Contemporary Clinical Neuroscience

Carolyn A. Fairbanks
Thomas J. Martin *Editors*

Neurobiological Studies of Addiction in Chronic Pain States

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ISBN 978-1-4939-1855-3 ISBN 978-1-4939-1856-0 (eBook)
DOI 10.1007/978-1-4939-1856-0
Springer New York Heidelberg Dordrecht London

Library of Congress Control Number: 2014953964

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Preface

In 2011, the Institute of Medicine published a consensus report entitled "Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research". This contribution documented and highlighted chronic pain as a public health problem. Those committed to improving prescription management strategies for chronic pain treatment, development of new approaches for pain management, and continuing the search for understanding the mechanisms underlying diverse chronic pains have great hope that the IOM emphasis will enable escalated advances in all three areas. The term "chronic pain" is attributed to a national annual burden of "up to 635 billion dollars per year in medical treatment and lost productivity". Not included in this figure is the immeasurable suffering experienced by patients with that chronic pain. The term "chronic pain" is, at best, an umbrella term used loosely to describe a broad spectrum of chronic pains of different characters, intensities, locations, durations, and etiologies (if known). Diverse chronic pains often share common neurological substrates and mechanisms but can also be distinct and/or multifactorial, rendering diagnosis and optimizing treatment challenging.

Opioid medications continue to be considered the most effective approach for treating various and multiple chronic pains. With the elevated consciousness and commitment to controlling pain, introduction of the sustained release opioid formulations in the 1990s and expansion of prescribing of opioids to chronically manage nonmalignant forms of chronic pain, a concurrent expansion in the incidence of the very serious side effects of addiction and respiratory depression arose. Additionally, the expanded use of opioids to manage pain chronically in patients with longer to normal life expectancy yielded new information as to immune-system related side effects and a neuroadaptive response of the sensory system to chronic inhibition of the pain system. Further, in response to chronic exposure to opioids the sensory system responds by establishing a state of hypersensitivity, a phenomenon previously described but less widely appreciated. Through these prescribing practices and neurobiological research it has become clear that long-term opioid pharmacotherapy and chronic pain both individually and together impact the nervous system

in a complex manner. Developing a greater understanding of that interaction is required in order to optimize pain management strategies for specific and multifactorial pain conditions. Until the 1980s, the tools available to study the neurobiology of chronic pain were fairly limited to acute sensory stimulation via reflex withdrawal methods. Our understanding of chronic opioid exposure has been greatly limited to subjects with normal pain thresholds. The need to expand our understanding of how the nervous system of a patient or subject in chronic pain responds to chronic opioid exposure is increasingly appreciated.

Chronic pain is a generic term to describe a complex state of hypersensitivity that arises from physical injuries, inflammation, internal disease or dysfunction, chemical or chemotherapeutic exposures, or unknown sources. The sensory pathways that traverse the peripheral and central nervous systems respond with physical pathological adaptations to such environmental encounters. During the last 25–30 years, the development and introduction of multiple animal models that mimic such conditions have yielded many examples of neuroanatomical and molecular adaptations specifically in the sensory pathways that help to explain the persistence of chronic pain. Similarly, there has been significant analysis of how chronic opioid exposure impacts the central nervous system, particularly in the widely applied models of opioid analgesic tolerance.

Clinically, patients with chronic pain present with a variety of symptoms that include not only hypersensitivity but also dysesthesia and spontaneous, non-elicited pain. These latter two symptoms are generally assessed in patients using verbal report, and for this reason laboratory animal models with face validity that mimic this symptomatology have proven to be more difficult to develop and interpret than reflexive withdrawal models of hypersensitivity. Pertinent to this volume, opioids are particularly useful in relief from spontaneous pain and this symptom is frequently reported to be the more troublesome and disabling component of chronic pain. Progress in developing preclinical models of spontaneous pain is also reviewed within this work when appropriate.

In contrast, there is minimal information as to how the maladapted nervous system with established chronic pain (regardless of etiology) responds to chronic opioid exposure. A limited number of investigators in the 1980s and the early 1990s initiated studies of opioid self-administration or conditioned place preference under conditions of inflammation-induced chronic pain and nerve injury-induced chronic pain. Following that approach, we have similarly assessed the responding of rats (Ewan and Martin) and mice (Wade and Fairbanks) with established chronic pain for opioid reward. Our results together with some of our colleagues represented in this volume (Wade, Koob, Narita, Suzuki) and others support the assertion that subjects with established chronic pain respond to analgesic reinforcers differently than do subjects with normal pain thresholds. Scientific interest and inquiry in the concept that chronic pain results in significant and clinically relevant alterations in addiction-related centers in the brain are escalating. We anticipate that the blending of the fields of chronic pain mechanisms with that of opioid and/or other reinforcing addiction will greatly expand our knowledge as to how chronic pain of differing etiologies does or does not impact a subjects' propensity toward addiction of analgesic substances.

Through this volume, we hope to provide the reader with a valuable summary of the two fields and how best to use the information already gained and the tools available to continue to pursue the knowledge that will aid in managing chronic pain safely and effectively.

We have organized the text into three primary sections:

Part I introduces the defined set of investigations that have blended the standard models of chronic pain and opioid addiction. *Fairbanks and Wade* summarize the early self-administration and conditioned place preference studies of opioid and non-opioid analgesics in chronic pain models that were initiated in the early 1980s and have continued to be investigated through to the present day.

Part II emphasizes current research that investigates the specific brain regions that may account for alterations in opioid or non-opioid responding in subjects with chronic pain. *Ewan and Martin* provide a more in-depth description of their recent studies of opioid and non-opioid self-administration under conditions of chronic pain. Additionally, they describe the use of intracranial manipulations in discrete brain regions in subjects with chronic pain as a means to answer the key questions as to which specific brain regions contribute to the clear pattern of alterations in opioid self-administration in subjects with chronic pain. *Ghandi*, *Becker*, *and Schweinhardt* provide a comprehensive consideration of how short-term and long-term pain influence reward processing, specifically featuring the intersection of cerebral regions that are involved in both pain processing and reward. *Narita and colleagues* describe specific molecular and neurobiological changes in the mesolimbic system under conditions of chronic pain that may account for altered opioid responding.

Part III focuses on methodological information important to the blend of chronic pain and addiction modeling. *Wade*, *Koob*, *and Vendrusculo* describe the models used for sensory assessment and to induce chronic pain states as well as addiction. *Fairbanks and Peterson* review and summarize the biopharmaceutical aspects that distinguish eight widely prescribed opioid analgesics as well as a review of the relevance of blood–brain barrier transport to opioid pharmacology.

Part IV concludes the collection with commentaries on the clinical impact of the expanded use of prescription opioids. *Lisa Schrott* focuses on the impact of prenatal exposure to prescription opioids with an emphasis on the impact on cognition and memory identified through animal modeling of prenatal opioid exposure. *Scott Strassels* summarizes three primary challenges associated with opioid pain management: opioid-induced hyperalgesia, how to best measure clinical outcomes, and challenges and opportunities associated with the development of prescription monitoring programs.

It is our hope that readers will find this collection informative regarding the current state of knowledge that has been gained from combining animal modeling of addiction and chronic pain. It is important to expand our knowledge of how subjects in diverse states of chronic pain respond to opioid as well as non-opioid classes of analgesic mediations.

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Part I
Introduction

Chapter 1
Opioid and Non-Opioid Drug Responding Under States of Chronic Pain: A Timeline Spanning 1980 to Present Day

Carrie L. Wade and Carolyn A. Fairbanks

Abstract It has been long recognized that chronic pain is a significant public health concern. After many decades of research and development investment for alternatives, the most effective pharmacological tools for managing diverse chronic pains remain the opioid analgesics. Several serious side effects including, the risks of addiction or diversion of opioid-containing dosage forms to nonpatient populations render the use of opioid medication for treatment of pain complicated. At the same time, it been asserted repeatedly that patients with established chronic pain demonstrate reduced propensity to acquire addiction to opioids than the general population. For over 30 years, neuropharmacological studies in rodent models of opioid self-administration have suggested that responding for opioids is, in fact, significantly altered under conditions of established chronic pain, and often reduced. However, with the introduction of the sustained release opioid preparations, the expansion of opioid prescribing, and appropriately heightened concerns regarding opioid-related addiction and mortality by respiratory depression, this long-standing assertion that patients with chronic pain are less susceptible to addiction has been recently challenged. In response to this challenge the opportunity arises, perhaps, to consider that chronic pain is a generic term that refers to a broad spectrum of painful conditions; these pain conditions may have common neurobiological mechanisms, but also key distinctions. Understanding the neurobiology underlying distinct chronic pain conditions as they relate to opioid addiction may help to better predict the therapeutic window and side effect risks associated with chronic opioid therapy. Progress has been made in this area, but it is currently recognized that more specific information is greatly needed. As a primer to planning such future studies, the pres-

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C.A. Fairbanks, T.J. Martin (eds.), *Neurobiological Studies of Addiction in Chronic Pain States*, Contemporary Clinical Neuroscience 17,
DOI 10.1007/978-1-4939-1856-0_1

ent chapter is intended to summarize the prior three and a half decades of neuropharmacological studies that have systematically evaluated opioid (and non-opioid) analgesic responding in animal models of opioid addiction.

Introduction

In 2011, the Institute of Medicine (IOM) report on chronic pain [1] importantly highlighted the prevalence of chronic pain in the USA and the associated economic costs. Additionally, the report systematically described the current complexities associated with treating chronic pain, particularly with opioid analgesics, the diversion of which has become a crisis parallel to and linked with chronic pain. Although the report appropriately acknowledges these very valid concerns regarding the use of opioids, the report also discusses concern surrounding the rising fear of analgesic medication that is prevalent both in the practitioner and patient population. Among a number of barriers to appropriate pain medication, the IOM report asserts that "Regulatory, legal, educational, and cultural barriers inhibit the medically appropriate use of opioid analgesics" [1]. Like all patients with neurological dysfunction, patients with chronic pain tend to seek medical treatment to improve their quality of life [2]. It is recognized that these patients sometimes encounter disapproval for seeking treatment and that they represent a stigmatized patient population. Although the introduction of the sustained release opioid preparations in the 1990s expanded access to high doses of opioids and more accessible media profiling of cases of conversion to addiction [3] may elevate cultural consciousness of risks, these barriers to pain management are not a recent phenomenon. The stigma and the debate about pain management has been ongoing for decades [2–4] just as patients with chronic pain have been seeking pharmacological management of their pain for decades [2]. What may confound the patient–practitioner interaction and contribute to a cycle of stigma and distrust is that patients with chronic pain may display similar characteristics as those that pursue prescription opioid with an intent to abuse [5–9]. This scenario, described as "pseudoaddiction" [3, 6], has been reported as often addressed when the chronic pain patient receives effective treatment [5–7]. There are parallels to this phenomenon in a subset of neuropharmacological studies in animal models of addiction that have studied responding for reinforcing drugs in animals with established chronic pain. In the last 30 years, there has been a limited but important set of studies that have evaluated how opioids are self-administered in animals with established chronic pain. In selected studies, opioid self-administration in chronic pain subjects is reduced when non-opioid analgesics are provided by the experimenter [10–12]. These studies suggest that, in these cases, the subjects' motivation for self-administration of opioids is for analgesic relief. In fact, a resounding theme across multiple studies and models of chronic pain is that the state of analgesia itself is a rewarding phenomenon, consistent with the clinical observation of pseudoaddiction. In this review, we will feature this literature to document the progression of knowledge acquired through

comprehensive and diligent consideration of self-administration of a spectrum of analgesic medications across a variety of animal models of established chronic pain.

Analgesic Self-Administration in Chronic Pain Models

It was recognized [13] decades ago that there was an urgent need to establish an animal model of chronic pain in order to study the mechanisms of chronic pain and analgesic pharmacology. As part of the effort to develop and characterize such a model, the first studies that considered operant self-administration of analgesic medications emerged. Among the first models was a model of hindpaw inflammation induced by intraplantar injection of various mycobacteria. It was inferred that the resultant inflammation would evoke a chronic painful state, the question being how best to demonstrate that the condition was, in fact, interpreted as pain by the subject. In a report as early as 1980, Colpaert and colleagues hypothesized [14] that if the mycobacterial injection in the tail base were, in fact, hyperalgesic, that subjects might demonstrate a preference for oral analgesic drugs when presented with an option to choose between a bottle containing an analgesic and no analgesic drug. They tested this proposal by offering rats treated with chronic Freund's adjuvant (CFA) the option to drink fluid from a bottle with the nonsteroidal anti-inflammatory drug suprofen or a bottle with a control solution. Since NSAIDs do not demonstrate addictive properties in rats [15], an elevation in suprofen self-administration in rats with hindpaw inflammation might be reflective of motivation to self-medicate presumptive associated inflammatory pain. Consistent with their hypothesis, the CFA-treated subjects consumed more from the bottle containing the analgesic suprofen than did normal rats. Similar to these results using suprofen, Colpaert and colleagues [16] reported in 1982 observations that inflamed rats self-administered oral fentanyl more than noninflamed controls. These complementary studies with suprofen and fentanyl provided very early evidence to support the concept that analgesic relief may be a reinforcing condition. Measurements that are frequently used to assess hypersensitivity under conditions of chronic pain [17] were not taken in these experiments; the assertion that the subjects experienced chronic pain was based upon several indirect observations. Specifically, the rats with CFA-induced inflammation displayed a decrease in body weight and an increase in spontaneous vocalizations, which are suggestive of states of distress or discomfort. Furthermore, the peaks of the increases in both suprofen [14] and fentanyl [16] consumption in CFA-treated rats were matched by the peak increases in the diameters of the inflamed paws and joints. Finally, when the inflammation subsided, the analgesic self-administration reduced to control levels.

Almost 20 years later, Colpaert expanded this analysis to consider the impact of the addition of systemic analgesics in arthritic rats with elevated intake of opioid. In 2001 Colpaert and his colleagues [11] showed, again, that rats with chronic arthritis drank significantly more from a bottle with fentanyl than a control bottle.

In contrast to the early studies from the 1980s, these experiments included experimenter-delivered systemic administration of the anti-inflammatory glucocorticoid, dexamethasone. In dexamethasone-treated rats, the self-administration of fentanyl diminished over time. The effect was interpreted as support for the concept that, under conditions of chronic pain, elevated responding for fentanyl in rats with chronic inflammatory pain may be due to motivation to seek pain relief.

In 1989, a second research group [10] evaluated the propensity of CFA-treated rats to lever press for intravenous delivery of morphine relative to controls. Their observations were comparable to that of Colpaert and colleagues with some striking differences. In contrast to the findings of Colpaert, in these experiments the CFA-treated rats self-administered significantly *less* morphine than their control counterparts. However, similar to the findings of Colpaert, experimenter-delivered administration of indomethacin (an NSAID) further reduced morphine self-administration in CFA-treated subjects. Indomethacin had no effect on morphine self-administration in normal rats. As the inflammation subsided, the CFA-treated rats increased morphine-self-administration. That the self-administration response converged to the level of the normal subjects as the inflammation resolved is congruent with the findings of Colpaert, although the direction of the effect is in notable contrast. It is noteworthy that in this study, unlike the first studies of Colpaert, a nociceptive reflex measurement was taken (tail pressure test) to determine the magnitude of induced hypersensitivity and to verify that the self-administered levels of morphine were, in fact, analgesic. The secondary observations of this study were consistent with those of Colpaert in that provision of the NSAID reduced morphine self-administration suggesting that the state of analgesia may, in and of itself, be reinforcing. On the other hand, their main observation that morphine self-administration was reduced under the state of inflammation-induced hyperalgesia, perhaps for the first time, suggested that the very state of chronic hypersensitivity reduced the reinforcing properties of morphine.

Other Pain Models

Nerve Injury

It has also been long recognized that various conditions of chronic pain are not biologically equivalent. For example, the pharmacology of opioid analgesics under conditions of inflammation is thought to differ vastly from that under the state of neuropathic pain. While opioids tend to demonstrate enhanced analgesic potency in states of chronic inflammation [18–20], opioid analgesics under conditions of nerve injury show reduction in potency [21–29] depending on the route of administration [21, 23, 30]. The nerve injury based models of chronic neuropathic pain [31–34], introduced in the 1980s and 1990s, facilitated the further consideration of opioid-maintained responding. In 1995, Kupers and Gybels [35] compared oral fentanyl self-administration (two bottle choice method) between neuropathic [32] and

arthritic rats [14], as well as the appropriate corresponding control groups. Consistent with the data presented in the 1980s by Colpaert [16], rats with CFA-induced inflammation demonstrated an increase in preference of the fentanyl-containing bottle relative to control. This increase took place at a time that matched the peak of hypersensitivity measured in a separate group of CFA-treated rats. Conversely, the rats with partial sciatic nerve injury, while confirmed to be hyperalgesic, did not show an increase in preference for fentanyl over the course of the experiment, in contrast to the inflamed rats. The preference of the nerve-injured rats between the two bottles was similar to control rats. Kupers and Gybels ascribed this effect to the aforementioned purported lower efficacy/potency of opioids under conditions of neuropathic pain. It should be noted here, however, that whether or not oral fentanyl reversed mechanical hyperalgesia in these specific subjects was not evaluated.

Twelve years later the observation that morphine self-administration was altered under conditions of nerve injury was confirmed and significantly expanded. In 2007 Martin et al. [12] contributed an extensive analysis of the self-administration profiles of multiple doses of a spectrum of opioids in rats subjected to the Chung method [36] of nerve ligation. These experiments are reviewed elsewhere in this volume by the authors themselves (Chap. 2), but merit some description in this chapter of their contribution to this *Timeline* of related studies. Martin et al. compared maintained lever pressing behavior in neuropathic rats and their respective controls in response to presentation of multiple doses (one dose per hour for 4 consecutive hours) of the well-known reinforcer heroin and four widely studied opioid analgesics (morphine, fentanyl, hydromorphone, and methadone). Briefly, dose–response analysis for the aforementioned opioids in almost all cases demonstrated decreased efficacy/potency in neuropathic rats compared to controls. In other words, the lower doses that support maintained responding in normal rats were not effective in nerve-injured rats. Therefore, in these rats, the activity that is typically interpreted as a model of addiction was not present at those doses. In the case of heroin and methadone, higher doses resulted in responding in nerve-injured rats; notably, these higher doses alleviated hypersensitivity. These results are consistent with two phenomena previously described (1) that the state of neuropathic pain, unlike inflammatory pain, results in a reduction in the presumed motivation of subjects to lever press for opioid reward, a finding consistent with that of Kupers and Gybel [35] and (2) the remaining rewarding effects of higher doses of higher efficacy opioids may be a consequence of the subject's motivation to achieve relief from chronic pain, consistent with the previous studies. This second interpretation is supported by additional observations that experimenter delivered clonidine (an alpha 2 adrenergic receptor analgesic agonist) resulted in reduction of heroin-maintained responding in neuropathic (but not control) rats [12]. Note that this finding paralleled that of Colpaert [11] with dexamethasone-mediated reduction of escalation of fentanyl intake in CFA-treated rats and Kupers and Gybel's demonstration that indomethacin reduced morphine self-administration in nerve-injured rats [35]. These observations would suggest that subjects in a state of neuropathic pain would maintain lever pressing for a non-opioid analgesic. In fact, in a complementary study Martin et al. [37] observed that, unlike control rats, neuropathic rats lever pressed preferentially

for the alpha2 adrenergic receptor agonist clonidine (an analgesic) when delivered spinally via an indwelling intrathecal catheter. These data are congruent with that of Colpaert who, as mentioned before, demonstrated increased suprofen intake over control solution in CFA-treated rats.

The aforementioned studies [12, 38] that assessed opioid self-administration under conditions of chronic pain represent operant sessions where the subjects have access to the reinforcers for a short duration of time (1–4 h). Wade and colleagues [39] have recently presented their evaluation of the self-administration of intravenous oxycodone in rats treated with CFA during 12 h periods of time (long access). In agreement with the studies described above, rats with unilateral CFA inflammation respond for oxycodone significantly less than vehicle-treated controls. This effect was studied for 13 days of established tactile hypersensitivity. Additionally, at the end of the study period, an assessment of breakpoints of progressive ratio of reinforcement (the maximum in the lever presses required to earn the next drug infusion) was made. It was noted that CFA-treated subjects demonstrate notably lower breakpoints than control counterparts. These observations are consistent with the concept that the motivation to lever press for opioids is altered in rats with chronic pain.

Mice

From the mid 2000s to present day, we [38] have also pursued studies of opioid self-administration under diverse conditions of established chronic hypersensitivity specifically in mice. These experiments revealed that mice with pre-established persistent hindpaw sensitivity resultant from either spinal nerve ligation [27], subcutaneous injection of CFA into the hindpaw, or repeated injections of vincristine fail to develop lever pressing preference for oral fentanyl, unlike normal control subjects. In these studies, subjects initiated daily 2 h self-administration sessions for 2–3 weeks following establishment of hindpaw hyperalgesia from one of the aforementioned treatments. During the session, pressing one lever resulted in delivery of either a 70-μL quantity of fentanyl available for oral consumption or a 20-mg food pellet. Pressing the other lever provided no reward. A noteworthy distinction is that while the mice with pre-established hypersensitivity did not develop maintained responding for opioid, they did develop food-maintained responding (similar to controls). Therefore, these data indicate that the reduction in opioid responding is directly related to drug treatment and is not evident with food reward.

Conditioned Place Preference

Similar to studies of opioid self-administration, there are a few key early reports using conditioned place preference (CPP) as a model to consider opioid dependence under conditions of persistent pain. In 1988, using the CPP assay, Shippenburg

and colleagues [40] explored, for the first time in a systematic manner, the reward associated with opioids in subjects with inflammatory pain. They observed that, like previous reports [18–20], the opioids morphine and the kappa agonist U-69594 showed increased antinociceptive potency under conditions of inflammation versus the control condition. In contrast to the observations of Colpaert using the two bottle choice approach, Shippenburg and colleagues observed that subcutaneously delivered morphine did not result in increased time spent in the morphine-paired chamber relative to control subjects, despite the fact that the doses used were analgesic. The reasons for the contrast are not clear, but Shippenburg's study represents the first in a series of evaluations of morphine CPP conducted under conditions of chronic pain, as well as other non-opioid analgesic drugs [41]. More recent studies of CPP using non-opioid analgesic drugs appear to indicate a response reflective of the proposal that the analgesic condition is, itself, rewarding [42]. In contrast, many CPP reports using morphine reveal diverse outcomes. These are summarized in Table 1.1. Recent observations by Cahill et al. [43] showed that doses of subcutaneously delivered morphine in the range of 1–2 mg/kg did not induce CPP in normal rats but did result in a place preference in neuropathic rats. These same morphine doses reversed tactile hyperalgesia consistent with the proposal that the pain-relieving properties of morphine may be attributable to its effect in CPP. While these results are compellingly supportive of the emerging organizing principle that the state of analgesia corresponds to reward-associated responses in nerve-injured subjects, there are a series of studies that stand in notable contrast. Morphine-induced CPP has been shown to be reduced in mice with inflammation based hindpaw hypersensitivity induced by CFA [44] and carrageenan [45]. Morphine CPP has been systematically and repeatedly shown to be reduced in neuropathic rats [46] and mice [29, 47–49]. CPP induced by tramadol and its primary metabolite M1 has also been shown to be reduced in nerve-injured mice [50]. Morphine-induced CPP has also been demonstrated to be reduced in mice with formalin-induced inflammation [45, 51]. The differences between these results [44–49, 51] that reveal reduced morphine-induced CPP under conditions of chronic pain, versus that of Shippenburg [40] (no change), and the more recent report [43] of enhanced morphine-induced CPP in chronic pain are not well understood. Some of the key parameters are summarized in Table 1.1. Where consensus can be found is that, by and large, the state of chronic pain most often changes the tendency of rodents to show a place preference for noncontingent administration of morphine.

Non-Opioid Reinforcing Analgesics: Cannabinoid

In addition to consideration of opioids, NSAIDS, and corticosteroid classes of medications, Gutierrez and colleagues [54] have compared the self-administration pattern of a selective agonist for the cannabinoid 2 receptor in neuropathic rats versus two distinct controls, sham-operated and naïve rats. Following the development of tactile allodynia, the rats were placed in daily sessions over 4 days where they could bar press either of two levers. Pressing one of the levers does not result in any

Table 1.1 Studies of morphine-induced conditioned place preference in rodent

Study	Species	Pain model	Dose of morphine and route of administration	Confirmed analgesic effect of morphine	Time in chamber during drug pairing	Morphine CPP outcome in subjects with chronic pain
Shippenburg [40]	Male Sprague Dawley rat, Charles River, Wiga, Germany	CFA, unilateral hindpaw injection	0.3, 1, 3, 5 mg/kg, S.C.	Yes, paw pressure threshold (Randall-Selitto)	60 min	No change
Sufka [52]	Male Sprague Dawley rat, Harlan, IN	CFA, unilateral hindpaw injection	3, 10 mg/kg	Yes, hot plate	60 min	Enhanced
Suzuki [45]	Male Sprague Dawley rats (Tokyo Experimental Animals)	Formalin, carrageenan	2, 4, 8 mg/kg, S.C.	Yes, paw pressure threshold (Randall-Selitto)	50 min	Suppressed
Oe [53]	Male ICR mice (Tokyo Experimental Animals)	PKC activator PDBU (1, 5, 10 nmol 5 day thermal hyperalgesia)	3, 5, 10 mg/kg, S.C.	Yes, hot plate (55 °C)	60 min	Suppressed
Ozaki [48]	Male Sprague Dawley rats (Tokyo Experimental Animals)	Partial sciatic nerve ligation	4 or 8 mg/kg, S.C.	Not specifically assessed	60 min	Suppressed
Ozaki [49]	Male, ICR mice (Tokyo Experimental Animals)	Partial sciatic nerve ligation	3, 10, and 30 nmol/ mouse, I.C.V.	Yes, tail flick test	60 min	Suppressed
Ozaki [46]	Male ICR mice (Tokyo Experimental Animals)	Partial sciatic nerve ligation	2.5, 5, 10 mg/kg, S.C.	Not specifically assessed	60 min	Suppressed
Niikura [47]	Mice: male and female C57BL/6J and 129S2/SvPas mixed background	Partial sciatic nerve ligation	5 mg/kg, S.C.	Not specifically assessed	60 min	Suppressed
Narita [51]	Rats: Sprague Dawley (Tokyo Experimental Animals)	Formalin unilateral hindpaw	2, 4, 8 mg I.P.	Not specifically assessed	60 min	Suppressed
Petraschka [29]	Male C57BL/6 mice (Charles River Laboratories, Wilmington, MA, USA)	Partial sciatic nerve ligation	2.5, 5 mg/kg, S.C.	Yes, tail flick test	30 min	Suppressed
Betourne [44]	Female C57BL/6 mice (Iffa Credo, L'Arbresle, France)	Cancer (melanoma cell) CFA	10 mg/kg, I.P.	Yes, hindpaw licking	20 min	Suppressed: cancer, CFA
		Carrageenan				No change: carrageenan
Cahill et al. [43]	Male Long Evans rat (Charles River, St. Constant, Quebec)	Chronic constriction injury	1, 2, 4, 8 mg/kg, S.C.	Yes, effective by 30 min	60 min	Enhanced

outcome, pressing the other lever resulted in an intravenous infusion of the CB2 receptor agonist (*R*, *S*)-AM1241. Unlike the opioid analgesics, but similar to NSAID analgesics, normal rats did not develop a preference for either lever. Neuropathic rats, however, showed lever-pressing preference for (*R*, *S*)-AM1241 i.v. delivery (but not vehicle), which alleviated tactile hypersensitivity measured following conclusion of each session. These data suggest that the lever pressing responses in neuropathic rats could be associated with the analgesic response of (*R*, *S*)-AM1241 delivery. An important observation noted in this study was that sham-operated rats (a common control for nerve injury models) also displayed active lever discrimination for intravenous (*R*, *S*)-AM1241. It is not very common for studies to include both naïve and sham-operated controls and so these findings are important for consideration of what the sham-operated control may represent. Sham-operated controls receive the same experience as nerve-injured rats in terms of anesthesia, incision, and all mechanical aspects of the surgery except the nerve injury itself. One might expect that there should be an aspect of postoperative pain that may not be detected in the standard reflex measurements and may (or may not) persist into the time of self-administration experimentation. We have similarly observed [38] an effect on self-administration in sham-operated subjects that may be interpreted as intermediate between nerve injured and naïve subjects. The primary importance of the contribution of Gutierrez and colleagues is to demonstrate that, like other non-opioid analgesic agents, the CB2 selective receptor agonist induced a lever preference that appears to be closely associated with analgesic benefit.

Conclusion

A prevalent observation from this review of over three decades of research appears to be that responding for opioids is different in subjects with chronic pain than subjects without chronic pain. As described above, that theme is observed repeatedly in many different experiments, across species, and pain-inducing conditions. These observations call for much greater investigation of opioid responding under conditions of chronic pain, identification and full characterization of the CNS altered systems so that the appropriate context can be considered when developing and optimizing patient pain management protocols. Currently, the discourse on patient response to opioid analgesics is primarily informed by our extensive decades-old literature on patient, nonhuman primate, and rodent responding to opioids under presumed pain-free conditions. Consideration of any alteration in the responding of chronic pain patients to opioid analgesics relative to the pain free human population has been acknowledged clinically for decades [2–4], but is eclipsed by our immensely greater knowledge and appropriate concern regarding the addictive properties of opioids in people without established chronic pain conditions. Second, experimental subjects with induced persistent pain, in many cases, appear to intentionally self-administer or seek the state of pain relief whether achieved by opioid or non-opioid analgesics. In other cases, opioid responding is diminished. This may be due to alterations in the reward pathways as is discussed further in this volume by Narita and colleagues in Chap. 4 of this volume. The general consensus of the literature

reviewed here is that pain relief is reinforcing or motivational. It is essential to significantly expand our consideration of the alterations in subjects' responding for opioid and other analgesics under diverse states of chronic pain in order to more fully address this public health concern from a scientific and objective platform.

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Part II
Basic Science

Chapter 2
Opioid Self-Administration in the Presence of Chronic Pain: Analgesia or Addiction?

Eric E. Ewan and Thomas J. Martin

Abstract Chronic pain is a major unmet clinical need and despite over two decades of preclinical research of the mechanisms of chronic pain novel therapies have been scarce. Opioids, alpha adrenergics, and antiepileptics continue to be the mainstays for treatment. In the early to mid 1990s, under treatment of chronic pain was highlighted as a major clinical problem, particularly concerning the conservative prescribing of opioids in sufficient doses to alleviate chronic nonmalignant pain (Jamison, J Pain Symptom Manage 11:231–241, 1996; Portenoy, J Pain Symptom Manage 11:203–217, 1996). The subsequent liberalization of guidelines and practices for prescribing opioids for the management of chronic nonmalignant pain has unfortunately been met with dramatic increases in the abuse of these medications. The economic burden of chronic pain in the USA is staggering, with an estimated cost of up to $635 billion annually (Gaskin and Richard, J Pain 13:715–724, 2012). In terms of the percentage of gross domestic product, the economic burden is similar or higher in several European countries as well (Breivik et al. BMC Public Health 13:1229, 2013). The total economic burden of nonmedical use of prescription opioids is estimated to be $53–$56 billion annually, with two-thirds of that cost attributable to abuse of oxycodone, hydrocodone, propoxyphene, and methadone (Birnbaum et al. Pain Med 12:657–667, 2011; Hansen et al. Clin J Pain 27:194–202, 2011). Clearly there is a need to understand mechanisms through which chronic pain produces suffering and limits productivity, as well as mechanisms through which opioids produce addiction and abuse both in the presence and absence of pain.

While opioid addiction and treatment of chronic pain with opioids may be related clinically, these two aspects of opioid pharmacology have typically been studied in isolation using preclinical laboratory animal models. This chapter highlights studies that have combined animal models of drug addiction, namely self-administration

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C.A. Fairbanks, T.J. Martin (eds.), *Neurobiological Studies of Addiction in Chronic Pain States*, Contemporary Clinical Neuroscience 17,
DOI 10.1007/978-1-4939-1856-0_2

and intracranial self-stimulation, with animal models of chronic pain. Although the clinical criteria to establish the existence of chronic pain or drug addiction are generally accepted, the preclinical animal models for these clinical states are not without some controversy, particularly regarding chronic pain. A short discussion of the animal models that have been used to assess opioid abuse liability in the presence of pain is therefore provided. The overall goal of this chapter is to summarize data from these studies and to provide evidence that chronic pain alters the reinforcing properties of opioid and nonopioid analgesics and to explore the extent to which these models provide a behavioral assessment of analgesia, abuse liability, or some combination of both.

Peripheral Nerve Injury Models of Chronic Pain: Do They Really Produce a Pain State That Has Clinical Relevance?

Numerous procedures have been described in the animal literature that involve surgical injury of peripheral sensory nerves, typically those innervating the hindpaw in rats or mice. Most if not all of these procedures involve surgical damage to dorsal spinal nerve roots that comprise a major sensory component of the sciatic nerve, of proximal branches of the sciatic nerve, or of varying degrees of injury to the sciatic nerve itself [4, 40, 45]. Regardless of the extent and location of the nerve injury, the primary behavioral outcome that has been used to validate these methods as animal models of neuropathic pain has been hindpaw hypersensitivity to mechanical or thermal stimuli. Typically, an increased response is observed to both nonnoxious stimuli (allodynia) and mildly noxious stimuli (hyperalgesia) [3, 45]. While hypersensitivity phenomena clearly exist in some patients with neuropathic pain, these endpoints are not typically used as the primary outcome measures for assessment of chronic pain in humans. Dysesthesias and paresthesias are as common, if not more common, in this patient population [24]. It has also been suggested that the presence of spontaneous pain at rest typically identified as having a dull, aching quality is the primary complaint of most patients with chronic neuropathic pain, and the symptom for which the majority of pain patients seek relief [2]. Perhaps more germane to this chapter, this is the symptom for which opioids appear to be particularly efficacious in neuropathic pain patients.

The use of hypersensitivity as a primary outcome measure for assessment of pain following peripheral nerve injury in rodents has provided a means to assess the relevance of a wealth of important physiological, biochemical, molecular, and pharmacological findings regarding the mechanisms through which nerve injury and the resulting plasticity produces such behavior. However, given the clinical presentation of neuropathic pain in most patients, perhaps it is not surprising that the use of hypersensitivity as the primary endpoint in preclinical studies has resulted in few novel medications that are efficacious in this population [36, 46]. For this reason, many investigators have sought to describe other behavioral phenomena that appear following peripheral nerve injury in rodents that might serve as surrogate measures

for spontaneous pain in neuropathic pain patients. Paw incision results in guarding behavior that coincides with spontaneous electrophysiological activity of sensory afferents [65, 66]. However, similar ventroflexion of the hindpaw following spinal nerve injury in rats was found to be abolished by either dorsal or ventral rhizotomy of the nerve root, suggesting involvement of a motor component in addition to a sensory component [48]. Other behaviors that are altered or appear with moderate acute or subchronic pain stimuli include locomotion or exploration [37, 63], facial expression or grimacing [32, 61], food-maintained operant responding or feeding [38, 62], intracranial self-stimulation [54], and a variety of home cage behaviors [57]. Unfortunately, most if not all of these behaviors are not altered or do not arise in rodents following spinal or peripheral nerve injury [47]. Behaviors that have been found to be altered or produced in rodents following spinal nerve injury include conditioned place aversion to suprathreshold mechanical stimuli, conditioned place preference to certain analgesics administered spinally, conditioned place preference to deep brain stimulation of motor cortex, alteration of intravenous opioid self-administration, self-administration of spinal analgesics, and diminished opioid potentiation of rewarding electrical brain stimulation [17, 20, 27, 41, 42]. The last three of these behaviors are discussed further and the others are discussed within the context of the findings from studies using these paradigms.

Drug Self-Administration in Rats with Neuropathic Pain

A major concern with the treatment of neuropathic pain using opioids is addiction, both from patients and physicians alike. Anecdotal evidence suggests that the subjective effects of opioids differ in the presence of pain, and appropriate use of these drugs for pain relief is possible even with chronic nonmalignant pain. Although a considerable amount of research has identified mechanisms of opioid analgesia and addiction, the influence of chronic pain on the abuse liability of opioids has not been studied to a great extent. Induction of persistent inflammatory pain using Freund's adjuvant in rats increases morphine intake through self-administration, an effect that is reversed by indomethacin [35]. Oral fentanyl self-administration is also increased in the presence of inflammation in rats [9, 10, 30]. These data suggest that the presence of acute or subchronic inflammatory pain alters opioid intake through self-administration in a manner consistent with titration of an analgesic effect.

In our laboratory, we sought to determine if animals with persistent neuropathic pain would self-administer opioids in order to reverse a subjective pain state, as opposed to normal animals that self-administer opioids to activate classical reward mechanisms. Our hypothesis was that only opioids that alleviated other behavioral measures of neuropathic pain, such as mechanical hypersensitivity, would be self-administered and only at effective doses. Further, we hypothesized that the rate of drug intake through self-administration would be consistent with the time course of reversal of neuropathic pain symptoms, and that alleviation of these behaviors by administration of adjuvant analgesics would decrease opioid intake selectively in

rats with neuropathic pain. Using the nerve ligation model of Kim and Chung [26], we examined the ability of a number of opioids to maintain self-administration in rats with neuropathy compared to normal uninjured animals [41]. Most opioids maintain intravenous self-administration in rodents in a manner consistent with their potency, efficacy, and half-life when examined over the full dose-effect range. At low doses, little to no responding is maintained and the rate of responding or number of infusions increases as a function of increasing dose to a maximum. As dose is increased further the rate of responding or number of infusions decreases due to increased duration of the subjective reinforcing effect at higher doses, increased incidence of effects that are inconsistent with operant responding such as sedation or catalepsy, or some combination of both. This typical inverted U-shaped dose-effect was observed in normal animals with all opioids studied with typical potency and efficacy for each compound. However, not all of the opioids studied maintained robust self-administration in nerve-injured rats. Notably, both fentanyl and morphine maintained very low rates of responding at all doses examined. These drugs had the lowest relative intrinsic efficacy at mu-opioid receptors of all the opioids studied [58, 59]. Heroin and methadone, conversely, maintained robust responding in rats with neuropathic pain but only at higher doses sufficiently high to produce reversal of mechanical allodynia. Higher doses of these two opioids were required to maintain responding in rats with neuropathic pain compared to normal animals. These two opioids were also found to be the most efficacious of all opioids studied in reversing mechanical allodynia following nerve injury, and the time elapsed between self-administered infusions of either heroin or methadone was consistent with the duration of their antiallodynic effect when administered intravenously. Hydromorphone displayed a profile in between those of heroin and methadone, and those of morphine and fentanyl. The maximum rate of responding that could be obtained in nerve-injured rats was significantly diminished compared to normal rats with hydromorphone; however, this compound did maintain responding in a manner consistent with the duration of it is antiallodynic effect. These data collectively suggest that rats with neuropathic pain were self-administering opioids to maintain a different subjective state than normal animals, or that the subjective state was similar between these groups but diminished in the presence of neuropathic pain with lower doses of high efficacy opioids or at all doses of opioids with relatively lower intrinsic efficacy.

Theoretically, if rats with neuropathic pain were self-administering opioids to maintain a subjective state related to pain relief then administration of an adjuvant analgesic prior to opioid access should diminish opioid consumption through self-administration. There are examples from a variety of drug classes that alleviate hypersensitivity in laboratory animals and humans with neuropathic pain; however, relatively few are efficacious against the more troublesome aspects such as ongoing pain. Clonidine given spinally alleviates both spontaneous pain and hypersensitivity in patients; however, adenosine given by this route alleviates hypersensitivity only [14, 15]. When rats with spinal nerve injury are trained to self-administer opioids, clonidine given intrathecally significantly diminishes opioid intake in a dose–responsive manner [41]. However, intrathecal (i.t.) clonidine is without effect

in normal rats self-administering opioids. Perhaps more interesting, i.t. administration of adenosine at a dose that is equiefficacious with the doses of clonidine given in reversing mechanical hypersensitivity has no effect on opioid self-administration in rats with nerve injury. Other investigators have found that clonidine, but not adenosine, induces a conditioned place preference selectively in rats with peripheral nerve injury [27]. These data have several implications. One is that rats with neuropathic pain appear to be titrating a different subjective state during opioid self-administration than normal rats. This is evidenced by i.t. clonidine reducing opioid consumption through self-administration only in rats with spinal nerve injury. Second, the subjective state does not appear to be strictly related to reversal of mechanical hypersensitivity. This idea is supported by the data showing that i.t. adenosine, while equiefficacious with clonidine in reversing mechanical hypersensitivity, has no effect on opioid intake. Lastly, these data demonstrate that spinal nerve ligation produces a subjective state in rats with a resultant behavioral pharmacology similar to that observed in chronic neuropathic pain patients. This last point is not trivial, as many investigators have suggested that these nerve injury models in rodents do not produce the full range of behaviors found with neuropathic pain in the clinic, but merely produce mechanical hypersensitivity that may have little to no relevance for treatment strategies in this population. One of the main primary outcome measures and goal for chronic pain treatment with novel analgesics is the reduction of opioid consumption. Opioid self-administration in rats following nerve injury appears to have significant face validity and displays pharmacology consistent with clinical data.

These data suggest that the neuronal mechanisms that are responsible for maintaining opioid consumption in the presence of neuropathic pain differ from those in the absence of chronic pain in rodents. Investigations into the mechanisms that contribute to opioid self-administration in rodents in a laboratory setting have utilized a variety of techniques to identify pertinent neurochemical, neurophysiological, and pharmacological mechanisms. A detailed discussion of these findings is beyond the scope of this chapter; however, many excellent reviews have been provided in the literature [28, 29]. Relatively few studies have specifically examined how the presence of pain might alter these mechanisms. In mice, peripheral nerve injury diminishes cFos activation in the ventral tegmental area [49]. This is accompanied by reduced mu-opioid receptor G-protein coupling in this region and diminished conditioned place preference to morphine [53]. Both mu-opioid and dopaminergic activity is reduced in the presence of acute and chronic pain [50]. These data are consistent with the opioid self-administration data reviewed above, namely that higher doses or more efficacious opioids would be hypothesized to be required to maintain self-administration in animals with nerve injury compared to normal. However, if this were the sole mechanism responsible for decreased self-administration in animals with nerve injury, then theoretically one might expect that alleviation of peripheral noxious input through intrathecal administration of an analgesic would restore activity of ventral tegmental neurons to normal, which would result in an increase in opioid self-administration. This clearly does not happen; however, suggesting that perhaps the conditioned stimulus that maintains operant

behavior upon which opioid intake is made contingent differs between nerve-injured and normal animals. There are several brain regions that coordinate peripheral noxious input and activity within the limbic system. The amygdala has been extensively studied in this context. Once again, a thorough review of this body of work is beyond the scope of this chapter; however, several excellent reviews have been provided [1, 18]. To investigate the relevance of the amygdala in opioid self-administration in the presence of pain, we utilized an irreversible inhibitor of mu-opioid receptors beta-funaltrexamine [39]. We have previously demonstrated that beta-funaltrexamine irreversibly inhibits mu-opioid receptors when administered intracerebroventricularly or into discrete brain regions for approximately 7 days after administration [43]. This compound has several advantages over typical opioid antagonists. One advantage is that the effect last for several days rather than a few hours. This is a particular advantage with drug self-administration as the drug can be administered on 1 day, and behavior assessed the following day minimizing behavioral disruption due to the injection procedure itself. Additionally, determining modest changes or differences in self-administration within a relatively short time frame can be problematic, particularly if the rate of responding is relatively modest to begin with such as with higher doses of opioids. Determining the effect across several hours of self-administration and across several sessions renders the study more powerful statistically. Additionally, the irreversible action of beta-funaltrexamine allows a detailed anatomical determination of the location and extent of mu-opioid receptor inactivation in vitro using either receptor binding or opioid-stimulated $GTP\gamma S^{35}$ binding by autoradiography. Utilizing these tools, we were able to target mu-opioid receptors in the lateral portion of the amygdala and reduce DAMGO-stimulated G-protein activation by 60 % following administration of beta-funaltrexamine. The effect of reduced mu-opioid receptor activation produced a modest increase in opioid self-administration in normal rats; however, the effect was approximately fivefold greater in rats with neuropathic pain. In the region of the opioid dose-effect curve that used for these experiments, an increase in rate of drug intake is typically interpreted as a decrease in the reinforcing effect of a single injection. The result is that animals must increase their rate of intake to achieve the same desired effect before the manipulation. Therefore, it appears that mu-opioid receptors within the lateral amygdala are more relevant for producing the subjective state motivating animals to self-administer opioids in the presence of neuropathic pain than in the absence of pain. There are several candidate neurons that could be differentially modulated by opioids and further investigation of how the presence of pain alters these inputs and the role of mu-opioid receptors merit further study. These data however further suggest that peripheral nerve injury models in rodents produce relevant effects on the behavioral pharmacology of opioids beyond production of hypersensitivity that can be measured using drug self-administration.

These findings however suggest that other drugs could potentially alter this negative subjective state and provide similar conditioned stimuli that would support self-administration. One drug in particular that would be hypothesized to maintain self-administration in the presence of neuropathic pain would be clonidine, particularly by an intrathecal route of administration. Clonidine would be expected to

be self-administered intrathecally in rats with neuropathic pain if the effect on reducing opioid intake in these rats were due to production of a similar subjective state as intravenous opioids. Given that intrathecal administration of clonidine had no effect on opioid self-administration in normal rats, it would be expected that normal rats would not self-administer clonidine by this route. If clonidine failed to maintain self-administration in rats with neuropathic pain, then it might suggest that clonidine's effect on opioid self-administration might be due to other effects not related to negative reinforcement, but rather production of effects that interfere with operant responding that are enhanced following nerve injury for unknown reasons. Therefore, demonstration that clonidine maintains self-administration intrathecally only in rats with nerve injury would add interpretive value to the studies described above. Studies in our laboratory indeed confirmed that intrathecal clonidine was selectively reinforcing in rats with nerve injury [42]. When both normal and nerve-injured rats were given access to intrathecal clonidine infusions through lever presses, the initial rates of responding were approximately equal. Over 2–3 days however, rate of responding increased in nerve-injured rats to a stable level, whereas the rate of responding decreased to only 3–4 lever presses daily in normal rats. In nerve-injured rats, decreasing the dose of clonidine per infusion increased responding, whereas increasing the unit dose decreased responding. These data support the hypothesis that clonidine was the salient reinforcer maintaining responding. When clonidine was replaced with saline, responding rapidly fell to three to four lever presses daily. Finally, rats with nerve injury failed to acquire intrathecal self-administration of a combination of clonidine and the α2 adrenergic antagonist idazoxan, consistent with the known antiallodynic and analgesic mechanism of clonidine's pharmacological effect. Once clonidine intake through self-administration became stable in nerve-injured rats, the daily consumption was greater than would be expected given this drug's maximal effect and duration of antiallodynic action using reflexive withdrawal measures. This increased intake occurred with a time course consistent with the development of tolerance to the antiallodynic actions of clonidine. However, the increased rate of intake could indicate that sufficient levels of drug were being achieved to have effects at peripheral or supraspinal sites. Indeed clinically, the pharmacological effects of clonidine that limit maximal dose are hypotension and sedation, which are not thought to be mediated by a spinal site of action. Following chronic intrathecal infusion of clonidine, we have found that α2 adrenergic receptors become desensitized in the central amygdala, suggesting that indeed sufficient levels of clonidine reach relevant supraspinal sites following intrathecal infusion to produce pharmacological effects (unpublished observations). To test the relevance of this finding, we found that administration of the nonselective receptor alkylating agent EEDQ into the amygdala reduced α2 adrenergic stimulated G-protein coupling by approximately 75 % and significantly decreased acquisition of intrathecal clonidine self-administration in nerve-injured rats (unpublished observations). These data support the idea that intrathecal clonidine provides a sufficient stimulus to serve as a reinforcer in rats with neuropathic pain, and only in rats with neuropathic pain, and that this stimulus is mediated through both spinal and supraspinal α2 adrenergic receptors.

The implications of these data go beyond the findings that intrathecal clonidine will maintain self-administration in the face of neuropathic pain however. As mentioned above, there is some controversy regarding the usefulness of peripheral nerve injury models in rodents as surrogates for clinical neuropathic pain. The concern is that reflexive paw withdrawal does not accurately reflect a clinically relevant painful stimulus, or that inhibition of this response is too nonspecific of a pharmacological effect to delineate between drugs that are likely to display clinical efficacy in patients with neuropathic pain from those that have relatively lower potential. The other primary concern and criticism is that these models produce only hypersensitivity but do not demonstrate the full range of behaviors found in the clinic, particularly ongoing or spontaneous pain. However, the finding that rats with peripheral nerve injury will self-administer intrathecal clonidine at a dose that produces an opioid-sparing effect in a self-administration model lends credence to the idea that these nerve injury models indeed produce a subjective state that is sufficient to result in selective reinforcement by administration of clonidine and results in a pharmacology of both clonidine and opioids that is consistent with clinical data. These data also support, and are supported by, findings from other investigators that intrathecal clonidine becomes selectively reinforcing in rats with neuropathic pain using the conditioned place preference model [27]. However, these data do support the idea that inhibition of reflexive withdrawal from mechanical or thermal stimuli is insufficient to delineate between drugs that have been found to be useful clinically for neuropathic pain treatment and from those that have been found to be ineffective or lacking sufficient efficacy relative to adverse dose-limiting effects. Self-administration methods become problematic for screening large numbers of potential therapeutics however due to the amount of time and resources required relative to more simple behavioral methods. However, clearly this technique has utility for identification or verification of potential novel therapeutic targets for clinical efficacy against neuropathic pain, as well as possess face validity for investigation of the basic neurophysiology, neurochemistry and pharmacology of nerve injury models of pain in laboratory animals.

While our lab has focused on the amygdala as a primary brain region involved in the reinforcing efficacy of analgesics in the presence of pain, clearly there are many other brain regions that are logical candidates for study. Others have investigated the role of the anterior cingulate cortex in the reinforcing efficacy of intrathecal clonidine in rats with nerve injury using conditioned place preference [56]. Regions that have significant populations of mu-opioid receptors and are known to be influenced by noxious stimulation include the anterior cingulate cortex and both medial and lateral thalamic nuclei. Recent data in our laboratory indicate that inhibition of mu-opioid receptors in either anterior cingulate cortex or medial thalamus produces similar effects on opioid self-administration as found previously with the amygdala, namely that opioid intake is selectively increased in rats with nerve injury relative to normal animals (unpublished observations). Therefore, examination of the mechanisms through which peripheral nerve injury alters the reinforcing effects of opioids could lead to the development of novel analgesics that either provide efficacious pain relief alone or provide substantial opioid-sparing effects.

Reinforcing Effects of Deep Brain Stimulation in Rats with Neuropathic Pain: Role in Defining Alterations in Reinforcement Mechanisms and Analgesic Pharmacology

The use of deep brain stimulation for pain therapy has been studied in the clinic; however, the response is highly variable depending on brain regions studied and pain conditions, with some success reported in thalamus, periaqueductal gray, and motor cortex [8, 13, 22]. However, tolerance to the analgesic effects of deep brain stimulation and the emergence of troublesome side effects limit its use in the clinic [34]. The recent emergence of deep brain stimulation as an effective therapy for treatment of movement disorders such as those associated with Parkinson's disease has increased interest in exploring this option for treatment of other disorders including chronic pain [33, 51]. In the animal laboratory, deep brain stimulation induced analgesia has been explored in rodents and the thalamus, periaqueductal gray, and motor cortex will support stimulation-induced analgesia [12, 31, 44]. Recent studies on spinal cord electrical stimulation has provided some evidence of selectivity for pain relief and the pharmacology of analgesics in potentiating these effects has been described [19]. Clinically, spinal cord stimulation is the primary treatment model for electrically induced analgesia in patients with chronic pain [60]. However, the primary use of electrical brain stimulation in laboratory animals has been for the study of reinforcement mechanisms related to drug abuse.

As a means to study reinforcement pathways, intracranial self-stimulation or ICSS was developed in the 1950s and remains a useful tool for studying drug abuse mechanisms [7, 52, 64]. This method is essentially the self-administration of electricity into discrete brain regions. Typically electrodes are implanted into either the ventral tegmental area or the medial forebrain bundle, and electricity delivered to either of these sites ultimately increases activity of ascending dopaminergic fibers from the ventral tegmental area to forebrain sites including the nucleus accumbens and ventral pallidum. Typical drugs of abuse such as psychostimulants including cocaine or opioids potentiate the ability of electrical stimulation to maintain operant responding. However, this technique has not been used to explore similar questions posed above using drugs as reinforcers, namely if electrical stimulation of certain brain areas that are known to be relevant for nociception or analgesia will maintain operant responding selectively in animals with neuropathic pain. Additionally, the use of ICSS allows one to ask questions related to the activity of drugs in potentiating the reinforcement produced by activation of specific brain regions as opposed to systemic drug self-administration.

We were interested in whether the effects of nerve injury on opioid self-administration were due to decreased positive reinforcing effects through diminished activation of the limbic dopaminergic neurons emanating from the ventral tegmental area as has been suggested with studies in mice. If this were the case, then one would expect that electrical stimulation of the ventral tegmental area would be less reinforcing or would require a greater frequency or intensity of stimulation to maintain behavior. Alternatively, if these effects were specific to opioids, then the ability

of opioids to modulate these neurons and potentiate ICSS in the ventral tegmental area might be selectively decreased following nerve injury. The latter of these two alternatives was found to be the case [17]. Rats with neuropathic pain had an identical frequency response curve as normal rats for ICSS maintained by stimulation of either the ventral tegmental area or the medial forebrain bundle. However, the ability of a variety of opioids to potentiate ICSS in these regions was selectively diminished in rats with nerve injury compared to normal animals. The ability of cocaine to potentiate ICSS in these regions was not altered by nerve injury. The ability of nerve injury to alter potentiation of ICSS in these areas was dependent upon the relative intrinsic efficacy of the opioid agonist administered, with an almost identical relationship as that observed with systemic self-administration of the same compounds. Electrical stimulation of either the ventral tegmental area or the medial forebrain bundle fails to alter mechanical hypersensitivity in nerve-injured rats, suggesting that these effects of nerve injury on opioid potentiation of ICSS is not related to the ability of these drugs to reverse allodynia in these animals. Rather, these studies suggest that opioids are selectively less capable of stimulating dopaminergic projections from the ventral tegmental area in the presence of neuropathic pain, and therefore should be relatively less capable of producing positive reinforcing effects that are mediated by these neurons. However, it is known that only a portion of opioid reinforcement in normal animals is mediated by dopaminergic systems. These data however are consistent with the findings in mice that nerve injury diminishes the ability of opioids to stimulate ventral tegmental area neurons and that there is diminished mu-opioid G-protein coupling in this area. Administration of intrathecal clonidine to nerve-injured rats did not alter ICSS in the ventral tegmental area, again suggesting that these experiments are assessing the effects of nerve injury on positive reinforcement systems rather than alteration of negative reinforcement through alleviation of pain, whether elicited or spontaneous. These data also highlight subtle differences in how these various procedures might be used to delineate positive and negative reinforcement of opioids in a chronic pain state in the laboratory.

Another potential use of deep brain stimulation in laboratory animals is to examine if stimulation-induced reversal of allodynia translates into negative reinforcement in animals with neuropathic pain. This idea is similar to that described above examining intrathecal self-administration or opioid-sparing effects of analgesics in the presence of pain. By examining intracranial self-stimulation in addition to reversal of allodynia with deep brain stimulation, the notion is that one can delineate between brain regions that support negative reinforcement in a pain state versus those that merely disrupt reflexive withdrawal behavior. Many regions are known to produce stimulation-induced analgesia in rodents, having been typically identified using reflexive withdrawal from a noxious stimulus in a normal animal. Two regions have been studied in some detail in rats following peripheral nerve injury, namely the periventricular nucleus of the hypothalamus and the motor cortex. Electrical stimulation of both of these regions will produce antiallodynic effects in rats following nerve injury [11, 12]. Rats with nerve injury, but not normal rats, will display a place preference when conditioned to electrical stimulation of the motor cortex, similar to the manner in which rats with chronic neuropathic pain display

conditioned place preference with intrathecal clonidine. The periventricular nucleus of the hypothalamus will support intracranial self-stimulation in rats with peripheral nerve injury, and the frequency–response relationship for maintenance of operant responding is similar to the relationship for reversal of mechanical allodynia [16]. Both electrically induced antiallodynic effects and self-stimulation are reduced in nerve-injured rats following intrathecal administration of the oxytocin/vasopressin antagonist atosiban, as well as following intrathecal administration of the mu-opioid antagonist naltrexone. Interestingly, normal animals will also self-stimulate the periventricular nucleus, presumably through oxytocinergic mechanisms. Intrathecal administration of atosiban did not influence ICSS in the PVN of normal rats however. This is reminiscent of opioid self-administration in normal rats compared to rats with nerve injury, in that both groups of animals will self-administer opioids with a differential pharmacology. Additionally, the ability of opioids to potentiate ICSS in the PVN is not diminished following nerve injury unlike in the medial forebrain bundle or VTA, suggesting that the mechanisms that support PVN ICSS and opioid potentiation are more germane to the reinforcing effects of opioids in the presence of pain than the classical dopaminergic reinforcement systems.

Conclusions and Future Directions

The studies highlighted in this chapter address several important questions regarding prescription opioid abuse and the role of chronic pain. While chronic neuropathic pain appears to alter the mechanisms through which opioids produce reinforcement in rodents and diminishes opioid self-administration, high efficacy opioids produce robust self-administration at higher doses and stimulate classical reward pathways at doses that reverse neuropathic pain symptoms. These studies however indicate that exploration of motivated behaviors in rodents, including self-administration of nonopioid analgesics or intracranial self-stimulation, could provide novel targets for chronic pain treatment or development of opioid-sparing strategies. Reduction in the need for opioid use in this population could significantly reduce the need for narcotics in pain patients and decrease the availability for diversion for nonmedical use.

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Chapter 3
The Influence of Pain on Reward Processing: Current Literature and Prospects

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Abstract Both short- and long-term pain influence reward processing. Albeit the literature is still scarce, a picture is emerging in which pain increases the motivational drive to obtain reward, whereas the pleasure that is felt when a reward is obtained seems to be unchanged or even decreased. In addition, brain systems that are important for pain modulation as well as reward processing are altered by pain, possibly leading to less efficient endogenous pain control and contributing to emotional sequelae of chronic pain. Altered reward processing, including increased motivational drive and urge, and increased pain sensitivity might contribute to problematic drug behaviors in some chronic pain patients.

Introduction

Interactions between pain and reward processing are well known from everyday experiences. One can think of several situations where incentives lose some of their attraction if pain has to be overcome in order to obtain the reward. The other way around, prospects of reward can decrease pain sensitivity and increase pain tolerance. Avoiding pain and seeking reward are two fundamental motivations crucial for survival. When they are activated simultaneously they likely compete for preference in the brain [1], as described by the Motivation-Decision Model [2]. The "decision" whether the potential reward or the avoidance of pain is valued as being more significant is dependent on situational factors, personal factors, and the state of the organism.

In this chapter, we explore the influences pain has on reward processing, how such influences might differ for short-term versus long-term pain exposure, and the significance this might have for addictive behaviors in chronic pain patients.

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C.A. Fairbanks, T.J. Martin (eds.), *Neurobiological Studies of Addiction in Chronic Pain States*, Contemporary Clinical Neuroscience 17,
DOI 10.1007/978-1-4939-1856-0_3

We first briefly discuss different aspects of reward processing (section "Different Aspects of Reward Processing"), followed by cerebral overlaps of pain and reward (section "Cerebral Overlaps of Pain and Reward Processing"). Section "Influence of Pain on Reward" concerns the impact pain has on reward processing and on brain systems underlying reward. In section "What Is the Significance of Pain-Induced Alterations in Reward-Processing Systems for Addiction?", we discuss the potential impact of pain-induced alterations in reward systems on addiction, before concluding the chapter with a summary and an outlook (section "Summary and Outlook").

Different Aspects of Reward Processing

Reward processing is conceptually complex embracing several facets such as the ability to feel pleasure ("liking," emotional response), motivation ("wanting"), reward sensitivity, and risk taking. These different aspects of reward processing are discussed in more detail in the following.

Emotion and Motivation

Emotion and motivation are essential to reward processing. Rewarding stimuli generally lead to an emotional response (perceived pleasure), and they are desired, implying that subjects are willing to work for a given incentive.

As shown by animal studies, the pleasure of obtaining a reward ("liking") is linked to opioidergic neurotransmission in the nucleus accumbens [3–7], with GABA/benzodiazepine and endocannabinoid neurotransmission also playing important roles for the generation and mediation of pleasure [5, 6, 8, 9]. Main output target region for the nucleus accumbens is the ventral pallidum [10] whose posterior part has also been strongly linked to "liking" [10, 11]. In humans, rewarding stimuli, such as drugs of abuse, sex, food, and money, lead to activation in the ventral striatum corresponding probably to the opiodergic "liking" spots in rats [10, 12–14]. Regarding addiction, pleasure plays a key role in its initiation: opioid consumption for instance can have strong euphoric effects associated with intense perceived pleasure [15]. This reinforces the behavior of drug intake and can lead, in turn, to enhanced reward-seeking behavior. However, once the drug effects wear off, dysphoria or displeasure is perceived which is then tried to be reversed by the drug of abuse; a resource that works only temporarily. An addictive vicious cycle is initiated and aggravated by unsatisfactory hedonic responses (reviewed in [16]).

Motivation describes the willingness to work for a rewarding stimulus [17, 18], implying that a given incentive is wanted. "Wanting" is based on incentive salience, which is the result of an implicit process of transforming sensory information of a stimulus (e.g., smell, sights) into an appetitive, attractive incentive [19]. The wanted incentive can then trigger appropriate behavior aimed at obtaining the reward. "Wanting" and "liking" a reward typically occur together and are therefore not

easily disentangled. Nevertheless, animal studies reveal different neural substrates underlying the two processes [20, 21]: "wanting" is predominantly mediated by mesolimbic dopaminergic neurotransmission [21–24], whereas "liking" is strongly linked to opioidergic transmission as discussed above. In the addiction literature, "wanting" has been discussed in relation to incentive-sensitization. Incentive-sensitization describes the process where the sensitivity to transform drug-related cues into a salient incentive is being increased. This process potentially leads to compulsive motivation to pursue drug intake (reviewed in [22]).

Reward Sensitivity

Reward sensitivity describes an individual's sensitivity and reactivity to appetitive stimuli [25]. The reward sensitivity theory by Gray [26] (revised by [27]) considers three neurobehavioral systems as the basis of reward sensitivity: the Behavior Activation System (BAS), the Behavior Inhibition System (BIS), and the Fight and Flight System (FFS). The BAS is characterized by the motivation to obtain rewarding stimuli [28] and is associated with relief when the reward is received [25]. The FFS is sensitive to aversive stimuli and is concerned with the avoidance of harm or loss. It is linked to emotional responses of fear and rage [25]. The BIS is understood as the system directing attention either toward the BAS (by inhibiting the FFS) or toward the FFS (by inhibiting the BAS). Accordingly, it is activated by approach/avoidance conflicts [29] and has been associated with worrying and rumination [28]. In people with high reward sensitivity, the BAS is "stronger" than the FFS or, in other words, the BIS directs more attention toward appetitive stimuli than toward potential harm. The concept of reward sensitivity is closely linked to motivation and emotion and can be seen as a basis of many reward-depending learning processes such as operant learning [30]. In humans, reward sensitivity can be assessed with the BIS/BAS scale [31]. On this scale, BAS encompasses three facets, namely drive (persistent pursuit of rewarding goals), reward responsiveness (high expectation of reward), and fun seeking (high desire to seek reward, active seeking of rewarding environments, and an impulsive pursuit of rewarding stimuli). Reward sensitivity has repeatedly been linked to increased alcohol consumption [32–34] and drug addiction [35].

Risk Taking

Risk taking is another important facet of reward processing as risks of a potential loss are accepted to maximize reward. According to Gray's reward sensitivity theory, the BIS tends to favor the FFS in risky situations to reduce the potential for harm [27]. In risk takers, disinhibition takes place and the attention is strongly focused on the pursuit of reward tolerating the exposure to potential harm. Disinhibition, i.e., increased risk taking, is associated with addiction and substance abuse [36].

Cerebral Overlaps of Pain and Reward Processing

Neuroanatomical and neurochemical data support the psychological links between pain and reward. Several brain regions, including dorsal and ventral striatum, amygdala, orbitofrontal cortex, and anterior and posterior insula, are implicated in pain as well as in reward processing (see [1, 37] for review). For reward processing, different functions have been identified for these areas and in particular the distinct roles of the orbitofrontal cortex and ventral striatum have been studied extensively. The orbitofrontal cortex appears to be central for the representation of subjective reward value by coding stimulus value for primary and secondary rewards (e.g., [38–42]). Further, the orbitofrontal cortex encodes and updates expectations of future reward, presumably in close interaction with other structures such as the amygdala and ventral striatum (e.g., [43–46]; see [47] for review). With respect to pain, the orbitofrontal cortex has been implicated in pain modulation by distraction as well as by emotions. Increased orbitofrontal activity during distractive tasks has been observed to correlate with decreased subjective pain perception [48–50]. Since none of these studies employed paradigms that would have allowed isolating distraction, other task-induced state changes, such as arousal or emotions, might have contributed to the observed pain modulations. Indeed, a study that carefully dissected attention and emotion [51] showed that orbitofrontal activity covaried with pain-related activity in the anterior cingulate cortex and periaqueductal grey and correlated with emotional modulation of perceived pain intensity. Similarly, activity in the orbitofrontal cortex predicted the effect of emotions on pain-related activation of the insula [52]. These studies indicate that the orbitofrontal cortex is an important site for pain modulation by emotions. Based on these studies identifying the orbitofrontal cortex as an important structure of mediating pain modulation by emotions, we hypothesize that the orbitofrontal cortex might also play a role in pain modulation by the emotional/hedonic component of rewarding stimuli, possibly via projections from orbitofrontal cortex to insular cortex, anterior cingulate cortex, and periaqueductal grey. Considering the function of the orbitofrontal cortex to compute subjective reward value and its pain-modulatory capacities, it might be a key structure of the Motivation-Decision Model by devaluing reward in situations in which pain is deemed more important and by decreasing pain in situations in which reward is deemed more important.

The ventral striatum emerges to be central for reward prediction, coding positive and negative reward prediction errors, and thereby promoting learning [53]. Accordingly, the ventral striatum responds strongly to unexpected rewards and omissions of expected rewards (e.g., [43, 54–56]; see [57] for review). Functions of the ventral striatum with respect to nociceptive processing are less certain. Nevertheless, the ventral striatum is activated in response to pain (reviewed in [1, 58]) and has been shown to modulate pain [59, 60], presumably through projections to the cingulate cortex, amygdala, medial thalamus, and hypothalamus [61–63]. We are not aware of literature that tests the influence of pain on reward-related ventral

striatum function but considering that the occurrence of reward might be less expected in the presence of pain, it could be hypothesized that a pain-induced increase of ventral striatum activity may lead to rewards becoming even more salient.

In addition to anatomical overlaps, pain and reward processing share at least two important neuromodulators: dopamine and endogenous opioids. Dopaminergic neurotransmission is a key player for reward processing [56] and the mesolimbic-cortical system connects brain regions crucial for reward processing by ascending dopaminergic pathways. These pathways originate in the ventral tegmental area (VTA) of the midbrain and target the nucleus accumbens, the amygdala, the hippocampus, and the medial prefrontal cortex. Dopamine's role in motivational drive ("wanting") is well supported by evidence from animal and human data (e.g., [64–69]; see [70] for review). These studies demonstrate that dopamine is needed and sufficient to encode motivation to work for reward. In contrast, dopamine release per se is not sufficient to explain hedonic responses to rewarding stimuli [1, 21, 71]. This function is mediated by opioidergic systems as already mentioned [20, 67]. In rodents, μ-opioid receptor activation is associated with positive hedonic shifts, indicated by increased pleasure or decreased aversiveness in response to opioid agonist injection to specific sites of the nucleus accumbens [20].

Dopamine [72–75] as well as opioids [76, 77] are also implicated in pain processing. Similarly to appetitive stimuli, aversive environmental stimuli, including short-term pain, trigger the activation of dopaminergic neurons in the VTA via the release of substance P and endogenous opioids [78, 79]. This activation leads to dopamine release in mesolimbic projection areas [80] such as the ventral striatum. Release of endogenous dopamine has been shown in response to experimentally induced acute pain in healthy participants [75, 81]. The function of dopamine for pain processing is currently not fully understood: while human studies show a positive association between the magnitude of dopamine release and pain sensitivity [75, 81], animal studies consistently indicate pain-decreasing effects of dopamine [82]. In particular, D2-receptor activation has been demonstrated to diminish pain behaviors [82–84]. Further, local anesthetic microinjections into dopaminergic structures or selective lesion of dopaminergic neurons lead to hyperalgesia in animals [85], indicating pain inhibiting effects of resting dopamine levels.

The importance of endogenous opioids for pain modulation is well established. Zubieta and coworkers [76] provided evidence in humans for significant supraspinal activation of the μ-opioid receptor system in response to experimental pain in several brain regions including the anterior cingulate cortex, lateral prefrontal cortex, anterior insular cortex, thalamus, ventral basal ganglia, amygdala, hypothalamus, and periaqueductal grey. Opioid activation in the ventral basal ganglia (nucleus accumbens/ventral pallidum), in addition to ipsilateral thalamus and amygdala, was inversely correlated with sensory pain ratings. This result suggests that supraspinal opioid activity plays a role in pain inhibition, in line with opioid function in descending pain pathways [86].

Influence of Pain on Reward

Considering the extensive overlap of pain and reward in the brain, it is conceivable that pain influences reward processing. In the following, we discuss the impact pain has on reward processing. Since evidence suggests that long-term exposure to pain might alter reward processing systems, we differentiate between short-term (acute) and long-term (chronic) pain.

Short-Term Pain

In general, studies in humans investigating the influence of short-term pain on reward processing are scarce. Results from one recent study suggest that afferent nociceptive signals can alter the attractiveness of reward via insular-orbitofrontal pathways [87]. This study showed that the individual variability in how pain affected reward-related decisions was reflected in orbitofrontal activity modulated by pain-related activity in the insular cortex, in line with the proposition that orbitofrontal cortex is a key structure for assigning subjective reward value. In one of our own studies, we specifically investigated the influences of acute tonic heat pain on reward motivation and hedonic responses to reward. We demonstrated that acute tonic pain influences the motivation to work for reward, whereas hedonic responses remained unaltered by pain [88]. Using a parametric incentive delay paradigm, we showed that healthy participants responded significantly faster to high incentives when in acute pain compared to a control condition. Despite the increased effort to work for high incentives under pain, participants did not like their winnings more in one condition than in the other. We interpreted these results as a pain-induced mismatch of increased motivational drive with a lack of increased hedonic responses. Our results in humans are in accordance with data from a rodent study that demonstrated increased time spent in proximity to food pellets in the middle of an open field arena in acutely injured rats in the absence of increased consumption [89]. Similar to our study, these data can be interpreted as a pain-induced increase in motivation to obtain the reward, but concurrently unaltered pleasure associated with obtaining the reward. Albeit not a pain study, a study in healthy men that induced a negative emotional state of sadness [90] might be relevant here because pain is per definition an unpleasant emotional (and sensory) experience [91] and might induce a negative emotional shift similar to sadness. Induced sadness altered participants' behavior toward more reward seeking by choosing riskier options in two different experimental paradigms, possibly in order to counteract the negative emotional shift [90]. Based on these results, we hypothesized that acute pain would increase risk taking behavior in healthy volunteers. However, extensive studies from our laboratory did not reveal any influence of experimental pain on risk taking in young healthy participants. In three separate experiments, participants played the well-established Balloon Analogue Risk Task (BART [92, 93]), while experiencing a tonic pain stimulus. The BART has been validated [93] and has been shown to be correlated

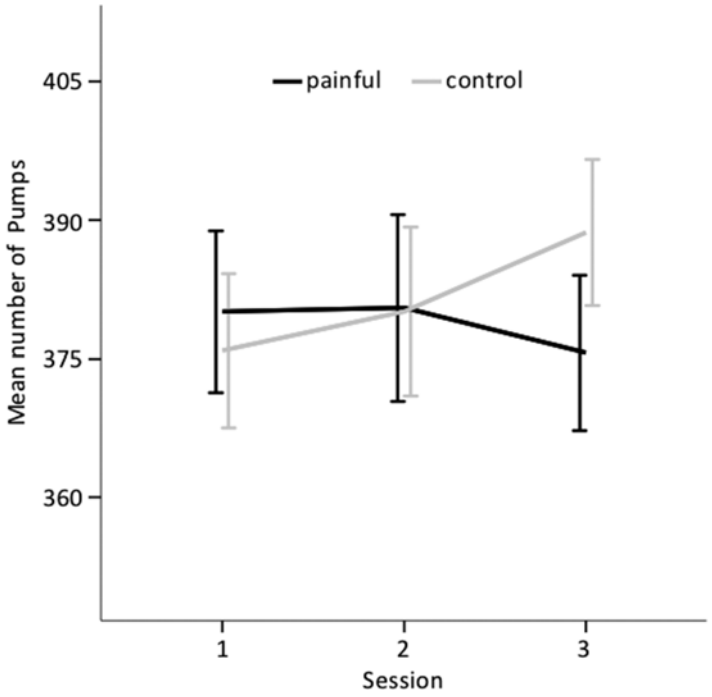

Fig. 3.1 Acute pain does not influence risk taking behavior. Here depicted: mean values +/− standard error of the mean for $N = 24$ healthy participants (third experiment of a series of three similar experiments) for two conditions (painful versus control) and three consecutive sessions of approximately 7 min each. The *y*-axis shows the average "number of pumps" (a measure of risk taking with higher number representing higher risk taking) for each session and condition. The graph is representative for all three experiments we conducted: acute pain has no effect on risk taking in an experimental setting

with relevant risk-related constructs and to measure risk unambiguously [93]. Using a within-subject design, we investigated the influence of experimental pain (foot immersion in ice-cold water) on the BART in female and male volunteers ($N = 71$ in total; 29 women, 42 men), compared to a nonpainful control condition (foot immersion in lukewarm water). Despite varying the duration of pain across experiments (between 2.5 and 22 min), controlling for hormonal status in females, and accounting for several personality traits and states such as mood and anxiety, we did not find any effect of experimental pain on risk taking behavior measured with the BART (Fig. 3.1). Of course, experimentally tested risk taking in humans might be influenced by more variables than we controlled for, such as current financial situation or affinity to engage in gambling. Alternatively, the pain model used (immersion in ice-cold water) might not have been effective in inducing a negative emotional shift and therefore had no effect on risk taking. Having investigated the effect of pain on risk taking in healthy humans thoroughly we conclude that the effect of experimental cold pain on risk taking behavior in healthy humans is at most weak.

Long-Term Pain

In contrast to short-term stress, long-term exposure, which encompasses persistent pain, is associated with stress-induced hyperalgesia rather than stress-induced analgesia [94]. Dopamine release in the nucleus accumbens has been shown to be reduced in chronically stressed rats [95, 96]. Similarly, dopamine release in response to experimental pain has been found to be reduced in patients with chronic widespread pain [81]. As discussed above, the role of dopamine for pain processing is currently not clear, but if dopamine had indeed pain-reducing properties as suggested by animal studies, stress-induced attenuation of phasic dopamine release might lead to hyperalgesia. Since tonic and phasic dopamine activity are inversely related [56, 97, 98] decreased phasic dopamine release in chronic pain/stress might be related to increased tonic dopamine levels [74]. To date, however, no direct evidence of increased tonic dopamine levels induced by long-term stress or pain exists to our knowledge. In fact, human dopamine receptor positron emission tomography (PET) studies show increased striatal binding potential in patients at rest compared to healthy controls [99, 100], suggesting either lower endogenous dopamine levels or increased receptor density/affinity [101]. Consequently, it is currently only safe to conclude that dopaminergic neurotransmission is altered in chronic pain. Considering the prominent role dopamine plays in motivation, altered dopaminergic neurotransmission in pain patients may change their motivational drive to obtain reward. Some preliminary evidence exists for alterations of motivational drive in chronic pain patients [102, 103]; however, we think that the direction of change can not necessarily be inferred from these studies that found reduced motivation, primarily because they did not control for depression.

In addition to its impact on the dopaminergic system, repeated exposure to stress has been shown to change the opioidergic system. In rats exposed to long-term stress (daily 1 h movement restraint on 5 days per week for 40 days in total), analgesic effects of morphine were significantly decreased compared to a nonstressed control group [94]. Results from animal stress studies are presumably important for clinical long-term pain as chronic pain can be understood as an unavoidable long-term stressor. In fact, human patient studies using opioid receptor PET have revealed decreased resting binding potentials in chronic pain patients suffering from neuropathic pain [104] and fibromyalgia [105]. Reduced resting binding potentials can result from increased endogenous opioid levels as well as decreased receptor density/affinity, as discussed above. Theoretically, both of these possible mechanisms might contribute to the reduced binding potential in pain patients: opioid systems might be chronically activated in patients in an attempt to reduce pain. To attenuate cellular responses to increased levels of agonists receptor internalization can occur, decreasing the density of available receptors in order to protect the cell [101]. If internalization of opioid receptors occurred also in neuronal assemblies concerned with reward processing, opioid release in response to rewarding stimuli might consequently be altered in chronic pain patients. In support of this hypotheses, anhedonia [106] has been observed in chronic pain patients.

There are further studies indicating that reward processing is impaired in chronic pain albeit they do not always allow pinpointing the specific aspect of reward that is altered. For instance, chronic pain patients suffering from fibromyalgia or complex regional pain syndrome have been shown to be impaired in improving their performance on reward-dependent operant learning tasks [107, 108]. These studies suggest that pain patients are malfunctioning in their reward processing on a cognitive [109] as well as on a perceptual level [107], which is possibly related to reduced hedonic responses, reduced motivation, and/or altered reward sensitivity.

In many instances, the existing literature on altered reward processing in pain patients does not allow excluding potential influences of medication or pain at the time of testing. Nevertheless, support for the influence of long-term pain on reward processing is provided by animal data. It has been shown that rats with neuropathic pain symptoms require higher doses of rewarding morphine than sham operated animals to learn a place-preference [110]. Similar to the human studies, this could be caused by decreased "liking" of the reward, decreased motivational drive or decreased reward sensitivity. These results are complemented by a study showing that rats with persistent inflammatory pain developed a preference for a higher risk option over a lower risk option, indicating potentially higher tolerance of not receiving reward, in the presence of a potentially decreased motivation to work for reward [111]. These results are not fully in accordance with the few human studies indicating reduced motivation in chronic pain patients. However, as pointed out above, it would seem important to control for depression and other comorbidities in chronic pain patients that might lead to reduced motivation. Animal models might in many instances not sufficiently model comorbidities that often accompany chronic pain in humans.

What Is the Significance of Pain-Induced Alterations in Reward-Processing Systems for Addiction?

Exogenously administered opioids are the most powerful analgesics available. Opioids are effective with short-term use [112–116] as well as with long-term use over months [117]. Nevertheless, opioid treatment has been discussed critically with respect to its potential to inflict tolerance, dependence, and/or addiction [118]. In the following, we speculate how pain-induced changes in reward processing as well as in dopaminergic and opioidergic neurotransmission might contribute to addictive behaviors in susceptible individuals.

As outlined above, chronic pain constitutes a constant stressor. Enhanced stress levels are well-known risk factors for addicted behavior and relapse (for review, e.g., [119]) suggesting that pain patients might be vulnerable to become addicted. Some studies suggest that pain increases motivational drive while the pleasure associated with reward is not changed or even decreased, although it is currently not known whether the effects of pain extend beyond the effects of stress. The constellation of increased motivation without an increase in pleasure may lead to a vicious circle of increased desire for and seeking of reward. In the context of opioid therapy

for long-term pain, decreased pleasure associated with reward translates into less pain relief, so that gradually increasing drug doses are required. Moreover, prolonged use of opioidergic drugs can lead to negative emotional states, caused by withdrawal symptoms or by a lack of expected drug effect due to tolerance. Increased negative emotions, decreased positive emotions and the constant exposure to stress lead to "hedonic worsening" over time, which can potentially exceed the capacity of the reward system to reestablish homeostasis leading to long-term changes in the reward system by establishing a new homeostatic set-point ("allostasis" [120]). Allostasis is often accompanied by physiological changes (i.e., "allostatic load"), which have been described in chronic pain patients as a result of increased stress exposure [121].

To make matters worse, opioid-induced hyperalgesia is observed with administration of opioids, both clinically as well as in healthy volunteers [122–125]. As a consequence of hyperalgesia following opioid administration, increased pain sensitivity might become the new homeostatic set-point in some patients. The physiological changes associated with the new set-point have been discussed with respect to exposing these patients to higher risks of problematic opioid use [118].

Thus, increased motivational drive for reward without simultaneously increased liking of reward, combined with a drug-induced negative emotional state and hyperalgesia, may have the potential to make some chronic pain patients vulnerable to developing comorbid addictive behaviors. Drug-induced negative emotional states might contribute to diminished self-control and compulsive behaviors, whereas increased motivational drive is likely to contribute to appetitive urge and craving. Further, a formerly neutral stimulus such as a tablet or a capsule might become associated with rewarding properties by classical conditioning [126]. Now, the cue itself can trigger increased motivation and craving, possibly resulting in inappropriate drug intake, even in the absence of excessive pain, i.e., the unconditioned cue. This process is well known from the addiction literature in that drug conditioned, formerly neutral, cues cause craving and compulsive behavior [127, 128].

Not surprisingly, brain systems that appear to be central in the interaction of pain and reward also play important roles in addiction (see [129] for review). For example, drug-induced dopamine release is blunted but dopamine release in response to drug-conditioned cues is increased [127, 128, 130]. Further, activity in the orbitofrontal cortex and ventral striatum has been associated with enhanced motivational drive in addiction (see [131] for review; [132–134]). As discussed for pain, addiction-related alterations in brain systems seem to favor increased motivational drive and urge without providing the expected outcome, i.e., pleasure or relief. Such parallels between pain and addiction might mean that some chronic pain patients suffer an increased vulnerability for developing addictive behaviors.

But of course, not all chronic pain patients pharmacologically treated develop addictive behaviors. In fact, although the available evidence is limited, it appears that only a small fraction of chronic pain patients using prescribed opioids become addicted [118, 135]. The results of a recent rodent study potentially help understanding the observed low risk of addiction in pain patients. In this study, pain relief was used as negative reinforcement (the termination of an aversive stimulus) in a

conditioned place preference (CPP) paradigm in rats with postsurgical pain [136]. The group found that negative reinforcement, i.e., pain relief, shares characteristics of appetitive rewards, such as a similar behavioral outcome, i.e., learning the place preference (e.g., [137–139]), and the involvement of VTA dopamine release in reinforcement (reviewed in [140]). However, a potentially important difference was that endogenous opioids in the VTA were not required to learn CPP by pain relief; in contrast, using appetitive stimuli such as nonopioidergic drugs, endogenous opioids have been repeatedly shown to be involved in learning place preferences [139, 141–143]. This might mean that pain relief by itself does not lead to opioid release in the VTA and thus might lack a euphoric sensation, which is an important driver of addiction [15]. Further, it is conceivable that chronic pain patients have protective factors such as decreased novelty seeking together with increased harm avoidance; both personality traits have been described in chronic pain patients [144], and they are negatively correlated with risk taking [145] which might act as protective factor against the development of addiction. Clinically, opioid-induced hyperalgesia has been mainly described in patients with a history of drug addiction, high-dose opioid treatment [123, 146], and in patients who are undertreated [147]. Hence, careful screening of patients before prescription of potentially addictive therapeutic agents and close monitoring is recommended and likely to decrease problematic medication use in pain patients [118].

Summary and Outlook

Taken together, pain influences reward processing on several accounts. Albeit limited, the data for acute pain are relatively clear. With respect to long-term pain, the evidence is more conflicting, mainly regarding motivational drive and risk taking. Such inconsistencies might well reflect the complex picture of chronic pain with its many constituents, including comorbidities and medication use. As discussed, changes of opioidergic as well as dopaminergic systems underlying reward processing induced by repeated exposure to unavoidable stress (chronic pain) are likely to explain the alterations of reward processing and impairments of reward-dependent learning abilities in chronic pain patients. But in order to better understand the consequences of long-term pain, it will be important to unravel which of these changes are caused by long-term exposure to pain and which by comorbidities such as emotional disturbances and dyscognition. Also, we need more studies on the effects of acute pain on specific aspects of reward processing, including hedonic responses, motivational drive, and reward-responsiveness, because their results will help interpreting studies in patients who experience pain at the time of testing. Once the links between pain and reward are better understood, it will be interesting to investigate potential moderating factors such as anxiety and mood. Since anxiety and mood influence pain perception [51, 148, 149] as well as reward processing [90, 150], it is conceivable that they have a modulating influence on the interaction between pain and reward. Clinically, an improved understanding of the consequences of pain is

likely to allow helping patients more effectively by addressing such sequelae specifically. Similarly, by comprehending pain-induced changes in reward systems better, we are likely to make progress regarding the issue of potential addictive behaviors in chronic pain patients. This seems particularly important considering the huge therapeutic benefits of pain medications, and in particular opioids, on one hand and the tremendous medical and political concerns associated with their use on the other hand.

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Chapter 4
Chronic Pain Stimuli Downregulate Mesolimbic Dopaminergic Transmission: Possible Mechanism of the Suppression of Opioid Reward

Minoru Narita, Keiichi Niikura, Akira Yamashita, Daigo Ikegami, Naoko Kuzumaki, Michiko Narita, and Tsutomu Suzuki

Abstract μ-Opioid agonists (μ-agonists), including morphine, are often used to treat the pain associated with cancer moderate-to-severe pain and moderate-to-severe noncancer pain due to other causes. However, μ-agonists also have various side-effects, in addition to potential for abuse or addiction. Recent clinical studies have shown that when μ-agonist analgesics are used appropriately to control pain, abuse and addiction usually do not develop. This chapter highlights recent findings regarding molecular adaptations observed in models of sustained pain, and discusses how such adaptations could reduce the abuse potential of μ-agonists under chronic pain.

Introduction

μ-Opioid agonists are the main analgesics used to treat the pain associated with cancer pain and moderate-to-severe noncancer pain due to other causes [1–3], even though they may be the subject of abuse and/or addiction. Due to this potential, their

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C.A. Fairbanks, T.J. Martin (eds.), *Neurobiological Studies of Addiction in Chronic Pain States*, Contemporary Clinical Neuroscience 17,
DOI 10.1007/978-1-4939-1856-0_4

use for the treatment of severe pain has become complicated. However, it has been reported that when high levels of somatic pain are treated with μ-agonists, abuse and addiction rarely develop [1, 4, 5].

This review presents recent experimental findings on the molecular and neurobiological changes that result from exposure to chronic pain stimuli [6–11]. These findings suggest that, due to these changes, the abuse potential of μ-agonists is reduced when they are used as analgesics under clinical pain conditions.

Usefulness of μ-Opioids for the Treatment of Chronic Pain

Most clinically important opioid analgesics target μ-opioid receptors. μ-Opioid receptors have been shown to transduce signals through pertussis toxin (PTX)-sensitive Gi/Go proteins to inhibit adenylate cyclase, increase membrane K^+ conductance, reduce Ca^{2+} current [12], and activate a phospholipase C (PLC)-IP_3 pathway depending on the stimulation of βγ subunits [13–15].

The typical μ-opioid receptor agonist morphine is considered a "gold standard" by the World Health Organization (WHO) for the treatment of moderate-to-severe cancer pain. In 1965, fentanyl, an anilidopiperidine-class μ-opioid agonist, was reported as a potent synthetic analgesic. Fentanyl has a high affinity for μ-opioid receptors and its analgesic activity is 50–100 times greater than that of morphine. Since fentanyl has a low molecular weight and is lipid-soluble, it can be delivered transdermally. On the other hand, oxycodone, which has been in clinical use for many years, is a semisynthetic μ-opioid analgesic that was obtained from the naturally occurring alkaloid thebaine. Oxycodone has been shown to have a structure and lipid-solubility comparable to those of morphine and is comparable or only slightly inferior to morphine with regard to its analgesic potency [16]. In the clinic, the peripheral administration of oxycodone is uniquely effective for relieving some symptoms of pain in patients with neuropathic pain. Thus, μ-opioids are considered to be the drug of choice for the treatment of patients with chronic pain.

Role of the Mesolimbic Dopamine System in Opioid Reward

μ-Opioid receptor agonists produce euphoria in human subjects and act as positive reinforcers in several species, i.e., they induce drug-seeking behavior, which promotes their administration. Indeed, their reinforcing effects may become so strong that they become the primary motivation for behavior, which can lead to compulsive drug-seeking or addiction [17–19].

Many studies have suggested that this effect originates in the mesolimbic dopaminergic system. The mesolimbic dopaminergic system originates in the ventral tegmental area (VTA) of the midbrain and projects to the nucleus accumbens (NAc.), which is closely associated with the limbic system. It plays a role in the

rewarding effects of intracranial self-stimulation, in the actions of abused drugs, including opioids, and in the intake of natural rewards such as food and water [20, 21]. μ-Opioid receptors in the VTA are known to be critical for the rewarding effects of opioids. For example, in an electrophysiological study, the systemic administration of morphine increased the firing rate of dopaminergic neurons in the VTA [22]. Furthermore, μ-opioids have been shown to increase both the release of dopamine and dopamine metabolites in the mesolimbic dopamine terminal fields [23–27].

The conditioned place preference (CPP) paradigm is an experimental paradigm that has been widely used to investigate the conditioned reward effects of drugs (e.g., μ-agonists) by repeatedly pairing them with a novel environment. After such repeated pairing, an experimental animal will spend more time in the environment that was paired with a rewarding drug than in a complementary environment that was paired with the vehicle. This is considered a drug-induced place preference. Use of the CPP paradigm has shown that intra-VTA injection of morphine produces a rewarding effect, and this effect is blocked by systemic administration of naloxone [28] or intra-VTA administration of naloxone methiodide [29]. This morphine-induced place preference can also be inhibited by the administration of dopamine antagonists or by neurochemical destruction of the NAc. [30, 31]. Furthermore, intra-VTA administration of the μ-opioid receptor antagonist D-Phe-Cys-Tyr-D-Trp-Orn-Thr-Pen-Thr-NH_2 (CTOP) or naloxone can induce place aversion, and these effects are inhibited by the intra-NAcc. Injection of 6-hydroxydopamine to induce the lesion of dopamine neurons [17]. Thus, dopamine-containing neurons in the midbrain VTA, which contains a high density of μ-opioid receptors, play important roles in the rewarding and aversive effects of μ-opioids.

Absence of Dependence-Liability of Opioids Under Chronic Pain

Opioid addiction is often not observed when opioids are used to treat pain. In some patients, withdrawal signs are only rarely observed when the opioid drug is withdrawn gradually after their pain is relieved. This observation supports the notion that opioids can be safely used to treat severe acute, cancer, and chronic pain [32, 33]. Studies in humans and animals support the idea that pain attenuates opioid-associated reward and euphoria [6, 7, 9, 11, 34, 35].

Chronic Pain Leads to Dysfunction of the Mesolimbic μ-Opioidergic System

In our experimental findings, spontaneous activity of the mesolimbic dopaminergic system and the release of dopamine in the NAc. after either the electrical stimulation of VTA neurons or systemic treatment with morphine are markedly suppressed by sciatic nerve ligation [9, 35, 36] (see Fig. 4.1), an animal model of neuropathic pain,

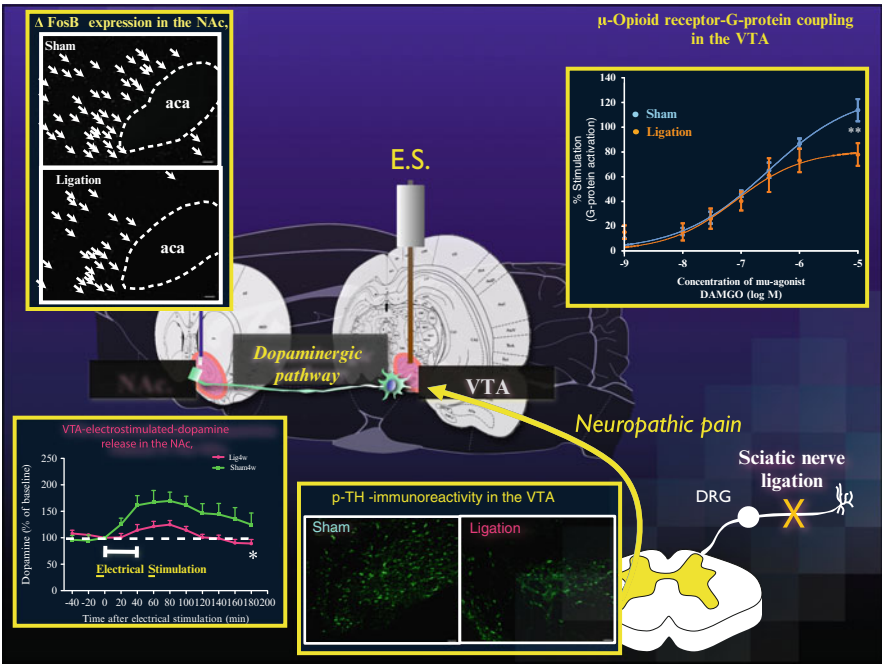

Fig. 4.1 Changes in the phasic activity of the mesolimbic dopamine system under neuropathic pain. *μ-Opioid receptor-G-protein coupling in the VTA*: Concentration–response curve for the effect of DAMGO on the binding of [^{35}S]GTP**γ**S to membranes of the lower midbrain from mice after sciatic nerve ligation or sham operation. *p-TH immunoreactivity in the VTA*: Immunofluorescent staining for phosphorylated-tyrosine hydroxylase (Ser31) (p-TH)-like immunoreactivity (IR) in the VTA of sham-operated or nerve-ligated rats. The images show p-TH-like IR in the VTA of nerve-ligated (*Right*) or sham-operated rats (*Left*). *VTA-electrostimulated-dopamine release in the NAc.*: Change in the dialysate levels of dopamine induced by electrical stimulation (ES) in the VTA. Effect of ES on dialysate dopamine levels in the NAc. *ΔFosB expression in the NAc.*: Images of ΔfosB-immunoreactivities in the NAc. of sham-operated or nerve-ligated animals. Scale bars = 50 μm. Figure adapted from [36], the author's original work

which is caused by the persistent application of noxious stimuli, such as heat, cold, or chemicals, or acute nerve injury. Under these conditions, we also measured the changes in the ability of morphine to activate G proteins in the limbic forebrain, which contains the NAc., the lower midbrain, which contains the VTA, and the pons and medulla regions of both sham-operated and sciatic nerve-ligated mice by monitoring the binding of [^{35}S]GTPγS to membranes [35]. Morphine concentration dependently increased the binding of [^{35}S]GTPγS to membranes in the mouse limbic forebrain, lower midbrain including the VTA, and pons/medulla through μ-opioid receptors. Interestingly, the morphine-induced increase in the binding of [^{35}S]GTPγS to membranes in the lower midbrain, but not the limbic forebrain or pons/medulla, was dramatically reduced by ligation of the sciatic nerve [35]. However, there was no difference between sham-operated and sciatic nerve-ligated mice with regard to the production of μ-opioid receptor in the lower midbrain [35].

This suggests that the neuropathic pain that is caused by ligation of the sciatic nerve ultimately reduces μ-opioid receptor function in the VTA. This selective reduction in μ-opioid signaling in the VTA is compatible with a reduction in the rewarding effects of μ-agonists, with the relative maintenance of analgesic effects, under neuropathic pain (see Fig. 4.1).

One possible explanation for the decrease in μ-opioid receptor signaling in the VTA under chronic pain is a sustained increase in the release of β-endorphin, an endogenous μ-opioid. Prolonged exposure to β-endorphin could result in the phosphorylation of μ-opioid receptors, the uncoupling of these receptors from effector systems, and ultimately desensitization. Notably, β-endorphin has a greater desensitizing effect than morphine [37]. G protein receptor kinase 2 (GRK2), a serine/threonine kinase, promotes the phosphorylation induced by μ-agonists [38]. In one study, nerve-ligated mice showed an increase in the level of membrane-bound GRK2 in the VTA, but not the pons or medulla [35]. This increased level of GRK2 in the VTA might suppress μ-opioid receptor function under ligation of the sciatic nerve associated with the increased release of β-endorphin [35].

The Change in the Release of β-Endorphin Under Chronic Pain Is Critical for Downregulation of the Mesolimbic μ-Opioidergic System

As alluded to above, in the presence of pain, β-endorphin is released in various regions of the brain, including the mesolimbic pathway [39, 40]. Interestingly, the intra-VTA administration of a specific antibody to β-endorphin counteracts the suppression of the place preference produced by the intra-VTA administration of DAMGO (a μ-selective agonist) under neuropathic pain [43]. Furthermore, neither the finding that sciatic nerve ligation suppresses the place preference induced by the systemic administration of morphine nor the parallel decrease in the DAMGO-stimulated binding of [^{35}S]GTPγS in the VTA are observed in β-endorphin knockout mice [36]. Furthermore, the finding that ligation of the sciatic nerve inhibits the morphine-induced release of dopamine in the NAc. is also not observed in β-endorphin knockout mice [36] (see Fig. 4.2). These findings suggest that the selective and sustained activation of mesolimbic β-endorphin might be important for suppressing the rewarding effects of exogenous μ-agonists under chronic pain.

Reduction in Activity of the Mesolimbic Dopaminergic Pathway Under Neuropathic Pain

Extracellular signal-regulated kinase (ERK) is a serine/threonine kinase that mediates cellular responses to a wide variety of signals, including opioid receptor-regulated signaling [41, 42]. ERK activity in the VTA is increased by the chronic

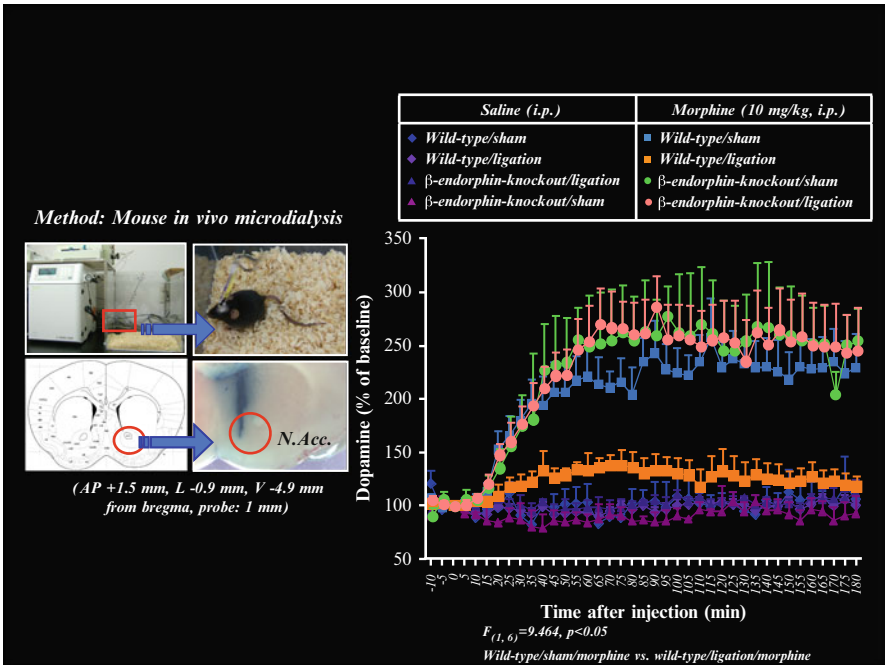

Fig. 4.2 Change in the increased dialysate dopamine level induced by morphine in β-endorphin knockout (−/−) mice. Localization of microdialysis probe sites in the mouse NAcc. (*Left*). Effects of treatment with morphine on the dialysate dopamine level in the NAcc. in sham- or nerve-ligated wild-type mice and β-endorphin knockout (−/−) mice (*Right*). Morphine (10 mg/kg, s.c.) or saline was injected at time 0. The data are expressed as percentages of the corresponding baseline levels with S.E.M. $p<0.001$; sham-operated wild-type mice treated with morphine vs. sham-operated β-endorphin knockout (−/−) mice treated with morphine. Figure adapted from [36], the author's original work

administration of morphine, and ERK activity in the VTA is associated with a morphine-induced increase in tyrosine hydroxylase (TH) [43], which is the rate-limiting enzyme in the biosynthesis of dopamine. Therefore, we examined whether ERK contributed to the rewarding effects of morphine and whether neuropathic pain could influence ERK activity in the mouse VTA [10]. Ligation of the sciatic nerve reduced the level of phosphorylated-ERK (p-ERK) in the VTA without any changes in the basal protein level of ERK. Furthermore, p-ERK immunoreactivity in the VTA that was mostly localized within TH-positive neurons was markedly decreased after sciatic nerve ligation [10]. Various protein kinases can phosphorylate TH at specific serine residues. ERK has been reported to phosphorylate TH at Ser31 in vitro [44]. Ligation of the sciatic nerve reduced p-TH (ser31)-immunoreactivity in VTA neurons that project to the NAc. [36]. These findings suggest that a persistent decrease in ERK activity in the VTA under neuropathic pain may reduce TH activity and result in reduced dopaminergic tone associated with potential dysphoria. This may in turn make the mesolimbic dopaminergic system less responsive to exogenously administered μ-agonists under neuropathic pain.

Upregulation of the Endogenous κ-Opioidergic System May Limit the Rewarding Effects of μ-Opioids Under a State of Continuous Inflammatory Nociception

Several animal models of continuous inflammatory nociception which resemble clinical conditions in humans have recently been developed. One of these models involves the injection of carrageenan, complete Freund's adjuvant (CFA), or formalin into the joints, tail, or paws to induce chronic inflammation. The reduction in the morphine-induced place preference is significantly attenuated under the inflammatory nociception induced by treatment with carrageenan or formalin [11].

κ-Opioid systems have been reported to have various negative effects on μ-opioid systems. κ-agonists, such as the endogenous neuropeptide dynorphin A(1-17), reduce levels of dopamine dialysates in terminal fields of the nigrostriatal and mesolimbic systems and can also attenuate the rewarding effects of abused drugs such as μ-agonists and psychostimulants [23, 45–49]. The repeated administration of μ-agonists upregulates the expression of both the κ-opioid receptor (KOR) and prodynorphin (pDYN) mRNA in the brain [50], and these effects may reduce the rewarding effects and abuse potential of such chronically administered μ-agonists in a clinical setting. Furthermore, inflammatory pain stimuli (such as in the formalin-injection model) decrease both the morphine-induced place preference and the release of dopamine in the NAc. induced by the systemic administration of morphine [7], and these effects are reversed by a selective κ-receptor antagonist and by dynorphin antibodies in the NAc. These findings suggest that the upregulation of endogenous κ-receptor function due to chronic pain may reduce the abuse potential of μ-agonist analgesics.

Conclusion

Our recent research suggests that animals with chronic pain exhibit the suppression of both the rewarding effect induced by μ-opioids and the μ-opioid-activated mesolimbic dopaminergic pathway, which is critical for the expression of an opioid reward. This result strongly supports the clinical observation that psychological dependence on morphine is not a significant concern in patients with chronic pain. Furthermore, injury of the sciatic nerve causes the specific uncoupling of μ-opioid receptors and G-proteins in the VTA and produces a prolonged decrease in ERK activity in dopaminergic neurons in this area. Interestingly, the deletion of β-endorphin eliminates all of these reductions, indicating that the release of β-endorphin in the VTA plays an important role in these events. In contrast, an upregulated κ-opioidergic system plays a direct role in suppressing the rewarding effect induced by μ-opioids under an inflammatory state. These findings suggest that functional plasticity occurs in mesolimbic μ- and κ-opioidergic systems related to mesolimbic dopaminergic transmission. We hypothesize that this could explain the suppression of the rewarding effects of

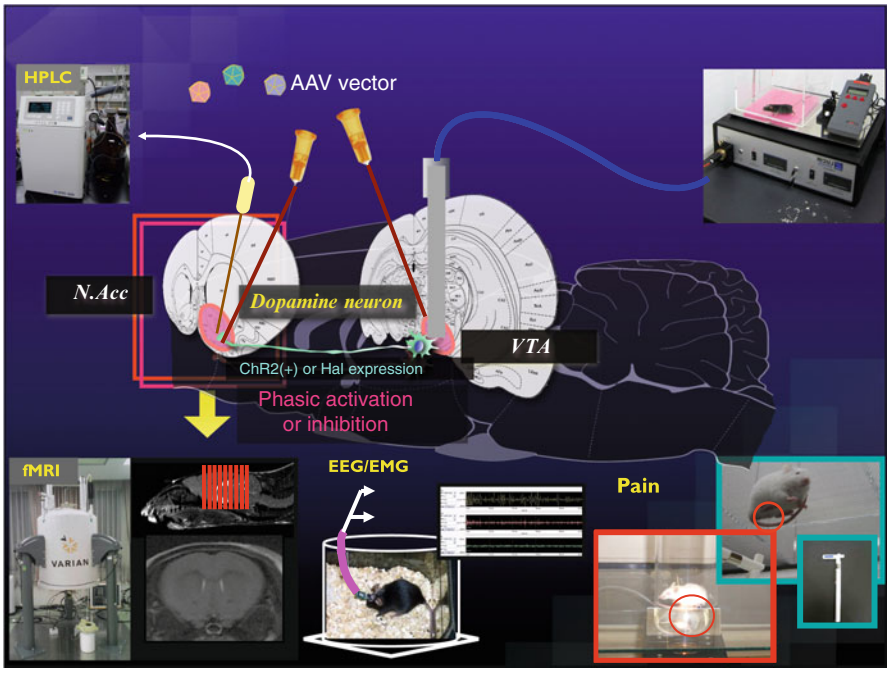

Fig. 4.3 Use of optogenetic tools to analyze the involvement of the mesolimbic dopamine nervous system in neuropathic pain. The recent development of optogenetic tools has provided a valuable opportunity to regulate the activity in genetically targeted neural populations with high spatial and temporal precision. An important advantage of optogenetic tools, such as channelrhodopsin-2 (ChR2) or halorhodopsin (Halo), a light-gated nonselective cation channel, is their cell-type specificity. We can clarify the role of the mesolimbic dopaminergic nervous system under neuropathic pain by specifically activating the mesolimbic dopamine nervous system using optogenetic techniques

μ-opioids under chronic pain. We will further investigate the critical role of downregulated VTA-dopaminergic neurons in the suppression of the rewarding effects of opioids using an optogenetic approach under chronic pain (see Fig. 4.3).

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Part III
Methods

Chapter 5
Drug Addiction and Chronic Pain: A Review of Animal Models

Carrie L. Wade, George F. Koob, and Leandro F. Vendruscolo

Abstract Animal models of pain play an important role in the characterization and development of therapeutics for several pain conditions. Models that mimic the development and maintenance of chronic pain conditions are especially important and have directly impacted the availability of treatments for many common pain conditions such as neuropathic, inflammatory, and visceral. The most efficacious and first choice treatment option for chronic pain is opioid analgesics. Besides being potent analgesics, opioids produce an intense pleasant feeling (reward), especially in individuals not suffering actual pain. This raises the concern that the chronic treatment of pain with opioids can cause opioid tolerance and dependence. This chapter discusses the animal models that are used to quantitatively measure nociception and analgesia, and animal models that are used to study inflammatory, neuropathic, and visceral pain. Additionally, we discuss the animal models used to study opioid dependence.

Introduction

The most pervasive and universal form of human distress is pain. It has an inverse relationship with one's quality of life [1, 2] and negatively impacts collective social productivity [3]. Pain is one of the most common reasons for a visit to a physician's office, community health center, and emergency rooms and is now considered the fifth vital sign. When pain interferes with and at times halts the activities of one's daily activities, pain becomes central to that person's daily existence.

While most acute pain can be easily treated and is essential for disease diagnosis, conversion to a chronic pain condition often becomes more difficult to treat and retains little value in terms of identification of pending damage, dysfunction, or disease. Such chronic pain conditions become challenging to treat for a variety of reasons. First, chronic pain can arise from a wide variety of central or peripheral nervous system dysfunctions such as inflammation, neuropathy, disease specific, or related to cancer. In many cases, the pain is caused by multiple points of dysfunction.

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C.A. Fairbanks, T.J. Martin (eds.), *Neurobiological Studies of Addiction in Chronic Pain States*, Contemporary Clinical Neuroscience 17,
DOI 10.1007/978-1-4939-1856-0_5

Such conditions are often difficult to treat pharmacologically [4–6] for reasons associated both with the neurobiology of pain and the chemistry of pharmacological agents used to treat pain. Specifically, chronic pain of differing etiology may evoke differential neurochemical and molecular changes at multiple levels of the central nervous system [7]. These alterations often occur at the neurotransmitter (e.g., endorphins, substance P, glutamate, etc.) and/or receptor (e.g., opioid, neurokinin, glutamate receptors, etc.) levels. The complexity of pain processing systems presents a challenge for pharmacological interventions for pain relief. For this reason, there currently are fairly limited options for pharmacological treatments for chronic pain. That is an area of universal disappointment for pain researchers, industry, practitioners, patients, and their families.

The primary and most effective class of pharmacological agents used to manage chronic pain remains the opioid agonists. Opioid receptors are inhibitory G protein-coupled receptors expressed at nearly every point in the pain signal conduction pathway (primary afferent peripheral nerve terminal, primary afferent spinal terminal, second order neurons, rostral ventral medulla, periaqueductal gray, and thalamus). Therefore, they are well positioned to regulate the pain signal and appear to be the most effective target for this purpose. Consequently, opioids have been used for centuries to control pain. However, opioid receptors are also expressed in brain regions that control emotion and reward, which can be dysregulated with chronic drug exposure and lead to drug dependence and addictive behavior.

For many years, the claim was made that chronic pain patients, who take opioid medication for treatment of their pain, self-administer the drug to attain the analgesic effect and rarely become addicted [8]. It was on that basis that prescribers have been increasingly educated and retrained to appropriately treat patients for their pain, which is often undertreated; it has been asserted that only 25 % percent of chronic pain patients receive adequate treatment [9]. Concerns were raised regarding practitioner bias against prescribing opioids starting at the level of medical school students [2] and other health professionals such as pharmacists and regulators [10]. It is noteworthy that among medical board regulators, the perceived legal and medical acceptability of treating patients with a history of opioid misuse, even for cancer-related pain, was significantly reduced relative to patients without a history of misuse [10]. The introduction of sustained-release opioids to the pain management armamentarium in the 1990s provided extensive initial enthusiasm [11] in terms of improved pharmacokinetics in that these new sustained-release formulations offered serum levels of opioids that could be maintained at steady state for 12–24 h. Such a pharmacokinetic profile meant that patients needing chronic pain management would be at significantly less risk for breakthrough pain associated with opioid regimens reflecting shorter half-lives that result in more frequent drops in serum levels below the minimal effective concentrations [11]. Therefore, the introduction of sustained-release opioid medications was considered a significant advance in treatment. However, concern regarding opioid therapy for pain management is still controversial for at least two reasons: the continued perceived misuse of opioids and the lack of efficacy in nonmalignant pain management.

It remains unclear whether there is a biological basis for restricting the use of opioids in patients with chronic pain, particularly of nonmalignant origin.

The National Institutes of Health (NIH) has recently acknowledged this problem and has attempted to address this issue by developing research programs specifically to investigate the relationship of prescription opioid use and misuse, CNS changes that occur with chronic pain, and how these changes parallel those that occur with drug addiction. In 2005 and 2008, requests for applications were announced by NIH that specifically addressed these issues with an emphasis on clinical research in the first case *Prescription of Opioid Use and Abuse in the Treatment of Pain* (NIDA/NIA/NIDCR) and an emphasis on basic research in the second case *Central Nervous System Intersections of Drug Addiction, Chronic Pain and Analgesia* (NIDA/NINDS).

Research investigating the effectiveness of morphine in neuropathic pain patients showed that morphine was not effective in certain forms of neuropathic pain [12]. However, this study was limited in scope in terms of patient population and dosing schedule. The patients received two doses of 10–20 mg morphine i.v. and were only evaluated 15 min following infusion. In addition, these patients suffered from severe neuropathic pain that had been unresponsive to nerve block, surgery, transcutaneous electrical nerve stimulation (TENS), and drug therapy including other opioids such as buprenorphine and pentazocine. The overall conclusions of the 1988 study are still used to support the argument against use of opioids for neuropathic pain; yet, these results have been challenged by many preclinical and clinical trials [13–15].

Using an animal model of neuropathic pain, La Buda and colleagues examined the efficacy of several pharmacological agents that are used for treatment of neuropathic pain. They found that the nonopioid drug gabapentin, which interacts with voltage-gated calcium channels and increases synaptic availability of γ-aminobutyric acid (GABA), reversed spinal nerve ligation (SNL)-induced neuropathic pain with complete efficacy [14].

Several reports have contributed to the growing acceptance of the assertion that patients with noncancer pain may achieve good pain control from opioid therapy [16]. However, there is also consensus that the current clinical literature on opioid use for the treatment of noncancer pain does not address issues of long-term opioid maintenance and that such studies are critical to inform management plans for treatment of noncancer chronic pain patients with opioid therapy [17, 18].

To provide an evidence-based animal model framework to move the field forward, this chapter discusses the animal models that are used to quantitatively measure nociception and analgesia, and animal models that are used to study inflammatory, neuropathic, and visceral pain. We also discuss the animal models used to study opioid dependence. Finally, we discuss how the use of models of chronic pain and opioid dependence can increase our knowledge on the neurobiology of the association of chronic pain and drug addiction.

Quantitative Measurements of Hyperalgesia

Many models have been developed to mimic human conditions and to study pain and its underlying mechanisms in whole animal systems. These models allow for quantitative and qualitative measurements and examination of alterations of the

physiology during the chronic pain state. Animal models of chronic pain are used to (1) induce a pain state that mimics common human conditions of pain, (2) quantitatively characterize the degree of pain resulting from the injury, (3) evaluate mechanisms responsible for pain, and (4) evaluate analgesic efficacy directed toward alleviation of the injury.

Animal models of pain include models of hyperalgesia, defined as increased sensitivity toward painful stimuli and models of allodynia in which normally nonnoxious stimuli are perceived as painful. These models are used to study neuroadaptive changes associated with chronic pain. These measurements, which are the dependent variables, are generally quantified as a deviation from the normal baseline threshold in each animal before induction of injury and the resulting pain. Following administration of potential analgesics measurements assessing hyperalgesia or allodynia can be taken again to evaluate the efficacy and potency of the analgesic of interest.

Hyperalgesia or allodynia can be examined using a variety of models that measure force applied to the affected area or time to withdraw the paw when exposed to a stimulus. It is important to consider the model of pain when choosing the method of hyperalgesia assessment. While hyperalgesia resulting from inflammation can effectively be assessed using mechanical, thermal, and static models, there has been mixed reviews regarding assessment of neuropathic pain. Most often neuropathic pain is assessed using mechanical stimuli and there has been limited data supporting the use of thermal hyperalgesia to assess neuropathic pain. An overview of common measurements is described below.

Mechanical (Von Frey) Paw Withdrawal

Maximilian Ruppert Franz von Frey developed the quantitative measurement of mechanical hyperalgesia. Individual filaments of specific calibrated forces, which determine nociceptive thresholds of individual subjects, were originally designed for diagnostic purposes and later incorporated to animal studies. The use of these filaments for the purposes of quantifying hyperalgesia in rats was described by Chaplan and colleagues [19]. Filaments of varying forces are applied to the plantar surface of the affected paw for a period of 3 s starting with the lowest force and increasing the filament force until the animal withdraws its paw. Following the first withdrawal, the next lowest force is applied. If the animal withdraws its paw the next lowest force is applied; if the animal does not withdraw its paw the next highest force is applied and this pattern continues for five applications following the first withdrawal. This pattern results in a threshold that determines the animal's individual withdrawal threshold. Low withdrawal thresholds indicate a state of hyperalgesia while higher withdrawal thresholds indicate normal (or baseline) withdrawal thresholds. When testing an analgesic for efficacy, a return to high withdrawal thresholds indicates analgesia. This test is typically responsive to opioid analgesics. Figure 5.1 shows that chronic infusion of the chemotherapeutic agent vincristine (see animal models of neuropathic pain) produces mechanical allodynia indicated

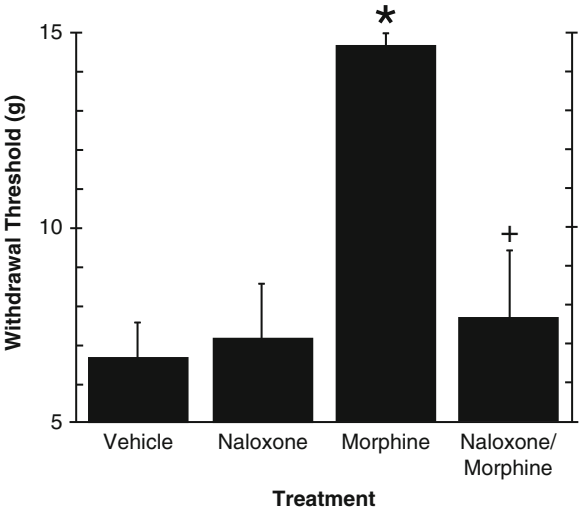

Fig. 5.1 Effect of naloxone hydrochloride or vehicle, administered 15 min prior to injection of morphine sulfate or vehicle, on mechanical allodynia. $^{*}p<0.05$ vs. vehicle. $^{+}p<0.05$ naloxone/morphine vs. morphine. Taken from Lynch et al. (2004), with permission

by low paw withdrawal thresholds. Morphine injected prior to testing substantially increased pain thresholds indicating potent analgesia. The analgesic effect of morphine was reversed by pretreatment with the opioid antagonist naloxone, indicating the participation of μ-opioid receptors on morphine-induced analgesia.

Randall–Selitto

Nociceptive thresholds here are determined using a paw-pressure vocalization test by which increasing pressure is applied to the top of the hindpaw until vocalization [20] using an analgesimeter. In general, a 600-g cut-off value is used to prevent tissue damage.

Thermal Paw Withdrawal

Paw withdrawal from a heat stimulus is also used to test hyperalgesia of affected areas. A thermal (light) stimulus is applied to the plantar surface of the affected paw and the time to paw withdrawal is recorded after which the stimulus is removed. The most commonly used apparatus for this test was developed by Hargreaves and colleagues [21]. A shorter latency to paw withdrawal indicates hyperalgesia and an increased time to paw withdrawal indicates either analgesia or normal baseline thresholds and can be calculated with the following formula: [(uninjured paw latency—injected paw latency)/uninjected paw latency] × 100. A cutoff time of 30 s is commonly used to prevent tissue damage from repeated tests.

Weight Bearing

The weight bearing model is not a model of evoked hyperalgesia, but is a static model that measures an important characteristic of most pain states, that of spontaneous or tonic pain. With a unilateral injury, animals will favor the injured area by putting most of their weight on the noninjured paw. Medhurst and colleagues (2000) first described this model [22]. The animal sits in the chamber with each hind paw on a balance that shows the amount of weight an animal is willing to put on each paw. The difference between the two paws (uninjured paw—injured paw) is calculated with the higher difference score indicating hyperalgesia.

Animal Models of Chronic Pain

There are several animal models (the independent variables) utilized to produce a state of hyperalgesia that mimic common ailments such as inflammation (arthritis, burns, and Crohn's disease, and other causes of acute or chronic inflammation) or neuropathic pain resulting from physical trauma, diabetes, chemotherapy, or from other etiologies. The use of these models has led to many insights regarding the physiology of specific pain states, receptor regulation, and possible treatments.

Inflammation

Animal models of inflammation have taught us important aspects of inflammatory pain that are specific to inflammation and different than pain arising from other origins such as nerve injury. Valuable information regarding recruitment of inflammatory mediators that result in chronic pain and upregulation of sensory transduction mechanisms that lead to sensitization in the periphery and central nervous system have also led to a deeper understanding of how to treat pain from an inflammatory origin. Several receptors respond to inflammation and contribute to hyperalgesia and sensitization. Below we describe the most common animal models of inflammation.

Carrageenan

Carrageenan-induced inflammation can be used as a model of acute inflammation with hyperalgesia occurring 3 h after injection and lasting out to approximately four days [21]. λ-carrageenan is a sulfated polysaccharide that induces an inflammatory response by activating microglial immune responses and activates mechano-heat sensitive C-fiber receptors [23]. Carrageenan is dissolved to a 2 % solution with physiological saline and injected subcutaneously in the plantar surface of the hindpaw in a volume of either 150 μl (rat) or 30 μl (mouse).

Complete Freund's Adjuvant (CFA)

CFA is a heat-killed mycobacterium that when injected into the hindpaw induces an inflammatory immune response. The advantage to this model is that it induces chronic inflammation that is apparent at 48 h and lasts out to approximately 3–4 weeks [24]. It is most commonly prepared by emulsifying suspended CFA in mineral oil with physiological saline in a 1:1 ratio. The resulting emulsification is injected subcutaneously into the plantar surface of the hindpaw at a volume comparable with carrageenan, 150 μl (rat) or 30 μl (mouse).

Polyarthritis

The polyarthritis model was first applied as a pain model by Colpaert and colleagues in 1980 [25]. CFA is injected into the base of the rat's tail. Under light anesthesia, animals are injected intradermally with 5 mg/ml of emulsified CFA in a volume of 50 μl. Following an incubation time of 2 days, animals develop widespread joint inflammation. Analysis has shown that chronic pain has been shown to peak between days 18–21 and terminate by days 35–40 [26]. Behavioral effects are similar, in scope, to other models of pain and have been validated by the use of analgesics. Measurements of hyperalgesia include, mechanical thresholds, and thermal paw or tail withdrawal.

Neuropathic Pain

Neuropathic pain is pain that originates from the nerves due to actual or perceived damage (International Association for the Study of Pain). Neuropathic pain can commonly arise from physical trauma, disease states such as diabetes, and as a result of treatment for other diseases, most commonly in conjunction with cancer chemotherapeutics. Tissue damage contributing to neuropathic pain can have lasting effects, following apparent recovery, to the surrounding nerves, which can severely impact quality of life and mobility. In general, neuropathic pain results in allodynia defined as where nonpainful stimuli or activity such as brush or movement become painful. During a neuropathic pain state, there is upregulation of several proinflammatory cytokines and increases in glutamatergic transmission that lead to sensitization of pain pathways.

Because of the unique nature of neuropathic pain, reliable and quantifiable models of neuropathic pain were developed. Each of the described models has unique profiles of nociception. SNL and partial nerve injury result in robust mechanical allodynia whereas chronic constriction injury (CCI) is more sensitive in thermal and cold nociception assays [27]. One specific advantage of these models is that the allodynia is contained to the side of the injured nerve, leaving the contralateral paw unaffected. This allows for a within subject control when evaluating possible analgesics.

Chronic Constriction Injury

CCI involves four loose ligatures of cat's gut suture around the common sciatic nerve. The suture irritates the nerve and it then becomes inflamed which induces neuropathic pain. This model, first developed by Bennett and colleagues, produces marked allodynia, as evidenced by radiant heat and mechanical withdrawal by day 2–3 and lasts out to 2–3 months [28].

Spinal Nerve Ligation

SNL is frequently used to induce neuropathic pain in rat and mouse and was first described by Kim and colleagues [29]. Tightly ligating around the lumbar nerves, five and six (L5/L6) of the spinal cord produces a robust and reproducible mechanical allodynia in the ipsilateral hindpaw that lasts indefinitely. A ligation around L5 before the nerve converges with the L4 and L6 nerve to become the sciatic nerve spares the anesthesia and paralytic effects associated with tight ligation of the entire sciatic nerve. The adaptation to mouse in which L5 (but not L6) is ligated was first described by Mogil and colleagues [30] in a comparative study on the impact of inbred strain differences on the development of nerve injury-induced hyperalgesia. Similarly, we and others have since observed that ligation of L5 is sufficient to establish tactile hypersensitivity of the hindpaw in rat (personal observations and communications).

Spared Nerve Injury

The spared nerve injury (SNI) was developed by Decosterd and Woolf [31] to elucidate contributions of each part of the sciatic nerve of which the sensory component is comprised of the tibial, common fibular, and sural nerves. SNI is a partial denervation model that provides minimal variability with regard to physical damage to the nerve. In this model, the tibial and common fibular nerves are axotomized leaving the sural nerve intact. Nerves are tightly ligated with 5-0 silk suture and sectioned distal to the ligation removing 2 mm of the distal nerve. This injury results in both mechanical and thermal sensitivity.

Chemotherapy-Induced Neuropathic Pain

Treatment with vinca-alkaloid chemotherapeutics often result in neuropathic pain, which is difficult to safely and effectively treat. Inhibition of microtubule growth leads to disruption of mitosis, which is the intended effect of the halting the progression of cancer; however, this also leads to painful neuropathy due to the effects on

microtubules in peripheral nerves [32]. Peripheral neuropathy is often first diagnosed in the hands and feet. The chemotherapy-induced peripheral neuropathy model was first described by Aley and colleagues using vincristine [33] and adapted by Nozaki-Taguchi to eliminate the need for daily injections [34]. The drugs paclitaxel, oxaliplatin, and other vinca-alkaloids [35, 36] have also been used in this model. The intensity of neuropathic pain is dependent on the dose and duration of treatment.

Animal Models of Opioid Reward, Addiction, and Withdrawal

Opioid abuse and dependence are major public health problems. According to the Substance Abuse and Mental Health Services Administration (2010), the number of people dependent on or abusing pain relievers increased between 2002 (1.5 million) and 2009 (1.9 million). Therefore, a major need exists for research into the neurobiology of opioid addiction with the hope of developing better strategies for the treatment of opioid dependence. Treatment options to date are largely limited to substitution-therapy with the use of long-lasting opioid drugs, such as methadone and buprenorphine, or limited use of α2-adrenergic agonists, such as clonidine [37, 38], which all have pronounced adverse effects.

Although addiction (or drug dependence as defined by the Diagnostic and Statistical Manual of the American Psychiatric Association) [39] is a typical human condition, physiological, psychological, and behavioral phenotypes have been described in several animal species and are thought to be analogous to human addiction. Depending on the scientific question to be investigated different models can be used to assess different aspects of drug dependence (e.g., intoxication, withdrawal, relapse, physical dependence, etc.). Here, we describe some of the most commonly animal models used in the addiction field with emphasis on intravenous (IV) self-administration.

Intravenous Self-administration

IV drug self-administration is the most widely accepted model for the study of the role of opioid reinforcement in drug addiction. Drug administration through the IV route results in nearly immediate drug effects and is among the most highly reinforcing delivery routes due to the rapid onset of drug effects. In this model, virtually all drugs with high abuse potential in humans, including prescription opioids, are voluntarily self-administered by laboratory animals. The animals (e.g., rat, mouse, and monkey) are prepared with a cannula into a vein (typically the external jugular vein) for direct access of the drug to the blood stream. The cannula is connected to tubing that often exits on the animal's back and serves as the port of entry for drug delivery [40]. The animals are trained in operant boxes (Skinner boxes) to press a lever (or nose poke a hole) to obtain an IV dose of the drug. For opioids, animals readily learn the operant behavior to self-administer the drug.

Measurements of Drug Taking and Compulsive Drug Intake (Fixed-Ratio and Progressive Ratio [PR] Schedules of Reinforcement)

The operant model is versatile in terms of measurements of reward and motivation. The use of different schedules of reinforcement can provide important information on motivation for drug intake and drug reward efficacy. A fixed-ratio 1 (FR1) schedule of reinforcement is a common procedure in which every lever press performed by the animal is reinforced with a dose of the drug. Because the workload in this schedule is low and the animal easily obtains the drug, it has often been considered an operational measure of drug intake. However, in a PR schedule of reinforcement, the number of lever press that the animal needs to perform to receive the next dose of the drug increases progressively, i.e., the "price/cost" for the drug progressively increases such that the animal has to work more vigorously to obtain the next drug infusion [41, 42]. While a fixed-ratio protocol is able to measure drug intake, PR protocols are more able to measure drug reward efficacy.

Escalation of Drug Intake

Although numerous published procedures exist that produce stable levels of opioid self-administration by rodents, it has also been shown that models of extended access to opioids produces escalation of the intake over time compared with animals maintained on a limited-access schedule [43–48]. Escalation of drug intake has been suggested to model the transition from controlled drug use to compulsive drug seeking, a hallmark of drug addiction [49]. This is further supported by evidence that passive induction of an opioid-dependent state increases the rate of subsequent opioids escalation [50]. Rats that exhibit steady heroin intake show lowered intracranial self-stimulation (ICSS) thresholds associated with reward upon heroin administration, whereas escalating rats show marked elevations in ICSS thresholds, indicating a diminished impact of opioid rewarding effects [51].

Vendruscolo et al. (2011) reported that rats with 12 h access to heroin per session showed significant escalation of heroin intake across session [43]. Animals having limited (1 h) access to heroin showed relatively stable levels of heroin intake (Fig. 5.2). Food intake in the 12 h group, but not 1 h group, concomitantly decreased over sessions, with a pattern that inversely followed the escalation of heroin intake, suggesting a disruption of other natural motivated behaviors. The escalation of heroin intake in the 12 h group is likely due to the repeated cycles of intoxication and forced abstinence associated with the 12 h schedule. The negative emotional state associated with abstinence during dependence has been shown to promote drug taking [52, 53]. Confirming this hypothesis, spontaneous withdrawal signs are observed in the 12 h group, including diarrhea, vocalization upon touch, hyperalgesia/allodynia, and abnormal posture, whereas minimal (or absent) signs of withdrawal were observed in the 1 h group [43].

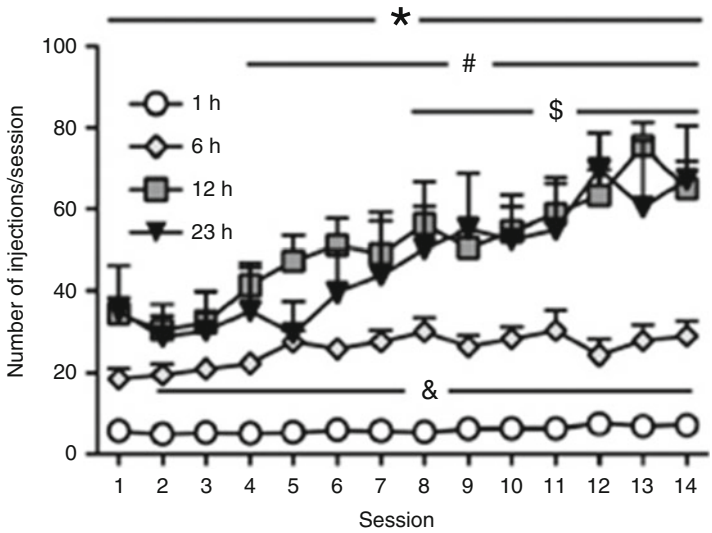

Fig. 5.2 Prolonged periods of drug access result in significantly increased heroin intake over time. All animals had identical pretraining in 1 h sessions to press the active lever for heroin infusions (60 **μ**g/kg/infusion). Animals were given continuous, unlimited access to heroin infusions for 1, 6, 12, or 23 h per day for 14 days. The 1 h access group maintained steady intake over repeated sessions. The 6 h (to a lower extent), 12 h, and 23 h access groups showed escalating patterns of intake across time. Overall, the 6, 12, and 23 h groups administered substantially more drug per session than the 1 h group. The 12 and 23 h groups self-administered significantly more heroin per session than the 6 h group, and intake in the 12 and 23 h groups had a similar magnitude. &$p<0.05$, 6 h group compared with 1 h group; *$p<0.05$, 12 and 23 h groups compared with 1 h group; $^{\#}p<0.05$, 12 h group compared with 6 h group; and $^{\$}p<0.05$, 23 h group compared with 6 h group. Taken from Vendruscolo et al. (2010), with permission

Deneau et al. have provided, perhaps, the first evidence of escalation of drug intake with extended access in laboratory animals by showing that monkeys having continuous access to IV morphine or codeine increased their drug intake over time [54]. More recent studies have reported that monkeys withdrawn from extended access to heroin (21 h per day for seven days) showed increased choice of heroin compared with food and signs of physical dependence compared with monkeys that had limited access to heroin self-administration [55].

Rats with extended access to opioids are clearly tolerant to the drug, reflected by their increased drug intake, and physical withdrawal signs are present. Motivational withdrawal, often described as psychological dependence [51] and drug-seeking behavior [46] are observed in rats with extended access to heroin as well as the appearance of a compulsive-like profile of heroin intake as revealed by increased willingness of animals to work to obtain the drug compared with rats with limited access to heroin [56]. Indeed, animals following extended access show higher break points on a PR schedule. Performance on PR can be linked to a DSM-IV criterion for addiction: "a great deal of time spent in activities necessary to obtain the substance," and considered as a measure of compulsive drug intake [39].

Escalation of heroin intake is also accompanied by disrupted sleep patterns and circadian rhythm [47], by hypophagia [43], weight loss, and self-injurious gnawing. Most of these features are also observed in human opioid dependence (DSM-IV). Therefore, although mimicking all of the symptoms present in human heroin addiction in animal models is difficult or impossible, the aforementioned findings support extended access to heroin as a useful model to study some aspects of opioid addiction.

Reinstatement of Drug-Seeking Behavior

Another important aspect of drug addiction that can be experimentally modeled in laboratory animals is "relapse." Animals are trained to self-administer a drug, usually in sessions of 2–3 h per day. Once stable responding is achieved, the lever press behavior is extinguished, during which lever pressing is no longer reinforced with the drug. This procedure leads to a progressive decrease in the number of lever presses performed by the animal and, at this point, the animals can be tested for cue-, stress-, or drug-induced reinstatement of drug-seeking behavior [57].

Cue-induced reinstatement: an initial neutral environmental stimulus that has been repeatedly associated with the drug effect can acquire reinforcing properties. Therefore, cues paired with drug self-administration can significantly reinstate lever press responding after extinction [58].

Drug-induced reinstatement: a noncontingent exposure to the drug (e.g., subcutaneous or intraperitoneal injections) that was self-administered can also produce a significant reinstatement of drug seeking. This procedure is also called drug-primed reinstatement [59]. Drugs from other pharmacological classes generally produce less robust effects on reinstatement of drug-seeking behavior.

Stress-induced reinstatement: the exposure to different stressful situations (e.g., foot shock, food deprivation, tail-pinch, swim stress, conditioned fear, social defeat, and pharmacological stress produced by drugs such as the α2-antagonist yohimbine) is another factor that reliably reinstates drug-seeking behavior [60]. Rats given extended access to heroin self-administration displayed slowed extinction of heroin-seeking behavior and increased stress-induced reinstatement after extinction [48].

Place Conditioning

This is a nonoperant model used to access drug reward or seeking behavior through the use of a classical Pavlovian conditioning. There are several variations in place preference procedures. In a simple version of this test, animals initially are allowed to explore two distinct compartments with tactile and visual differences and the time spent in each compartment is recorded. During the conditioning, that can be variable in number of trials and duration, the animal is given a drug and confined to one of the two compartments for a certain amount of time. In alternating occasions,

the animal receives vehicle and is confined to the other compartment (i.e., nondrug compartment). In the test day, the animal, typically in a drug-free situation, is again allowed to freely explore the two compartments. The increase in the time spent in the drug compartment relative to the preconditioning (baseline) time is used as a measure of the rewarding value of a drug [61].

A variation of the place-conditioning paradigm is place aversion. This model is typically used to measure aversion produced by drug withdrawal. In this model, the animal receives an opioid receptor agonist. Withdrawal is subsequently precipitated with the use of an opioid receptor antagonist. For example, the animal receives a dose of morphine and subsequently it receives a dose of naloxone [62]. Immediately after the injection of naloxone, at the time the animal is experiencing opioid withdrawal, it is confined in one compartment. In alternating occasions, the animal receives no antagonist injection and therefore does not experience withdrawal, and is confined in the other compartment. After a single or multiple pairings between environment and drug withdrawal, the animal is given the opportunity to freely explore the two compartments of the apparatus. The time spent by animal in the compartment paired with drug withdrawal, which is typically less than the time spent in the other compartment, is considered an index of place aversion. Depending on the severity of dependence and the dose of the antagonist, the animal experience different levels of withdrawal ranging from motivational to physical signs of withdrawal [63].

Naloxone-Precipitated Physical Signs of Withdrawal

To directly evaluate whether and to what extent extended access to opioids produces signs of opiate dependence, naloxone-precipitated withdrawal scores can be measured using a modified Gellert and Holtzman (1978) scale of somatic opiate withdrawal [64, 65]. In this model, animals dependent on opioids are given a challenge dose of naloxone (typically 1 mg/kg, s.c.) and immediately placed in a Plexiglas box for the observation of somatic opiate withdrawal. Two classes of withdrawal signs are measured for 10 min: graded signs (body weight loss in 60 min, escape attempts, wet dog shakes, and abdominal constrictions) and checked signs (defecation/diarrhea, teeth chattering, swallowing movements, salivation, ptosis, penile erection/ejaculation/grooming, hyperirritability upon touch, and abnormal posture). Each withdrawal sign is assigned a multiplier based on a weighted measure of somatic opiate withdrawal [66]. This model is useful to test the severity of opioid dependence and to the development of treatments to block opioid withdrawal.

Applying Models of Opioid Self-Administration to Models of Chronic Pain

Most rodent studies of opioid-induced antihyperalgesia in pain make measurements acutely at one time point during the progression of the pain state. However, the most valuable information to be gained from models may require evaluation of opioid

pharmacotherapy over a significant period of time. Models of neuropathic and inflammatory pain present an opportunity to make controlled comparisons of the complexity of opioid pharmacotherapy in terms of opioid sensitivity or insensitivity, development of tolerance (controlling for progression of disease), and factors predisposing to or protecting from addiction.

There are many important considerations in applying animal models of pain and addiction including the choice of animal strain appropriate for each application and incorporation of hyperalgesia measurements into the self-administration paradigm. While many strains of rats and mice display robust pain phenotypes for most pain models, it is important to consider that not all strains will display the same pain phenotypes or be conducive to behavioral studies in addiction.

It is also important to consider the timepoints at which hyperalgesia measurements are taken. It has been shown that both alcohol and opioids produce withdrawal-induced mechanical hyperalgesia. However, immediately following drug self-administration animals are in a state of analgesia thus masking detection of hyperalgesia. Therefore, a control group of animals that do not self-administer opioids to parallel the time course of hyperalgesia is necessary to control for drug-induced hyperalgesia.

Edwards et al. (2012) reported that mechanical paw thresholds were reduced to around 50 % of levels observed at baseline conditions in rats with extended access (12 h per day) to heroin self-administration and were also significantly lower than thresholds measured in animals maintained under limited (1 h per day) access to heroin self-administration (Fig. 5.3) [67]. Whether the same effect would be observed in animals experiencing pain during heroin self-administration remains to be determined.

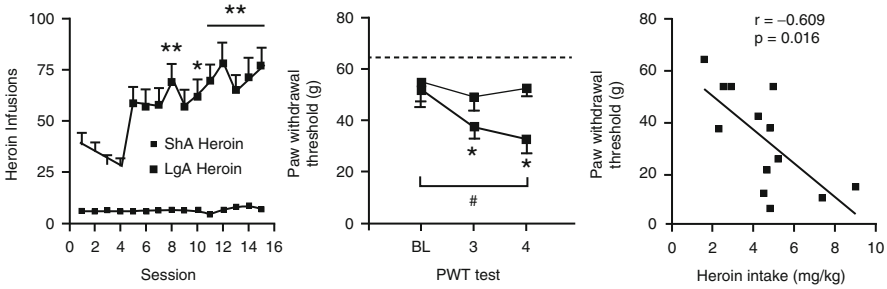

Fig. 5.3 Heroin self-administration and paw withdrawal thresholds in rats with limited (1 h/day, ShA) and extended (12 h/day, LgA) to the drug. (*Left*) LgA animals display escalation of drug intake over time, whereas ShA animals display stable levels of drug intake $^{**}p<0.01$ or $^{*}p<0.05$, significantly higher intake versus session one. (*Middle*) Paw withdrawal threshold (PWT) tests conducted during withdrawal revealed a development of mechanical hypersensitivity selectively in LgA animals following 7 and 15 sessions of extended access conditions (PWT tests 3 and 4, respectively). $^{\#}p<0.05$, significantly lower PWTs in LgA vs. ShA animals. $^{*}p<0.05$, significantly lower PWTs in LgA animals versus baseline (BL) test. (*Right*) Individual paw withdrawal thresholds at PWT 4 were significantly and negatively correlated with individual preferred levels of heroin intake during session 15 in LgA animals. Modified from Edwards et al (2011), with permission

Much has been learned about the basic biological and environmental factors that influence addiction in animal models using the self-administration paradigm [68]. The self-administration paradigm is used as a sensitive measure of a drug's rewarding effects, and the potential addiction liability of drugs can be inferred from the results. Generally, drugs that are addictive in humans are readily self-administered by laboratory animals such as amphetamines, cocaine, heroin, cannabinoids, and alcohol [61, 69, 70]. Several groups have shown that rodents with pain will self-administer opioids differently than normal controls [71–74]. Self-administration of fentanyl can be correlated with the amount of spontaneous pain associated with different pain conditions, monoarthritis and mononeuropathy [75, 76]. Similarly, the examination of the self-administration behaviors of rats experiencing chronic nociceptive pain in an arthritis model shows that rats with CFA-induced polyarthritis self-administer fentanyl for analgesic effects based on a decrease in self-administration rates when given forced fentanyl IV [74]. In addition, these animals do not self-administer opioids when pretreated with a nonopioid nonsteroidal anti-inflammatory drug (NSAID) such as indomethacin [74]. When given a choice between two bottles, one with fentanyl and one with water, mice with arthritis consumed more fentanyl than the nonpain control [74].

Another study demonstrated a reduction in IV self-administration of morphine in rats with CFA-evoked polyarthritis compared to pain-free control rats [73]. Tail pressure evoked nociception in rats self-administering morphine or indomethacin, a potent nonopioid anti-inflammatory also show a decreased sensitivity. There was also a reduction in opioid self-administration in the rats that received indomethacin [73]. Overall, these results show that it is possible that rats in pain self-administer for the analgesia alone and not for extra-nonanalgesic reward. These results further suggest that activation of neurocircuitry involved in acute pain processing may disrupt reward circuitry and processing. However, this hypothesis is limited in scope and does not account for the complex stress and suffering that humans experience when treating chronic pain, which may exacerbate stress surfeit disorders that lead to addiction and addiction type behavior.

Conclusion

The use of animal models of chronic pain and addiction have led to many important breakthroughs in understanding the biological basis of disease as well as targeted drug therapies for each condition. The combination of these separate lines of study have, in fact, led to valuable insights regarding the potential for opioid addiction in the context of chronic pain. It is clear that chronic exposure of animals that are not in pain to opioids may lead to compulsive-like behavior toward the drug and this compulsive-like responding for opioids can lead to a pain state. The same is expected in humans receiving chronic treatment with opioids for pain management if pain is not evaluated and treated properly. However, there are several studies that suggest that this may not be a simple conclusion when appropriate pain management is present.

Indeed, chronic opioid exposure during pain is less likely to lead to addiction. Clinical advocates for opioid use in pain management have, for decades, asserted that when used appropriately patients on opioid treatment for chronic pain conditions rarely convert to addiction [77]. This clinical assertion has support in several epidemiological reports [78]. More recently, a growing concern regarding broad spectrum opioid pain management and a reconsideration of the previous claims of lower rates of iatrogenic opioid addiction has emerged [79] concurrent with the increased diversion and abuse of the sustained opioid release dosage forms.

Important questions that remain to be answered are: why individuals in pain and chronically exposed to opioids are less likely to develop opioid dependence than individuals taking opioids while not in pain, and why some individuals are vulnerable to compulsive drug seeking when being treated for chronic pain? Given the ability to exquisitely control pain condition, opioid exposure, and social factors, the animal models described here are essential tools available to design the experiments to answer these questions. Animal models are helping dissect the neuropharmacology of pain and addiction and will ultimately lead to better strategies for prevention, diagnosis, and effective treatment of pain conditions with minimal comorbidity with drug addiction.

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Chapter 6
Biopharmaceutical Considerations of Opioid Analgesics in Models of Self-Administration: Review and Summary

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Abstract Throughout this volume we have discussed the opioid analgesics and the propensity for subjects with established chronic pain to develop opioid-induced addiction. The class of opioid analgesic compounds and pharmaceutical dosage forms include not only chemicals with similar characteristics but also some significant distinctions that can impact the ultimate pharmacological effects on both analgesia and potential for addiction. In developing and/or implementing animal models of opioid addiction in the state of chronic pain it is valuable to be cognizant of the physicochemical and pharmacological characteristics of specific opioid analgesics. The objective of this chapter is to feature biopharmaceutical aspects of a series of the most common prescription analgesics opioids.

Introduction

Chronic pain is a broadly experienced debilitating condition that represents a significant public health concern [1]. The most effective pain relievers, opioids, are associated with risk of conversion to addiction and/or diversion from the patients for whom use is intended; these perceived risks constitute a recognized national health problem [1]. It is well known that a wide spectrum of opiates carry abuse potential. Most of these opioids are known mu receptor selective agonists and it is now thought that they may activate heterodimers of mu and delta opioid receptors [2]. Each of these opioids carries distinct physicochemical characteristics ranging from

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C.A. Fairbanks, T.J. Martin (eds.), *Neurobiological Studies of Addiction in Chronic Pain States*, Contemporary Clinical Neuroscience 17,
DOI 10.1007/978-1-4939-1856-0_6

hydrophilic to hydrophobic, half-lives of varying duration, and distinct metabolic pathways. The mechanisms underlying the propensity for misuse and transition to opioid addiction have been studied for decades in animal models of self-administration, primarily under normal conditions [3] using many of these same reinforcers that are abused or misused by humans. Evaluation of these same reinforcers under the condition of established chronic pain has been considered by a limited number of investigators. However, interest in evaluation of the reinforcing properties of the standard opioid receptor agonists under conditions of established chronic pain is elevating. This interest appears to stem from the recognition of the negative physiological and social side effects associated with the elevation in opioid prescribing and use during the course of the last 15–20 years. Currently, there is limited information available; much of what is known has been reviewed in the other chapters of the present volume. Expansion of our understanding of how distinct pain conditions may influence opioid responding has potential to improve strategies for pain management. Therefore, interest in the design and implementation of experiments to address these gaps in knowledge has the potential to yield great benefit. There are currently few investigators trained in the combined methods of establishing chronic pain, opioid neuropharmacology, and addiction modeling. Each area carries unique knowledge and challenges. The present collection as a whole is intended to help guide such future studies. This specific chapter provides a summary of the major reinforcers that have been evaluated historically in subjects with presumptive normal pain thresholds. Unique aspects of each opioid compound discussed include, but are not limited to, physicochemical characteristics, route of administration by which it is administered in preclinical models and in the clinical arena, metabolic pathways, operant animal models in which the reinforcing properties have been assessed, and human abuse experience. The objective is to provide qualitative biopharmaceutical information to investigators as to how the opioid reinforcers are similar and distinct.

Morphine

General Use and Routes of Administration. Morphine was isolated from opium derived from the poppy plant over 200 years ago by a German chemist [4]. It was later distributed by his pharmacy and then by Merck in 1827. The use of morphine greatly expanded in the mid 1850s following introduction of the hypodermic needle. It was used as an adjuvant to anesthetics, in surgical procedures, and for management of postoperative and chronic pain [4]. Since then, morphine has been and remains the gold standard opioid analgesic for the treatment of pain. It can be delivered by multiple routes of administration ranging from intravenous, oral, transdermal, rectal, intrathecal, and epidural drug delivery [5].

Metabolism. The uridine diphosphoglycosyltransferase (UGT) super-family, and specifically the UG2 family, is largely responsible for elimination of 86–96 % of

morphine given systemically [6]. The primary metabolites of morphine are morphine 3-glucoronide (57 %) and morphine 6-glucoronide (10 %), the latter of which is a potent analgesic. UGT2B7 is thought to primarily form M6G [7] whereas a wide variety of UGT enzymes (UGT1A1, 3, 6, 8, 9, 10) have been shown to form M3G [8, 9]. The UGT enzyme is expressed primarily in the liver, but UGT2B7 and UGT1A6 are also expressed in human brain samples [10] where M6G and M3G have been shown to be formed [11]. Pathophysiological alterations in these liver enzymes may impact serum concentrations of morphine and its main metabolites. It has been shown, for example, that patients with liver inflammation exhibited significantly decreased (~40 %) levels of UGT2B7 enzyme mRNA relative to controls [12].

Addiction Profile. The reinforcing properties of morphine have been well established through many decades of study in nonhuman primate [13–17] but have also been robustly demonstrated in rat [18–22] and mouse [23–25]. It is noteworthy that a series of studies have demonstrated strain differences in morphine self-administration under fixed [26] and progressive ratios [27]. For example, Lewis rats were observed to more rapidly establish morphine self-administration behavior than Fischer F344 rats. There are known to be a variety of neurochemical variations in CNS regions that mediate addiction (e.g., nucleus accumbens and ventral tegmental area) [27]. These regional neurochemical differences may contribute to difference in morphine responding between these strains [27]. Similarly, strain differences have been considered in a study where 15 mouse strains were assessed for oral morphine consumption. In this comprehensive analysis, a dramatic 23-fold range was observed from 6 mg/kg consumed daily in the SWR/J strain contrasted to 134 mg/kg range in to C57BL/6 J strain [28]; similar results were observed by Milligan and colleagues [29]. Strain differences in operant responding for morphine were substantially pronounced in several additional mouse studies including one comparison of four distinct strains of mice over a wide range of concentrations (0.125–2 mg/mL) [30]. CBA and DBA mice demonstrated classic inverted U-shaped dose–response curves with the optimal drug concentration as 1.2 mg/mL for CBA and 0.63 mg/mL for DBA mice. For C57Bl/6 mice, the concentration response dependence was not predictable. BalbC mice did not exhibit evidence of morphine self-administration. These studies illustrate the importance of consideration of strain in experimental design and comparison of results across studies and laboratories. Further, for over five decades, the vast majority of morphine self-administration studies have been conducted in normal subjects with assumed normal sensory thresholds. When combining studies of opioid administration and chronic pain, consideration of strain becomes particularly important given that there have also been comprehensive evaluation of the impact of strain on development of chronic pain of various origins as well as acute sensory assessment in both rat [31] and mouse [32].

Preclinical Models of Pain. Increasingly, consideration is being given to the fact that the responses of reinforcing agents likely differ in subjects with established chronic pain. It has been shown in animal models of addiction that morphine reward is

altered under conditions of chronic pain. From 1988 to 2013, nine of twelve studies of morphine-induced conditioned place preference showed significantly reduced place preference for morphine in rodents with chronic pain established by inflammation (CFA [33], carrageenan [34], and formalin [34, 35]), nerve injury rats [36–40], and other pain models [33, 41]. One previous report showed no change in morphine place preference in inflamed rats [42] whereas two showed enhanced responding [43, 44] (all of these studies are reviewed in Fairbanks and Wade, Chap. 1 of this volume). It is proposed that the analgesic effect of morphine in the chronic pain condition accounts for the enhanced CPP of morphine in these latter two studies. However, the discrepancy in outcome between these two studies and the aforementioned nine is not clear. Congruent with this pattern, Martin and colleagues [45] demonstrated that Fisher 344 rats with established neuropathic pain responded significantly less for morphine delivery compared to control rats at equivalent maximal doses of responding. Further, the maximum responding for morphine at any dose was significantly diminished in rats with chronic pain [45]. This effect was not unique for morphine; comparable results of other opioids assessed in models of chronic pain will be reviewed in the following sections.

Fentanyl

General Use and Routes of Administration. Fentanyl is prescribed very frequently for pain management [46]. The lipophilic physicochemical characteristics render it optimal for delivery by nearly every route of administration ranging from intravenous [47], oral/sublinqual [47, 48], transdermal [47, 48], intranasal [48] intrathecal [5], and epidural [5]. Concern for its profile as a misused prescription analgesic escalates as misuse is documented, particularly via the transdermal dosage form [49], by transmucosal delivery with multiple patch application [50, 51], direct oral ingestion [52], oral ingestion following hot water extraction [53], and rectal insertion [54].

Metabolism. Fentanyl is reported to be metabolized by the CYP3A4 in human [55, 56] and nonhuman primate [56] and by CYP3A1/2 [57] in rat to norfentanyl. Fentanyl analgesia is known to have high intersubject variability which may relates to mu opioid receptor polymorphisms [58], but may also be attributable to variation in protein expression and catalytic activity of CYP3A4 [59]. A CYP3A4 single nucleotide polymophism (SNP) in the Chinese population is represented by a CYP3A4*1G, a G to A, substitution in intron 10 [60]. This mutation is reported to result in reduced consumption of fentanyl for postoperative pain control in women following complete hysterectomy [61, 62]. It has been shown that fentanyl metabolism is inhibited by co-administration of acetaminophen (paracetamol) in *in vitro* models of human and rat liver microsomes for CYP3A [63]. Based on pharmacokinetic parameters it is proposed that oral (but not intravenously) delivered fentanyl may be impacted by concomitant delivery of acetaminophen (or paracetamol).

Addiction Profile and Preclinical Models of Pain. The reinforcing properties of fentanyl have been studied for many decades in nonhuman primate (i.v [64–66].), rat (i.v [18, 67], oral [20, 21, 68, 69]), and mouse [70]. In a limited number of studies, the reinforcing properties of fentanyl have been evaluated in rats [45, 71, 72] and in mouse [73] under conditions of chronic pain induced by various means. In two studies, rats with inflammation-induced chronic pain showed increased preference to drink from a bottle containing fentanyl than an alternative solution [45, 71, 72]. In contrast, subjects with chronic pain induced by nerve injury showed no preference for oral fentanyl in the two bottle choice test. This was explained by the authors by the asserted lower efficacy/potency of opioids under conditions of neuropathic pain. Consistent with these data, Martin and colleagues [45] demonstrated that nerve-injured rats with chronic pain did not maintain responding intravenous fentanyl delivery over a range that resulted in a standard inverted U-shaped dose–response curve control rats. In short, operant responding for fentanyl was blunted in rats with chronic pain. Likewise, Wade and colleagues [73] demonstrated that mice with chronic pain induced by either inflammation, nerve injury, or chemotherapeutic exposure demonstrated significantly reduced motivation to lever press for oral fentanyl. These observations are consistent with those previously described for morphine.

Oxycodone

General Use and Routes of Administration. Oxycodone has been used to treat pain since the early part of the twentieth century [74, 75]. With the introduction of the oral immediate- and controlled-release formulations to the market in the 1990s, clinical use dramatically escalated [74]. The lipid solubility of oxycodone is comparable to morphine [75]; it is delivered intravenously [76], intramuscularly [77], and orally by various release mechanisms. The potency of oxycodone is reported to be comparable to [78], or greater than morphine when given clinically despite the notable lower affinity of oxycodone for the mu opioid receptor relative to morphine [79] and equivalent lipophilicity [80]. These observations would appear incongruent were affinity the only indication of relative potency. Evaluation of influx and efflux tendencies of oxycodone at the level of the blood–brain barrier (BBB) may help to explain the pharmacology. There is disagreement as to whether or not oxycodone is substrate for the P-glycoprotein (P-gp) efflux transporter. One report did not observe competitive inhibition of oxycodone by an established P-gp inhibitor [81] whereas another study [82] demonstrated significant elevation of brain oxycodone levels in P-gp glycoprotein knock-out mice *mdr1a/b* (−/−). Interestingly, this same study demonstrated that P-gp protein was upregulated in multiple tissues following chronic exposure to oxycodone. Such a relationship could contribute to development of analgesic tolerance [82]. However, at steady state, oxycodone levels in rat brain are three times higher that that of blood [83]. In contrast, morphine levels are 2–3 times lower in the central nervous system (CNS) than in blood [83].

These data indicate that oxycodone readily crosses the BBB perhaps by an active transport mechanism [83]. Also in contrast to morphine, oxycodone has high oral bioavailability (60–87 %) [84].

Metabolism. Oxycodone is metabolized by the CYP2D6 [77, 85] to oxymorphone [77, 85] (an active metabolite) and noroxycodone [77, 85]. It is proposed that variability in metabolism efficiency (rapid versus poor metabolizers) or hepatic impairment may significantly affect oxycodone pharmacology [85]. Variability in CYP2D6 metabolism appears to affect oxycodone pharmacokinetics [86]; the impact on pharmacodynamics remains inconclusive [86, 87] though a number of case reports are consistent with the proposal [88]. The impact of inhibitors of CYP2D6 or CYP3A4 has been examined, and an impact on oxycodone pharmacokinetics has been noted [89]; in contrast, several studies have not found pharmacological alterations in oxycodone analgesia when delivered concomitantly with inhibitors of CYP2D6 [90, 91]. In addition, moderate alterations in oxycodone pharmacodynamics were identified in patients that received a CYP3A4 inhibitor [92–95] and CYP2D6 inhibitor [93–95]. In one case report, a patient taking a combination of immediate- and controlled-release oxycodone had three negative oxycodone urine screens. Upon investigation for potential noncompliance it was discovered that the patient had been simultaneously taking rifampin, which is a known inducer of CYP3A4, CYP3A5, and CYP3A6 [96]. Therefore, it is clear that the metabolic profile can significantly impact oxycodone pharmacological outcomes.

Addiction Profile. Although oxycodone was synthesized nearly 100 years ago, substantive pharmacological characterization of the drug began only recently in the 1990s with the introduction of the sustained release formulations. The consequent increases in opioid prescriptions for these new formulations are, in part, associated with increases in the diversion and misuse of oxycodone [97]. The reinforcing properties of oxycodone have been studied comparatively recently in rat (i.v [98, 99] and mouse (i.v. [100]) confirming a pharmacology consistent with an addictive substance.

Preclinical Models of Pain. Consistent with the prior reports that show reduced opioid responding in animal models of chronic pain, Wade and colleagues [101] observed that rats with established chronic pain induced by inflammation showed reduced discrimination for a lever press resulting in delivery of intravenous oxycodone versus control lever (control rats readily demonstrate such discrimination). In this particular study, a comparison of breakpoints of progressive ratio of reinforcement was made between rats with inflammatory pain and their controls. This is a measure of motivation to lever press for reward. It was observed that rats with inflammatory pain persist in their responding for opioid significantly less than their control counterparts, reflecting a diminished motivation for opioid. These observations agree with many prior reports in animal models of addiction that opioid responding appears to be greatly reduced in rodents with chronic pain. Given the widespread use of oxycodone sustained release preparations in pain management and the prevalence of oxycodone misuse and abuse, it is imperative to expand our

understanding of how potential alterations in the CNS centers that govern opioid addiction impact oxycodone responding under various chronic pain conditions.

Hydrocodone

General Use and Routes of Administration. Hydrocodone was developed in 1920s and later introduced to the United States to be used as an analgesic and an antitussive [102] medication. A derivative and metabolite of codeine or thebaine, it has 5–6 times greater potency than the parent compound. In the United States, hydrocodone has been formulated as a combination with acetaminophen, ibuprofen, and guaifenesin; since 2004 hydrocodone combined with NSAIDS have been significantly increasing in prescriptions for management of pain [102]. The hydrocodone/acetaminophen formulation is reported to lead the list of most prescribed drugs in 2008 with 121 million prescriptions filled [103, 104]. In 2010 [103, 104], 139 million prescriptions of hydrocodone were dispensed, rendering the formulation the most prescribed opioid [105].

Prior to March 2014, hydrocodone was principally available in as a combined oral formulation with NSAIDS; it is now available as a single product [106]. Hydrocodone can also be delivered intravenously [107]. With an octanol/water partition coefficient greater than morphine, it crosses the blood brain barrier and may be a substrate for P-glycoprotein [108].

Metabolism. Hydrocodone is O-demethylated by CYP2D6 (human) [109] or CYP2D1 (rat) to hydromorphone, which is a potent active mu opioid analgesic [109, 110] with 4–6 times greater potency than hydrocodone [111]. Hydrocodone is also N-demethylated to norhydrocodone by CYP2D6 [110]. It has been proposed that individuals with genetic variations in CYP2D6 that result in elevated activity may be at greater risk for abuse [112]. Conversely, inhibition of CYP2D6 may reduce abuse liability as well as therapeutic potential of hydrocodone [112]. Administration of CYP2D6 and CYPD2D1 inhibitors budipine or quinidine results in diminished conversion of hydrocodone to hydromorphone in rhesus monkeys and in rats [112]. Additionally, bupidine treatment resulted in rightward shifts in the dose-effect curve for hydrocodone discrimination [112]. These data were in contrast from observations of Tomkins and colleagues [113] where bupidine and quinidine did not shift the discrimination dose-effect curve. The source of this response in monkeys may be due to some competitive activity of these agents at the mu opioid receptor [112]. It is known that when extensive metabolizers receive hydrocodone that their hydromorphone levels are 5–10 higher than in poor metabolizers [114]. Poor metabolizers (7 % of the Caucasian population) have an altered pharmacological response to hydrocodone [114]. However, extensive metabolizers with active enzyme, extensive metabolizers with inhibited enzymes, and poor metabolizers respond equivalently pharmacodynamically (e.g., response to pupil dilation) to hydrocodone [115]. This is not surprising because hydrocodone, though less potent

than hydromorphone, is not merely an inactive prodrug but a mu opioid receptor agonist itself. Further, morphinan agonists have been reported to have greater transfer to the CNS than O-demethylated metabolites [116] and the effective concentrations may be higher than serum concentrations suggest. Therefore, it is presumed that alterations in CYP2D6 metabolism will not impact the addiction liability of hydrocodone [115].

Addiction profile. As with expanded prescribing of fentanyl and oxycodone, substantial misuse of hydrocodone is an area of great concern [117]. One recent study [116] indicates that hydrocodone is second only to oxycodone in terms of likelihood to be selected as a prescription opioid of abuse. In this study [116], the decision-making of prescription opioid abusers in selecting oxycodone versus hydrocodone was assessed. It was discovered that inclusion of acetaminophen (APAP) in the hydrocodone oral dosage form contributes to the decision of some abusers to choose oxycodone over hydrocodone, due to risk and fear of APAP-induced liver toxicity. Inclusion of APAP in the dosage form, therefore, has served, in some cases, as a deterrent to abuse. A recently introduced extended release oral dosage form containing only hydrocodone [118] has been the subject of much debate and consideration since it does not contain an abuse deterrent mechanism as the oxycodone extended release formulations have been redesigned to include. These reports highlight the fact that dosage formulation and design can have significant (and sometimes unexpected) impact on the general public's responding to the drug. An additional biopharmaceutical influence on the use of hydrocodone is featured in the practice of intranasal abuse of the oral dosage form [119]. Significant toxicity to the upper aerodigestive tract caused by intentional misuse of the oral dosage form by crushing and engaging intranasal ingestion has been reported [120]. Interestingly, in this study it was noted that several patients (with documented chronic pain syndromes) reported initially electing (with the encouragement of friends and/or family) to deliver their pain medication intranasally intentionally for a perceived benefit of faster time to onset of pain relief than what is achieved by standard oral intake. It may be that, in these particular cases, the state of analgesia may have been the motivation, at least initially, as seems to be the case in many preclinical studies of addiction under condition of chronic pain [71, 121–125]. Hydrocodone reinforcing properties have been established in rat [113] and rhesus monkey [112] studies of self-administration. To our knowledge, its activity as a reinforcer has not yet been studied specifically in an animal model of chronic pain; such studies would be valuable.

Hydromorphone

General Use and Routes of Administration. Hydromorphone was developed and introduced as an analgesic in the 1920s [126]. It has been used clinically as an analgesic second-line alternative to morphine when patients are unresponsive to morphine or when morphine-induced side effects are limiting. It is available in a wide

variety of oral dosage forms including sustained release preparations. Hydromorphone can also be delivered by the intravenous, intramuscular, subcutaneous, and epidural routes of administration [126]. With lipophilicity intermediate between morphine and fentanyl, it readily crosses the BBB [126].

Metabolism. Hydromorphone is metabolized by UGT2B7 [127] to dihydroisomorphine glucuronide and hydromorphone-3-glucuronide (an active neuroexcitatory metabolite [128]) analogous to but more potent than morphine-3-glucuronide. In the clinic, high concentrations of hydromorphone-3-glucuronide may arise from high doses of hydromorphone and may result in myoclonus, allodynia, and/or seizures observed in patients [126], particularly in those with renal toxicity [129–131]. There is evidence also for hydrocodone metabolism to norhydrocodone by CYP3A4, CYP3A5, CYP2C9, and CYP2D6 [132]. The significance of this more minor metabolic pathway, however, is not clear.

Addiction Profile and Preclinical Models of Pain. Concurrent with expanded prescribing of opioid medications for treatment of pain, increased misuse of hydromorphone has been noted [133]. As with morphine and oxycodone, the controlled-release formulation was introduced in the 1990s [134]. More recently an oral delivery system has been introduced in the United States [135] that takes advantage of Alzet osmotic controlled-release technology. Hydromorphone is a high potency mu agonist and the reinforcing properties of hydromorphone have been established in nonhuman primate [136, 137] and more recently in nerve-injured rat [45]. In their comprehensive study of five opioid analgesic substances in nerve-injured rats, Martin and colleagues [45] demonstrated that lever pressing for hydromorphone is greatly reduced in the chronic pain condition relative to control. These findings are in agreement with those described earlier in the sections on morphine, fentanyl, and oxycodone.

Methadone

General Use and Routes of Administration. Methadone was first synthesized in the late 1930s [138]. Since 1965 it has been used internationally as a substitute for heroin due to its high oral bioavailability (70–90 %) and exceptionally long half-life [139] which enables once daily dosing to avoid opioid withdrawal. It is clinically used often as an analgesic option for opioid rotation when patients become unresponsive to first-line opioid analgesics [138] such as morphine or fentanyl. It is available in a wide variety of oral dosage forms including oral, rectal [140], and parenteral formulation [141]. In most cases both the R and S racemates are delivered as a racemic mixture. Methadone is highly lipophilic and adheres to tissues where it forms a depot with slow re-release to plasma, which accounts for its signature long half-life of 30 h [142].

Methadone readily crosses the BBB [143] and both R- and S-methadone are substrates for P-glycoprotein [144, 145].

Metabolism. The pharmacokinetics of methadone have been known for decades [146]; while the bioavailability is generally agreed to be high, there is significant inter-individual variability [147], which challenges the established standard dosing regimens. The wide inter-individual variation in methadone may be due to variable gene expression and polymorphisms of its metabolic enzymes (CYP3A4, CYP2C8, CYP2B6, and CYP2D6) or efflux transporters. Methadone is N-demethylated to form the primary metabolite 2-ethyl-1,5-dimethyl-3,3-diphenylpyrrolinium (EDDP) and further N-demethylated to 2-ethyl-5-methyl-3,3-diphenyl-1- pyrroline (EMDP) [148]. These metabolites are not considered to be active in the CNS. The R-methadone racemate is thought to be metabolized by CYP2C19 and the S-methadone forms by CYP2B6 [149]. Considerable investigation has taken place to assess the impact of pharmacological induction and inhibition of CYP3A4 on methadone [148]. The protease inhibitor ritonavir is a known CYP3A4 inhibitor and concomitant decreases in plasma methadone have been observed [150]. However, when a ritonavir/indinavir anti-retroviral combination was delivered concurrently with methadone, while significant inhibition of CYP3A4 activity was observed, there was no impact of the combination on methadone pharmacokinetic parameters [151]. Consistently, the protease inhibitor, indinavir, induced CYP3A4 activity, but had no impact on methadone plasma concentrations or distribution in healthy volunteers [152]. Further, in a separate study, the co-administration of anti-retroviral drug nelfinavir inhibits the CYP3A4 enzyme, but reduces methadone plasma concentrations and elevates methadone clearance, suggesting that CYP3A4 did not impact methadone pharmacokinetics, in this instance [152]. For example, it has been recently found that efavirenz, a first-line anti-retroviral agent to treat HIV, induces hepatic CYP3A4 and CYP2B6 activity [152]. Efavirenz is also associated with a 50 % reduction in plasma methadone as well as precipitated opioid withdrawal [152, 153]. This short summary of a few of the multiple evaluations of CYP enzyme pharmacological induction or inhibition compared against the impact of methadone pharmacokinetics in the same subjects illustrates the complexity of methadone pharmacology. It is likely that multiple factors account for the extensive intersubject variability of methadone, which may be difficult to sort out on a case-by-case basis.

As mentioned above, methadone is most often delivered as a racemic mixture and, like other racemic mixtures, the enantiomers are thought to target distinct receptors. The R racemate exerts its effects on the mu opioid receptor and S racemate on other off-target sites which may account for adverse side effects such as QT interval prolongation [144]. Pharmacological responses of the racemates given separately and as mixture are consistent with these mechanistic distinctions [154]. The S racemate is also an NMDA receptor antagonist [155] which confers additional anti-hyperalgesic properties and protects against the development of analgesic tolerance.

Addiction Profile. As with other opioids, prescribing for methadone increased during the 1990s. From 2003 to 2008, methadone represented about 5 % of all opioids dispensed in United States, but accounted for about 30 % of opioid-related fatalities [156] reported between 1999 and 2004. The reason for this apparent discrepancy is

likely due to multiple factors including, but not limited to, inadequate clinician understanding of the pharmacokinetics of methadone (e.g., long elimination-life), inaccurate presumption of opioid tolerance from prior opioid use, and patient noncompliance by taking too much without physician approval or taking their medication in combination with other CNS active agents (e.g., alcohol and benzodiazepines) [156].

As stated previously, the R racemate of methadone is a mu opioid receptor agonist and the opioid receptor dependent [157] reinforcing properties of methadone have been demonstrated in human [158, 159], nonhuman primate [157, 160–162], and rat [45, 163–166].

Preclinical Models of Pain. Martin and colleagues [45] demonstrated that the dose–response curve for lever pressing for methadone is shifted rightward in the chronic pain condition relative to control. This means that establishment of lever pressing for methadone in rats with chronic pain required higher doses than controls. These doses were also doses that alleviated chronic pain behaviors, which may indicate that the state of analgesia, in this case, was rewarding. These findings are consistent with those reported before in the morphine, fentanyl, oxycodone, and hydromorphone descriptions.

Tramadol

General Use and Routes of Administration. Tramadol was first synthesized in 1962 and introduced as an analgesic in 1977 in Germany [167]. During the 1990s tramadol use expanded much more broadly internationally with registration in the UK and US as well as other nations [138, 167]. With the introduction of the oral immediate- and controlled-release formulations to the market in the 1990s, clinical use escalated [74]. Like methadone, tramadol is delivered as a racemic mixture which is thought to account in part for its analgesic efficacy [168]. Tramadol is delivered intravenously, intramuscularly, subcutaneously, rectally, or orally by various release mechanisms (intermediate and sustained) [167]. It crosses the BBB in rat in an apparently stereoselective manner [169]. (+)-Tramadol has weak affinity for the mu opioid receptor (2.4 μM), 400-fold lower than the affinity of morphine (0.62 nM) [170]. In contrast, tramadol's active metabolite, metabolite (+)-*O*desmethyltramadol (M1) has much greater affinity (3.5 nM) for the μ opioid receptor in the same preparation and, consequently, the mu receptor dependent aspect of tramadol may rely on the conversion of tramadol to this active metabolite [170]. Additionally, (+)-tramadol inhibits serotonin reuptake whereas (−)-tramadol inhibits norepinephrine reuptake. These actions are thought to result in elevated extracellular concentrations of serotonin and norepinephrine, both of which act upon their target receptors to enhance analgesia synergistically with mu opioid receptor analgesic effects. Therefore the actions of tramadol may result in a triple receptor mediated and, thus, auto-synergistic effect.

Metabolism. Tramadol is nearly 100 % absorbed following oral delivery and has high oral bioavailability (70 %), the difference accounted for by first-pass metabolism. Bioavailability is higher following rectal delivery (77 %) likely due to reduced first-pass metabolism (e.g., not all products will enter the hepatic circulation) [167].

Tramadol is thought to be O-demethylated by CYP2D6 to (+)-*Odesmethyl-tramadol* (M1) (an active metabolite) and N-demethylated by CYP2B6 and CYP3A4 to *N*-Desmethyl-tramadol (M2) [167]. Biotransformation of tramadol is more rapid and complete in rat (99 %) than in human (68–75 %) [171]. As with oxycodone and methadone, it is proposed that CYP2D6 polymorphisms may significantly affect tramadol pharmacology. In a population of poor metabolizers, the ratio of tramadol/M1 was significantly elevated relative to extensive metabolizers [172]. Further, the tramadol/M1 ratio is strongly correlated to gene-dose status (two versus one functional alleles) in extensive metabolizers. Therefore, as with several of the other opioids reviewed here, the pharmacokinetic variability of tramadol may be, in part, attributed to CYP polymorphisms. Alteration in the pharmacokinetics can have an impact on serum concentrations of tramadol and its metabolites which can subsequently impact the pharmacological responses. Therefore, consideration of the metabolic genotype of population of study should be considered when tramadol is used or tested.

Addiction Profile and Preclinical Models of Pain. As stated previously, the R racemate of tramadol is a weak affinity mu opioid receptor agonist. Reinforcing properties of tramadol have been assessed in nonhuman primate [173] and rat [174, 175] where it was observed in both cases to be a weak reinforcer. The outcomes of these animal models of tramadol self-administration are consistent with clinical and epidemiological reports of tramadol that historically indicated limited abuse liability [171]. However, recent experimental human self-administration in self-reported opioid prescription abusers indicated that tramadol demonstrated evidence of reinforcing properties in a dose-dependent manner [176]. It may be that experienced opioid abusers may be more susceptible to tramadol misuse [177, 178]. To our knowledge, the reinforcing properties of tramadol have not been assessed in study of chronic pain subjects in a model of tramadol self-administration. However, there has been one report of the place preference of nerve-injured subjects in the conditioned place preference model of addiction. In these experiments, Nakamura and colleagues [179] showed that normal rats develop conditioned place preference for tramadol and its primary metabolite M1. In contrast, rodents with established chronic pain from spinal nerve ligation demonstrated significantly reduced place preference induced by either tramadol or the M1 metabolite. This study is congruent with the prior observations that, in most cases, morphine-induced place preference is reduced in conditions of chronic pain.

Remifentanil

General Use, Routes of Administration, and Metabolism. Remifentanil was introduced in the early 1990s with classic opioid receptor pharmacological effects but unique pharmacokinetic aspects that distinguish it from other mu agonists [180]. Remifentanil is an ultra-short acting opioid that is metabolized not by the liver (as are most opioids) but by nonspecific serum or tissue esterases that target its ester linkage which is unique among opioids [181]. Two resultant metabolites are inactive [181]. Remifentanil is most frequently given as an i.v. infusion and used typically for anesthetic sedation. Intranasal delivery of remifentanil solution has also been demonstrated to enhance sevoflurane anesthesia for pediatric intubation [182]. Spinal delivery of remifentanil has demonstrated analgesia in a rodent model of intrathecal cannulation [183]. The half-life of remifentanil is typically on the order of four minutes post-cessation of infusion, which offers an advantage of more rapid recovery from anesthesia than fentanyl or fentanyl analogues [106].

Addiction Profile. The pharmacology of remifentanil is that of a standard mu agonist with a naloxone-sensitive pharmacological profile including miosis [184] peripheral [185] and central [183] analgesia, and development of opioid analgesic tolerance [186, 187] (although some reports indicate no evidence for tolerance [188]). In contrast to other opioids, the use of remifentanil as an anesthetic has not translated into widespread reported misuse possibly due to several factors. First, the delivery method most typically involves intravenous which, infusion combined with the ultra-short half-life, may diminish the practical abusability of remifentanil. Notably, there are few descriptions of remifentanil abuse in the literature [189]. The few existing reports describe cases of abuse in the clinic. One case report reveals misuse by a health care professional trainee by inhalation of remifentanil in its powder (unconstituted) form. The pharmacological effects were described as somewhat aversive due to elevated nausea and withdrawal symptoms. However, having been initiated to opioid pharmacological effects, the patient progressed to begin abusing fentanyl intravenously. Therefore, in this case, remifentanil was thought to serve as an initiating opioid that led to a more pharmacokinetically abusable opioid (fentanyl). As with older opioid agonists the reinforcing properties of remifentanil have been established in rat [190–194] and rhesus monkey [195, 196]. To our knowledge, the addiction profile of remifentanil has not been characterized in an animal model of chronic pain.

Summary

Up to this point, we have covered a number of very commonly misused opioid agonists individually in terms of their origin, physicochemical characteristics, common routes of administration, pharmacokinetic aspects, receptor selectivity, and what has been learned from the study of their reinforcing properties in a variety of

Table 6.1 Preclinical animal models of addiction: routes of administration and doses of representative studies

	Nonhuman primate	Rat	Mouse
Morphine	IV 0.5, 2.5 mg/kg [13]	IV 0.2–2 mg/kg PR [19]	IV, dose unknown [24]
	IV 0.1 mg/kg [14]	0.2–2 mg/kg PR [18, 22]	IV: 0.1 mg/kg/infusion [25]
		PO	
	IV 0.25 mg/kg/inj [15]	Oral (bottle choice) 0.25–0.5 mg/mL [68]	IV(0.125–4.0 mg/mL) [23]
Fentanyl	IV(0.001, 0.0003, 0.0001 mg/kg/inj; FR32-1000 [65, 66]	IV [18, 67], Oral bottle choice: 5–25 micrograms/mL [20]	Oral (0.070–0.70 μg/70 μL receptacle delivery) [70, 73]
	IV(0.003, 0.001, 0.0003, 0.0001, 0.00003 mg/kg/inj; FR30 [65, 66]	Oral 50–75 μg/mL, FR4, FR6, PR [21]	
		Oral (bottle choice): 25 μg/mL [68]	
Oxycodone	SC (0.20 mg/kg) [99]	IV (0.1 mg/kg/infusion) [98]	IV (0.25–0.75 mg/kg/infusion, FR1-FR3) [100] SC (1 mL/kg) [99]
		(0.0003–0.3 mg/kg/infusion) [99]	
Hydrocodone	SC (0.032–10 mg/kg. Note: 32.00 mg/kg lethal dose) [112]	IV (0.02–32 mg/kg/infusion) [113]	–
Hydromorphone	IV (1 mg/kg/day) [136]	IV (10–100 μg/kg) [45]	–
Methadone	Oral (low to high- 0.05, 0.2, 0.8 mg/mL given in 0.65 mL volumes) [161]	IV (0.01, 0.03, 0.3 mg/kg/injusion) [164] (3 mg/kg hourly to prevent somatic withdrawal from heroin) [45]	–
	IV (0.03–0.25 mg/kg/inj) [162]		
	IV (0.179–11.86 mg/kg/day) [137]		
Tramadol	IV (0.1, 1.0 mg/kg/inj) [173]	Oral (32–56 mg/kg, FR10) [174]	–
		IP (10 mg/kg) [171]	
Remifentanil	IV (0.0003, 0.0001, 0.00001 mg/kg/infusion, FR 32-320) [65, 66]	IV (0.25–32 μg/kg) [190]	–
		(10–0.10 μg/kg/infusion FR1) [191]	
	IV (0.0001 mg/kg/infusion, FR 30) [196]	(0.4, 0.8, 1.6, 3.2, or 6.4 mg/kg/infusion, FR1) [192]	
	IV 0.025–0.8 μg/kg/injection, PR) [195]	IV (0.25, 0.5, 1, 2, 4, 8, 16, and 32 μg/kg per infusion, PR) [194]	
	IV: 0.09–2.9 μg/kg/inj [197]		

species, some of them under conditions of chronic pain. A summary of routes of administration and representatives doses of the featured opioids is provided in Table 6.1.

Blood–Brain Barrier Transport

An important aspect of drug distribution involves a set of proteins positioned within the endothelial cells of the CNS vasculature [198]. These proteins form the essence of what is commonly referred to as the Blood Brain Barrier (BBB). The proteins of the BBB involve structural proteins that line the intercellular walls between endothelial cells and form physical barriers (tight junctions) to prevent paracellular diffusion of chemicals. The BBB also includes a set of proteins that enable transport of molecules into the endothelial cell from the lumen of the capillary for trafficking intracellularly and exit on the brain side. Conversely, the BBB includes a complementary set of proteins that enable transport of molecules to enter the endothelial cell from the brain for trafficking intracellularly to exit to the capillary lumen. Both forms are described as transcellular transport. Finally, the BBB also contains a specific set of proteins (ABC transporters) that essentially capture passively diffusing molecules as they enter the endothelial cell and efflux to the lumen of the capillary. These proteins are known as BBB efflux proteins. It has been appreciated for some time that a number of opioids are substrates for one specific member of this class of transporter, P-glycoprotein (P-gp) [199]. Evidence in support of this includes enhanced brain uptake of morphine, methadone, and fentanyl in P-gp knock-out mice following intra-arterial perfusion [200], or microdialysis [201]. It is known that P-gp both contributes to preventing entry of opioids circulating in the blood to the brain as well as efflux opioids circulating in the CNS extracellular space to the blood [202]. Additionally, another member of the ABC BBB transporter family, the multidrug resistance protein (MRP), has recently been shown to similarly reduce the BBB transport of morphine from the systemic circulation to the CNS and to efflux morphine from the brain to the blood [203]. Specifically, it has been observed that antisense treatment to downregulate the expression of either P-gp [202] or MRP [203] or use of their respective knock-out mice resulted in enhanced analgesia induced by systemically administered morphine. This enhancement occurs presumably by enabling increased CNS levels of morphine. Interestingly, it has also be demonstrated that when opioids are delivered centrally, a component of the drug is efflux by BBB transport proteins to the periphery where activation of peripheral opioid receptors contributes to the overall analgesic effect synergistically with central opioid receptors [202]. Specifically, when p-glycoprotein [202] or MRP transporters [203] are reduced either by antisense or knock-out technology, the analgesic dose–response curves of *intracerebroventricularly* (i.c.v.) delivered morphine are shifted *rightward*, indicating *diminished* potency of the overall effect of i.c.v. morphine, presumably due to reduced efflux of morphine from the brain to the systemic

circulation and, consequently, reduced activation of peripheral opioid receptors. These data are important observations in support the concept that P-gp and MRP also contribute to the efflux of opioids from the brain to the systemic circulation.

Analgesia of morphine [202, 204], fentanyl [204], and methadone [204] has been reduced in either P-gp KO mice or in the presence of P-gp inhibitors. It is, however, unclear what the therapeutic impact of P-gp influenced alterations in opioid concentrations may be. There is increasing evidence to suggest that P-gp levels are altered following a variety of environmental or physiological processes. Chronic administration of opioid has been reported to upregulate P-gp levels in a variety of tissues [205]; this would suggest that CNS concentrations under such conditions would be lowered and this may contribute to development of apparent opioid tolerance [206]. It would stand to reason that alterations in expression and/or function P-glycoprotein could arise under conditions of chronic pain that could influence the analgesic responsiveness of P-gp substrates, such as opioids. In fact, a study of peripheral inflammatory hyperalgesia using the standard intraplantar carrageenan model has demonstrated 40 % elevation in P-gp expression with a corresponding reduction in the antinociceptive efficacy of morphine [207]. Further, more detailed analysis has revealed that carrageenan-induced hypersensitivity results in protein trafficking alterations in P-gp at the level of the bilipid membrane [208]. Therefore, these studies provide the proof-of-concept that the condition of chronic pain can influence protein expression and function of P-gp. Peripheral inflammation is one model of chronic pain. More work is needed to understand the status of P-gp under a wide variety of pain conditions of diverse origin. There is clinical evidence to suggest that genetic variability in the ABC1 gene contributes to variability in patient responsiveness to opioids. Specifically it has been shown that methadone [209] or morphine [210] dosing for addiction and pain treatment respectively was associated with genetic variants of ABCB1, the gene that encodes P-gp. It seems that the interaction of the opioids with the P-gp and other transport proteins is highly complex involving both substrate interaction with P-gp and/or modulation of the expression of the P-gp system and/or patient genotype for the P-gp gene [205]. It would be greatly beneficial, therefore, to consider the status and impact of P-gp under the varied conditions of chronic pain and opioid self-administration models that are currently used separately and increasingly combined to further our understanding as to how subjects with established chronic pain respond to chronic opioid treatment.

Conclusion

When the condition of chronic pain is introduced into the complexity of the system, there are a number of points in the pharmacokinetic profile of each compound that may influence the reinforcing effects of a particular opioid. These aspects have been featured in this chapter. Although opioid receptor agonists are thought to converge on a common target, their pathways to the target, activities at the target, and retreat

and distributions away from the target and out of the organism can be distinct. In experimental design and analysis of data, these considerations will be valuable to investigators intending to initiate studies of opioid self-administration in models of established chronic pain.

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Part IV
Clinical Perspectives

Chapter 7
Prenatal Exposure to Opioids

Lisa M. Schrott

Abstract Prescription opioid abuse is a growing healthcare concern in this country. In particular recent data have shown substantial increases in use among the young and women in comparison to more traditional abused opioids like heroin. The changing demographics of opioid abuse are leading to rises in neonatal narcotic abstinence syndromes (NNAS), which can require substantial hospitalization. In addition to NNAS there can be long-term effects on health and behavior. To characterize the acute and longer-term effects, rodent models of prenatal opioid exposure have been developed. The majority of models have considered exposure to methadone, morphine, and heroin. We will review the data from these models, as well as more recent data on prenatal exposure to prescription opioids. We also consider the acute effects of the drugs in utero and the early postnatal period, as well as longer-term effects in the juvenile and adult.

Introduction

Currently buprenorphine and methadone are approved for use in the treatment of opioid dependence, but only methadone is approved for use during pregnancy in the United States [1, 2]. Fetal exposure to methadone, however, results in a neonatal abstinence syndrome that can be prolonged and require pharmacological management [3, 4]. Withdrawal signs include irritability, high shrill crying, poor suckling, and inability to sleep [5]. Prenatal methadone exposure also results in long-term consequences in children, including fewer goal-directed behaviors, more speech and cognitive deficits, and poorer social skills [6, 7]. These children also show greater anxiety and aggression and poorer fine and gross motor coordination [8, 9]. However, human studies may be confounded by environmental factors such as socioeconomic status and maternal care, making it difficult to determine direct effects of prenatal opioid dependence [10].

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C.A. Fairbanks, T.J. Martin (eds.), *Neurobiological Studies of Addiction in Chronic Pain States*, Contemporary Clinical Neuroscience 17,
DOI 10.1007/978-1-4939-1856-0_7

While earlier studies failed to find a relationship between dose of methadone and neonatal withdrawal or health measures, a recent study from New Zealand found that higher doses of methadone during pregnancy were related to increased likelihood of preterm birth, smaller at birth (weight, length, and head circumference), a longer postnatal hospital stay and increased mortality [11]. Also of interest are findings indicating that the reason for methadone use during pregnancy can affect the outcome of the infant. The offspring of women who were receiving methadone for pain management had a significantly reduced neonatal abstinence syndrome compared to infants whose mothers received similar dosing for opioid addiction. They also had higher body weights at birth and larger head circumference. There was no difference in premature labor between the two groups [12]. These data suggest that the other factors beyond drug pharmacology can mediate the effects of developmental exposure. Because of the difficulty in separating environmental factors from pharmacological factors in clinical populations, animal models of prenatal drug exposure have been developed and have been useful in identifying pharmacologically-induced vulnerability factors.

Prenatal Opioid Exposure in Rodents

Animal models have also demonstrated long-term dysfunction following prenatal opioid exposure in behavioral, endocrinological, and immunological domains. There is convergent evidence that certain behaviors, such as measures of emotionality, subsequent drug self-administration, operant responding, and place preference are sensitive to developmental opioid exposure [13–17]. One postulated mechanism for these effects is the direct pharmacological action of opioids on brain development, since prenatal opioid exposure affects morphological [18, 19] and neurochemical parameters, including those of the endogenous opioid, dopamine, adrenergic, and cholinergic systems [20–24].

One of the major systems affected by prenatal opioid exposure is the nociceptive system. As early as the 1970s it was noted that prenatal exposure to morphine led to an attenuated antinociceptive response when affected offspring were given morphine prior to hotplate testing at 3, 5, and 11 weeks of age [25]. The attenuated response was similar to that of rats that had been made tolerant to morphine prior to test and the authors speculated that in utero exposure led to the development of tolerance. These results have been replicated by other groups using different morphine exposures [26] as well as other different prenatal opioid exposure models (e.g., levorphanol [27]; methadone [28, 29]). There are some important caveats to note. In some paradigms an enhanced antinociceptive response has been noted. Kirby et al. [30] found that when 20 mg/kg/day morphine was divided across fours doses a day from gestation days 12–20 there was an enhanced response in comparison to saline-exposed offspring, while when the dose was divided into two doses a day they had similar tail-flick latencies as the saline-exposed offspring. The direction and the magnitude of the effects can also be dependent on the age when nociception is

assessed. Prenatal methadone exposure enhanced analgesic action of morphine on postnatal day 4, but attenuated it on postnatal day 21 [28]. Prenatal morphine attenuated the antinociceptive response to morphine on postnatal day 14 [26].

Reward properties of drugs in adulthood are also affected. An early study by Glick et al. [31] found that prenatal morphine decreased the number of days needed to acquire morphine self-administration as an adult. Similarly prenatal methadone increased the amount of morphine consumed in exposed adult rats in the two bottle choice test [32]. Prenatal exposure to morphine increased rates of heroin and cocaine self-administration in adulthood, increasing the sensitivity to lower doses [33]. Because both cocaine and heroin self-administration were enhanced, it is unlikely due to solely to changes in opioid receptor density or affinity.

One of the most robust findings in the prenatal opioid literature is the effect on the cognition, specifically the acquisition and retention of new information. Spatial learning models have been extensively examined. We have found that exposure throughout gestation in rats to the long-acting opiate, l-α-acetylmethadol (LAAM) resulted in poor performance in acquisition of the radial arm maze [34]. Prenatal LAAM-exposed rats had more reference and working memory errors, but were able to acquire the task after 5 days of training and there was no difference from prenatal water controls in retention trials 24 h later. Similar effects were found in the Morris water maze for rats exposed to oxycodone in utero, where differences in the search strategy utilized by the prenatally exposed rats were noted [35]. Radial arm maze [36] and Morris water maze [37] deficits were also observed after exposure to prenatal heroin in rodents. Morphine administered to rats in embryonic days 11–18 increased latency in the radial arm maze [38]. Exposure to morphine on embryonic days 12–16 caused a deficit in long-, but not intermediate-term memory in the one-trial passive avoidance task paradigm in the chick [39].

Prenatal opiate exposure has also been known to result in cellular and molecular alterations related to learning and memory. For example, prenatal exposure to heroin caused pre and postsynaptic alterations in the septo-hippocampal cholinergic system [40]. These changes, which include choline transporter activity, G-protein levels, as well as basal and carbachol-stimulated PKC activity, are postulated to play a role in changeS in long-term potentiation (LTP), widely considered as a cellular mechanism for learning and memory [41]. Prenatal morphine caused impairment in Morris water maze performance that was concomitant with alterations in hippocampus LTP and LTD (long-term depression), as well as NMDA receptor-mediated plasticity and phosphorylation of CREBSerine-133 [42]. In an in vivo study, prenatal morphine attenuated the maintenance phase of LTP in the lateral perforant path in the hippocampus, while not altering induction or intermediate LTP in the lateral or medial perforant paths [43].

The consequences of opioid exposure are not limited to the nervous system. The immunosuppressive properties of opioids have been well documented and will not be detailed here [44, 45]. However, with respect to opioid exposure during development, Shavit et al. [46] found that prenatal morphine blunted natural killer cell activity and the fever response to the endotoxin lipopolysaccharide (LPS) in adult rats. We found a blunted fever response to LPS in hatchlings exposed in ovo

to the l-alpha acteylmethadol (LAAM) metabolite NLAAM [47]. Similarly, we found a blunted fever response to LPS in adult rats that had been prenatally exposed to LAAM. There was no change in basal body temperature or in response to saline injection. There were indications that the neural-immune network was altered because levels of the mature form of the IL-1b protein were elevated in the hypothalamus of prenatally LAAM-treated rats. Interestingly, circulating levels of IL-1b were not affected, nor were protein levels in the spleen [48].

Mechanisms for Prenatal Opioid Effects

There are multiple mechanisms by which opioids exert their effects on the developing nervous system. Not surprisingly, opioid receptor signaling has been indicated, specifically mu opioid receptors are involved [49]. Darmani et al. [50] found that prenatal methadone altered mu receptor affinity in both gestation day 7 and on postnatal day 7. Scatchard analyses revealed that the receptor density was unchanged, but the affinity for the mu selective ligand DAMGO was decreased (Darmani et al., 1992).

Studies examining prenatal morphine exposure have demonstrated involvement of NMDA receptors. For example, Tao et al. [26] found that the NMDA antagonist dextromethorphan when co-administered with morphine throughout pregnancy and for the first postnatal month reduced neonatal mortality, normalized body weight, attenuated postnatal withdrawal, and prevented the down-regulation of hippocampal NMDA receptors that were associated with the developmental morphine exposure. Interestingly, the role of glutamatergic neurotransmission in the effects of opioid exposure may vary on the specific receptor subtype and the developmental stage. NMDA receptors antagonists have low efficacy in blocking withdrawal effects during the first postnatal week, but high efficacy in the second and third postnatal weeks. In contrast, antagonists to the AMPA and metabotropic glutamate receptors are equally effective throughout the postnatal—preweaning period [51, 52]. Alterations in the cholinergic system have been suggested to underlie some of the cognitive deficits associated with prenatal opioid exposure. Vatury et al. [53] found that choline transporter sites were distributed in a different pattern in the CA1, CA3, and dentate gyrus regions in the hippocampus of mice exposed prenatally to heroin than in vehicle controls.

Studies using various pharmacological manipulations in animals have suggested that neonatal opioid withdrawal may be involved in some of the acute and long-term effects of prenatal opioid exposure [54–56]. This may be a consequence of the neurochemical changes associated with opioid withdrawal and/or some of the metabolic and neuroendocrine manifestations. Neonatal opioid withdrawal is mediated by multiple neurochemical systems, with the serotonin$_2$ receptors and alpha$_2$ adrenergic receptors playing important roles [57–61]. Studies have also implicated a role for nitric oxide [51]. Other potential mediators are changes in metabolic demands and respiration, as well as activation of the hypothalamic–pituitary–adrenal (HPA) axis that can occur as the neonate undergoes withdrawal [61]. In the chick embryo,

we found that precipitated withdrawal from chronic opioid exposure activated the HPA axis, increasing corticosterone concentrations [62]. In the absence of drug exposure itself, these physiological and metabolic changes associated with opioid withdrawal on their own could affect development of multiple organ systems and impact long-term health and behavior.

Animal models of prenatal opioid exposure have corroborated some of the findings of the human clinical literature, in particular, alterations in cognitive functioning and processing of nociceptive signals. Mechanisms for these effects include dysregulation of neurotransmitter systems and molecular signaling pathways. These findings suggest therapeutic targets via both pharmacological as well as environmental regimens.

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Chapter 8
Opioids in an Evidence-Based World

Scott A. Strassels

Introduction

There is no question that pain of all types is common and that the resulting epidemiologic, economic, and human burden is substantial. In 2011, the Institute of Medicine estimated that 100 million American adults are affected by chronic pain of any type and that associated costs (including lost productivity) are as high as $635 billion [1]. Pain is also an expected outcome of surgery. In 2010, 51.4 million inpatient surgical procedures were performed, and outpatient surgeries accounted for approximately 63.6 % of total surgeries in community hospitals [2, 3]. Cancer-related pain is also an important problem in people with current disease and in individuals with a history of cancer. In 2007, the pooled prevalence of pain across all cancer types was estimated to be greater than 50 % [4]. Furthermore, breakthrough pain in cancer patients can represent a challenging complication. While published estimates of the prevalence of breakthrough pain vary widely (due in part to use of different definitions and inclusion criteria), three estimates published in the last few years provided estimates of approximately 40 %, 44 % (incident pain), 41.5 % (spontaneous pain), and 73 %, suggesting that a significant proportion of people with cancer have relatively complex pain [5–7]. People with current cancer may have pain related to the tumor or from surgery, chemotherapy, or radiation treatment. It is somewhat ironic that as individuals with cancer live longer, the prevalence of cancer-related pain may also increase, even after there is no remaining evidence of disease [8].

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C.A. Fairbanks, T.J. Martin (eds.), *Neurobiological Studies of Addiction in Chronic Pain States*, Contemporary Clinical Neuroscience 17,
DOI 10.1007/978-1-4939-1856-0_8

While the drugs available to treat pain come from a wide variety of pharmacologic classes, mechanisms of action, and routes of administration, the opioid analgesics are among the most important of these tools. At the same time, there remain important gaps in understanding the pathophysiology of pain, opioid pharmacology and toxicology, and the clinical, economic, and human outcomes of pain and of its treatment [9, 10]. The purpose of this chapter is to review and discuss three issues that pertain to this interface: opioid-induced hyperalgesia, measurement of the clinical effectiveness of the opioids, and efforts to reduce abuse, misuse, and diversion of opioids (and other controlled substances) as part of efforts to reduce drug-related adverse outcomes and deaths.

Hyperalgesia

Hyperalgesia refers to an increased response to a painful stimulus at either a normal or increased threshold [11]. In contrast, the term opioid-induced hyperalgesia (OIH) is broadly defined as patients becoming more sensitive to pain due specifically to the use of opioids [12–15]. Yet, there are significant gaps in understanding the mechanisms underlying OIH as well as the clinical relevance of this phenomenon [12, 16].

Pathophysiology. The pathophysiology of OIH is incompletely understood, and it remains important to emphasize that decreased analgesia from opioids may reflect hyperalgesia, tolerance, worsening disease, or a combination of these phenomena [17].

Having said that, the science underlying increases in pain sensitivity is growing rapidly. Specifically, hyperalgesia appears to occur in a wide variety of clinical settings and patient populations, including persons on maintenance or withdrawal of opioid use, as well as persons receiving methadone for opioid maintenance and surgical patients [18]. There also appears to be variation in the type of increased painful response to different stimulation. For example, in persons being maintained on methadone, hyperalgesia was found to occur to cold, but to a lesser degree for electrical stimuli and not to mechanical pain. In persons who underwent surgery, the development of hyperalgesia appeared to be associated with receiving higher opioid doses, although this finding has not been consistent, nor is it always easy to separate hyperalgesia from tolerance.

Risk factors. Risk factors for development of OIH are not yet well understood. In the 2010 research guideline on future research pertaining to the use of opioids for chronic non-cancer pain, the authors note that several critical topics have yet to be addressed, including the epidemiology of OIH, the likelihood of developing OIH as a function of clinical and demographic characteristics, the interaction between hyperalgesia and acute pain, and, notably, dose and duration of therapy [16]. While facets of a patient's clinical presentation such as dose, duration of therapy, and quantitative sensory testing may be helpful to identify patients at increased risk for altered pain sensitivity, these factors are neither sensitive nor specific.

Treatment. While data on treatment for suspected opioid-induced hyperalgesia is limited, suggested treatment regimens generally include dose increase (to rule out tolerance), dose decrease, and adding (or changing to) *N*-methyl-D-aspartate receptor antagonists (such as ketamine and methadone), clonidine, and dexmedetomidine. Buprenorphine may be useful, and multimodal analgesic regimens may be useful due to the opioid-sparing effect of these regimens. Propranolol may also have some role in preventing OIH. Remifentanil, a potent opioid used primarily in surgical settings, is known to produce a post-infusion hyperalgesia. In a recent study of ten patients, persons who received remifentanil and propranolol did not experience mechanical hyperalgesia, while individuals who received remifentanil and placebo did have hyperalgesia [19]. In a separate publication, these authors also demonstrated in a study of adults with chronic nonradicular low back pain who used sustained-release morphine, these authors demonstrated that tolerance can occur independently from OIH [20].

Clinical Outcomes

Evidence-based medicine plays an important part of clinical practice in many countries, from reimbursement decisions through pay for performance incentives. Yet, the evidence base for the use of opioids is often uneven. Although there are a variety of clinical practice guidelines (CPGs) focused on the treatment of pain, there are also important gaps, such as recommendation for the treatment of pain in children and adolescents [10]. Furthermore, CPGs for conditions like hypertension and hypercholesterolemia tend to be relatively prescriptive. In contrast, CPGs for pain management tend to be very general. The result is that, in the absence of high-quality evidence, clinicians are often left to practice according to habit, which may or may not result in optimal outcomes.

Additionally, clinicians may not know which outcomes are best to assess or recommended methods (surveys, questionnaires, etc.). For example, it is generally easy to assess a patient's pain (and, indirectly, the quality of care) using a numeric analog 0–10 or verbal rating scale, but pain intensity is just one of many facets of a complex multidimensional experience [21]. Similarly, the expected duration of pain and subsequent treatment play an important role. For example, acute pain studies typically last just a few days, with single-dose regimens commonly used, and chronic pain studies typically last no more than a few months at most.

Other dimensions of the pain experience, such as the ability to function in ways that are important to the patient, family, and caregivers, are also likely to be important. In a consensus statement regarding the core competencies for pain management across all healthcare disciplines, four domains were identified as being of primary importance: the multidimensional nature of pain, pain assessment and measurement, management of pain, and context of pain management [22]. Similarly, the domains identified in the revised American Pain Society Patient Outcome Questionnaire as reflecting the quality of care were pain severity and relief, impact of pain on activity,

sleep, and negative emotions, side effects of treatment, helpfulness of information about pain treatment, ability to take part in pain treatment decisions, and use of nondrug treatments [23].

In designing clinical trials, a set of domains recommended for consideration of inclusion in clinical chronic pain studies has been published by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group. These recommendations emphasize the importance of these core domains: pain, physical and emotional functioning, participant ratings of improvement and satisfaction with treatment, and participant disposition, including adherence to treatment and withdrawal from the study [24]. More specifically, patients reported that the most important ways that pain affected them in daily life were pain reduction, enjoyment of life, emotional well-being, fatigue, weakness, and sleep [25] In studies of acute, chronic, and recurrent pain in children and adolescents, the domains considered to be of importance were generally similar to those suggested for studies of adults [26]. Specifically, the domains recommended for studies in children were pain intensity, satisfaction with treatment, symptoms and adverse effects, physical recovery and emotional response, and economic factors, with physical and emotional functioning, role functioning, and sleep added for chronic pain studies.

Prescription Monitoring Programs

There is significant concern about the potential for opioids to be misused, abused, or diverted, resulting in adverse events and deaths. In 2011, the US Centers for Disease Control and Prevention estimated that the rate of deaths related to prescription analgesic overdose had increased by more than threefold since 1990, that the number of these events was greater than that of motor vehicle deaths and larger than deaths attributed to cocaine and heroin overdoses [27, 28]. While these data do not tell us important information such as where the drugs were obtained, whether the overdose was intentional or accidental, and if the event was due to use of one drug or multiple medications, it is clear that there is a serious problem. It is also clear that solving this problem will requires interdisciplinary efforts on a wide variety of facets to help ensure that safe and effective pain management is available for people who need it, and that access to potent medications is minimized for people who do not.

As of October, 2012, 41 US states have an operational Prescription Monitoring Programs (PMP) in place and an additional 10 (including the District of Columbia and Guam) have enacted legislation, but the program has not yet begun operating [29]. These programs generally collect information about the patient, the drug and amount being prescribed, the date the prescription was written and the date it was filled, and the pharmacy that filled the prescription. States differ in terms of what data are collected, what time lag between filling the prescription and submitting the information is allowed, who is responsible for maintaining the dataset (In Texas, it is the Department of Public Safety, in other states, the Board of Pharmacy or other groups

are responsible), who is allowed to see or use the data, and whether prescribers are alerted to potential problems passively or actively. Yet, despite the prevalence of PMPs, it remains unclear how to best use this information to achieve optimally safe and effective pain management. Here are a few challenges and opportunities that remain for healthcare providers and health policy decision makers before the promise of these data can be fully realized.

Much of the PMP-related literature and discussions focus on drug abuse, often using prescriber- or pharmacy-shopping as markers of inappropriate use of controlled substances. Despite this emphasis, aside from extremely high levels of use in a short period of time, we don't know the right number of prescribers or pharmacies, the right time period to consider, or whether there is even a right number. For example, in a literature search of "prescription monitoring program" AND "opioid," time intervals used to define either doctor- or pharmacy-shopping included zero (concurrent use of opioids or controlled substances from different prescribers), 6 months, 30 days (prescription for the same medication from at least two practitioners filled by at least two pharmacies), and 1 year, although one consensus statement published in 2004 defined use of multiple prescribers as at least six prescribers over a 1-year period [30–37]. In a recent analysis, Wilsey and colleagues used California PMP data to assess differences between people who used only one prescriber compared to individuals who used 2–5 prescribers over a 1-year period [32]. These investigators found that people who used 2–5 prescribers were not different in terms of male sex, younger age, or location in larger geographic areas—factors thought to be associated with drug abuse.

To make things more complex, the allure of considering data in isolation is powerful, even though looking at a broader picture often provides insight that a simple view cannot. As Mencken (1917) said, "There is always an easy solution to every human problem—neat, plausible, and wrong" [38]. One example of this idea is that the period of time in which the prescriptions were filled may help explain the observed numbers of prescribers and pharmacies. The longer that period, the more likely it is that multiple explanations for a patient's behavior are important in understanding their medication use.

Along these lines, it is worth looking beyond the absolute number of prescribers and pharmacies from multiple prescribers or pharmacies to ask why people might get prescriptions, aside from potential abuse, misuse, or diversion. A single medical practice may include several people writing prescriptions, individuals may see other prescribers when their usual caregiver is not available, and people who are medically complex may have good reasons for obtaining controlled substances from multiple prescribers. Similarly, there may be important differences between groups of people who use prescription opioids nonmedically, but for pain only as opposed to persons who obtain these drugs for nonmedical and non-pain use [39]. The count of pharmacies is also suspect. People may choose to go to different pharmacies for any number of reasons, and this is not necessarily a problem. In many places, it is common for pharmacies to offer financial incentives to people who transfer prescriptions, convenience of location is often important, and pharmacies don't always carry (or can't get)

the specific medication the patient is looking for in the needed timeframe. Despite the potential to limit legitimate access to pain management services, in November 2011, the pharmacy chain CVS/Caremark (2011) announced a new policy to refuse to fill prescriptions for Schedule II controlled medications from some prescribers in Florida [40]. Similarly, Walgreens's Good Faith Dispensing program represents an effort to identify "red flags" regarding opioid prescriptions [40].

There are many questions about the CVS and Walgreens programs. In the case of CVS, very little information about the number, location, or identification of prescribers included under this policy. Additionally, the policy included all C-II drugs, not just opioids. Under the Walgreens policy, it is unclear how information collected will be stored and used, and who will have access to these data. These are not trivial questions, particularly as these efforts may directly and indirectly encourage pharmacists to refuse to fill legitimate prescriptions, to not carry certain medications, or to simply adopt a blanket refusal to fill prescriptions for controlled medications. The result of these efforts is likely to result in unnecessary suffering among the vast majority of pain patients who use their medications appropriately and to increase the barriers to needed health care these people must face.

Data quality is another issue that needs close attention [42]. The information that comes out of PMPs is only as good as the data that are put in. These data are generally input at busy pharmacies, patient names and birthdates may be the same, and prescribers often have multiple offices. Data may also be missing, misspelled, or otherwise incorrect. Furthermore, as a result, interpretation of these data may be challenging, and prescribers and pharmacists must not jump to conclusions and inadvertently contribute to difficulties in access to appropriate pain management services.

Assessment and identification of prescription drug abuse or misuse in pediatric populations presents challenges in addition to those that apply to adults. For example, while many discussions of PMPs and prescription drug abuse, misuse, and diversion focus on opioids, we must recognize that these drugs and prescribing rates do not tell the whole story. Individuals being treated for chronic pain are often on multiple psychoactive medications, such as muscle relaxants, benzodiazepines, and antidepressants, and that these combinations may have their own problems. For example, in a 2006 editorial on whether being on chronic opioid therapy should be a contraindication to driving, Zacny counsels caution, since we don't know to what extent different combinations of drugs result in what outcomes [43].

Although much of the discussion surrounding PMPs emphasizes their use as tools for drug enforcement, they can also be used to better understand patient outcomes, including estimating the present and future needs for pain management services based on incidence and prevalence trajectories, and use of geospatial tools to better understand access issues. Prescription monitoring program data are also useful to better understand and improve the safety of opioid use, whether these drugs are used alone or in combination with other analgesics. Last, it may be possible to link these data to other population-level resources to better understand the results and consequences of using pain management resources, including unintended consequences of public policy.

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C.A. Fairbanks, T.J. Martin (eds.), *Neurobiological Studies of Addiction in Chronic Pain States*, Contemporary Clinical Neuroscience 17,
DOI 10.1007/978-1-4939-1856-0