: what does it add to our preclinical understanding of drug reward? *Psychopharmacology (Berl).* 2000; 153:31–43. [PubMed: 11255927]
4. Barrot M. Tests and models of nociception and pain in rodents. *Neuroscience.* 2012; 211:39–50. [PubMed: 22244975]
5. Bernard JF, Besson JM. The spino(trigemino)pontoamygdaloid pathway: electrophysiological evidence for an involvement in pain processes. *J Neurophysiol.* 1990; 63:473–490. [PubMed: 2329357]
6. Bian D, Nichols ML, Ossipov MH, Lai J, Porreca F. Characterization of the antiallodynic efficacy of morphine in a model of neuropathic pain in rats. *Neuroreport.* 1995; 6:1981–1984. [PubMed: 8580422]
7. Buvanendran A, Kroin JS. Useful adjuvants for postoperative pain management. *Best Pract Res Clin Anaesthesiol.* 2007; 21:31–49. [PubMed: 17489218]
8. Chou R, Fanciullo GJ, Fine PG, Adler JA, Ballantyne JC, Davies P, Donovan MI, Fishbain DA, Foley KM, Fudin J, Gilson AM, Kelter A, Mauskop A, O'Connor PG, Passik SD, Pasternak GW, Portenoy RK, Rich BA, Roberts RG, Todd KH, Miaskowski C. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain.* 2009; 10:113–130. [PubMed: 19187889]
9. Colpaert FC, Meert T, De Witte P, Schmitt P. Further evidence validating adjuvant arthritis as an experimental model of chronic pain in the rat. *Life Sci.* 1982; 31:67–75. [PubMed: 7109855]
10. Colpaert FC, Tarayre JP, Alliaga M, Bruins Slot LA, Attal N, Koek W. Opiate self-administration as a measure of chronic nociceptive pain in arthritic rats. *Pain.* 2001; 91:33–45. [PubMed: 11240076]
11. Condés-Lara M, Rojas-Piloni G, Martínez-Lorenzana G, Rodríguez-Jiménez J. Paraventricular hypothalamic oxytocinergic cells responding to noxious stimulation and projecting to the spinal dorsal horn represent a homeostatic analgesic mechanism. *European Journal of Neuroscience.* 2009; 30:1056–1063. [PubMed: 19723290]
12. Davoody L, Quiton RL, Lucas JM, Ji Y, Keller A, Masri R. Conditioned place preference reveals tonic pain in an animal model of central pain. *J Pain.* 2011; 12:868–874. [PubMed: 21515090]
13. Dib B. A study of intrathecal self-injection of morphine by rats, and the difficulties entailed. *Pain.* 1985; 23:177–185. [PubMed: 3840877]
14. Eisenach JC, DuPen S, Dubois M, Miguel R, Allin D. Epidural clonidine analgesia for intractable cancer pain. The Epidural Clonidine Study Group. *Pain.* 1995; 61:391–399. [PubMed: 7478682]
15. Eisenach JC, Rauck RL, Curry R. Intrathecal, but not intravenous adenosine reduces allodynia in patients with neuropathic pain. *Pain.* 2003; 105:65–70. [PubMed: 14499421]
16. Ewan EE, Martin TJ. Intracranial Self-stimulation of the Paraventricular Nucleus of the Hypothalamus: Increased Facilitation by Morphine Compared to Cocaine. *Anesthesiology.* 2012
17. Ewan EE, Martin TJ. Intracranial self-stimulation of the paraventricular nucleus of the hypothalamus: increased facilitation by morphine compared to cocaine. *Anesthesiology.* 2012; 116:1116–1123. [PubMed: 22421421]

18. Ewan EE, Martin TJ. Opioid facilitation of rewarding electrical brain stimulation is suppressed in rats with neuropathic pain. *Anesthesiology*. 2011; 114:624–632. [PubMed: 21293250]
19. Ewan EE, Martin TJ. Rewarding electrical brain stimulation in rats after peripheral nerve injury: decreased facilitation by commonly abused prescription opioids. *Anesthesiology*. 2011; 115:1271–1280. [PubMed: 21946150]
20. Helmstetter FJ, Tershner SA, Poore LH, Bellgowan PS. Antinociception following opioid stimulation of the basolateral amygdala is expressed through the periaqueductal gray and rostral ventromedial medulla. *Brain Res*. 1998; 779:104–118. [PubMed: 9473612]
21. Hunt SP, Mantyh PW. The molecular dynamics of pain control. *Nat Rev Neurosci*. 2001; 2:83–91. [PubMed: 11252998]
22. Kim SH, Chung JM. An experimental model for peripheral neuropathy produced by segmental spinal nerve ligation in the rat. *Pain*. 1992; 50:355–363. [PubMed: 1333581]
23. King T, Vera-Portocarrero L, Gutierrez T, Vanderah TW, Dussor G, Lai J, Fields HL, Porreca F. Unmasking the tonic-aversive state in neuropathic pain. *Nat Neurosci*. 2009; 12:1364–1366. [PubMed: 19783992]
24. Koob GF, Volkow ND. Neurocircuitry of addiction. *Neuropsychopharmacology*. 2010; 35:217–238. [PubMed: 19710631]
25. Kupers R, Gybels J. The consumption of fentanyl is increased in rats with nociceptive but not with neuropathic pain. *Pain*. 1995; 60:137–141. [PubMed: 7784098]
26. Kupers RC, Gybels JM. Electrical stimulation of the ventroposterolateral thalamic nucleus (VPL) reduces mechanical allodynia in a rat model of neuropathic pain. *Neurosci Lett*. 1993; 150:95–98. [PubMed: 8469409]
27. Lyness WH, Smith FL, Heavner JE, Iacono CU, Garvin RD. Morphine self-administration in the rat during adjuvant-induced arthritis. *Life Sci*. 1989; 45:2217–2224. [PubMed: 2601574]
28. Martin TJ, Buechler NL, Kim SA, Ewan EE, Xiao R, Childers SR. Involvement of the lateral amygdala in the antiallodynic and reinforcing effects of heroin in rats after peripheral nerve injury. *Anesthesiology*. 2011; 114:633–642. [PubMed: 21293255]
29. Martin TJ, Eisenach JC. Pharmacology of opioid and nonopioid analgesics in chronic pain states. *J Pharmacol Exp Ther*. 2001; 299:811–817. [PubMed: 11714863]
30. Martin TJ, Hairston CT, Lutz PO, Harris LS, Porreca F. Anti-allodynic actions of intravenous opioids in the nerve injured rat: potential utility of heroin and dihydroetorphine against neuropathic pain. *Eur J Pharmacol*. 1998; 357:25–32. [PubMed: 9788770]
31. Martin TJ, Kim SA, Buechler NL, Porreca F, Eisenach JC. Opioid self-administration in the nerve-injured rat: relevance of antiallodynic effects to drug consumption and effects of intrathecal analgesics. *Anesthesiology*. 2007; 106:312–322. [PubMed: 17264726]
32. Martin TJ, Kim SA, Eisenach JC. Clonidine maintains intrathecal selfadministration in rats following spinal nerve ligation. *Pain*. 2006; 125:257–263. [PubMed: 16806709]
33. Mayer DJ, Liebeskind JC. Pain reduction by focal electrical stimulation of the brain: an anatomical and behavioral analysis. *Brain Res*. 1974; 68:73–93. [PubMed: 4549764]
34. Mogil JS. Animal models of pain: progress and challenges. *Nat Rev Neurosci*. 2009; 10:283–294. [PubMed: 19259101]
35. Negus SS, O'Connell R, Morrissey E, Cheng K, Rice KC. Effects of peripherally restricted kappa opioid receptor agonists on pain-related stimulation and depression of behavior in rats. *J Pharmacol Exp Ther*. 2012; 340:501–509. [PubMed: 22128346]
36. Neugebauer V, Galhardo V, Maione S, Mackey SC. Forebrain pain mechanisms. *Brain Res Rev*. 2009; 60:226–242. [PubMed: 19162070]
37. O'Connor EC, Chapman K, Butler P, Mead AN. The predictive validity of the rat self-administration model for abuse liability. *Neurosci Biobehav Rev*. 2011; 35:912–938. [PubMed: 21036191]
38. Pahwa R, Lyons KE, Wilkinson SB, Simpson RK Jr, Ondo WG, Tarsy D, Norregaard T, Hubble JP, Smith DA, Hauser RA, Jankovic J. Long-term evaluation of deep brain stimulation of the thalamus. *J Neurosurg*. 2006; 104:506–512. [PubMed: 16619653]

39. Pereira Do Carmo G, Stevenson GW, Carlezon WA, Negus SS. Effects of pain- and analgesia-related manipulations on intracranial self-stimulation in rats: further studies on pain-depressed behavior. *Pain*. 2009; 144:170–177. [PubMed: 19435650]
40. Przewlocki R, Przewlocka B. Opioids in neuropathic pain. *Curr Pharm Des*. 2005; 11:3013–3025. [PubMed: 16178760]
41. Reynolds DV. Surgery in the rat during electrical analgesia induced by focal brain stimulation. *Science*. 1969; 164:444–445. [PubMed: 4887743]
42. Rosenberg MB, Carroll FI, Negus SS. Effects of monoamine reuptake inhibitors in assays of acute pain-stimulated and pain-depressed behavior in rats. *J Pain*. 2013; 14:246–259. [PubMed: 23332494]
43. Tasker RR, Vilela Filho O. Deep brain stimulation for neuropathic pain. *Stereotact Funct Neurosurg*. 1995; 65:122–124. [PubMed: 8916340]
44. Wise RA. Addictive drugs and brain stimulation reward. *Annu Rev Neurosci*. 1996; 19:319–340. [PubMed: 8833446]

Highlights

- ❖ Rats with nerve injury self-administer opioids for relief of spontaneous pain.
- ❖ Neuropathic pain alters supraspinal mechanisms of opioid self-administration.
- ❖ Intrathecal clonidine is self-administered selectively by rats with neuropathic pain.
- ❖ Acute but not chronic pain reduces reinforcement from electrical brain stimulation.
- ❖ Neuropathic pain reduces opioid stimulation of dopaminergic reward areas.