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Opioid-induced Hyperalgesia

A Qualitative Systematic Review

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Opioids are the cornerstone therapy for the treatment of moderate to severe pain. Although common concerns regarding the use of opioids include the potential for detrimental side effects, physical dependence, and addiction, accumulating evidence suggests that opioids may yet cause another problem, often referred to as *opioid-induced hyperalgesia*. Somewhat paradoxically, opioid therapy aiming at alleviating pain may render patients more sensitive to pain and potentially may aggravate their preexisting pain. This review provides a comprehensive summary of basic and clinical research concerning opioid-induced hyperalgesia, suggests a framework for organizing pertinent information, delineates the status quo of our knowledge, identifies potential clinical implications, and discusses future research directions.

OPIOIDS are the cornerstone therapy for alleviating moderate to severe pain. Whereas opioids have long been used for alleviating acute and cancer-related pain, they recently have gained significant popularity for the treatment of chronic nonmalignant pain. Today, opioids are second only to nonsteroidal antiinflammatory drugs in terms of prescription frequency for chronic pain.[1] Common concerns regarding the use of opioids are the potential for detrimental side effects, physical dependence, and addiction. However, recent research suggests that opioids may yet cause another problem, often referred to as *opioid-induced hyperalgesia* (OIH). Patients receiving opioids to control their pain somewhat paradoxically may become more sensitive to pain as a direct result of opioid therapy. That is, the use of opioids may be a double-edged sword. They provide straight analgesic and antihyperalgesic effects initially, but subsequently are associated with the expression of hyperalgesia likely reflecting upregulation of compensatory pronociceptive pathways.

Several recent articles have reviewed and highlighted important aspects of OIH, which reflects the growing interest and rapidly expanding body of literature regarding this phenomenon.[2–5] The aim of this article is to provide a comprehensive and systematic review of the literature pertinent to OIH. The primary intent of such an undertaking is to provide the interested reader with an all-inclusive and current overview of a topic that may be difficult to grasp as a whole because new evidence accumulates quickly and in quite distinct research fields. As such, a comprehensive review may serve as a source document. However, a systematic review also uses a framework for presenting information, and such a framework may facilitate and clarify future communication by clearly delineating various entities or aspects of OIH. Finally, a systematic review aims at defining the status quo of our knowledge concerning OIH, a necessary task to guide future research efforts and to identify potential clinical implications.

For the purpose of this review, it is important to point out that OIH occurs in several distinct settings characterized by the opioid dose administered and the pattern of administration. Most work reported OIH during ongoing (maintenance) therapy or withdrawal from opioids. Other bodies of literature documented OIH while administering either very high or very low opioid doses. Although the opioid dose offers a convenient way to categorize different types of OIH, it is less certain to what degree these phenomenological differences are mirrored by distinct mechanisms. Nevertheless, in this review we use separate sections to discuss OIH in the context of (1) maintenance dosing and withdrawal, (2) at very high or escalating doses, and (3) at ultra-low doses. Each section is divided further into a human and animal/basic science data subsection. At the end of each section, we draw conclusions and outline potential clinical implications. The review ends with a discussion of future research directions.

Literature Search

Strategy

The three major databases, PubMed, BIOSIS, and PsycInfo, were searched for identifying articles pertinent to OIH. PubMed, BIOSIS, and PsycInfo index publications relating to human health, the biologic and biomedical sciences, and the field of psychology, respectively. The search included all work published between the inception of a database (PubMed, 1966; BIOSIS, 1969; PsycInfo, 1887) and September 2004.

PubMed. Ideally, a search in PubMed using the mesh terms *hyperalgesia/chemically induced* AND *analgesics, opioid* would have retrieved most of the relevant articles. However, such a search missed important articles when comparing results with an *a priori* index of all relevant articles known to the authors. A more complex search accounting for variations in indexing was neces-

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sary to retrieve most of the pertinent articles without listing an abundance of irrelevant publications. The final search in PubMed was based on four "hedges" of free-text terms and medical subject headings. Hedges one and two, and hedges three and four were combined for the search. Title rather than title/abstract searches were used to minimize retrieval of irrelevant citations. The hedges were as follows:

- Hedge 1 (induced hyperalgesia): hyperalgesia/chemically induced [mesh] OR hyperalgesia/etiology OR antianalges* OR ((allodyni* [ti] OR hyperesthesi* [ti] OR hyperalg* [ti]) AND (produc* [ti] OR elicit* [ti] OR cause* [ti] OR trigger* [ti] OR refer* [ti] OR induc* [ti]));
- Hedge 2 (opioids): opioid* [ti] OR opiate* [ti] OR morphine [ti] OR fentanyl [ti]) OR analgesics, opioid [pa] OR "opioid-related disorders"[mesh] OR "receptors, opioid"[mesh] OR "analgesics, opioid"[mesh];
- Hedge 3 (drug tolerance or withdrawal): (toler* [ti] OR withdrawal [ti] OR adapt* [ti]) OR "substance withdrawal syndrome"[mesh] OR "drug tolerance"[mesh] OR "adaptation, physiologic"[mesh];
- Hedge 4 (increased sensitivity to pain or sensation): hyperalgesia [mesh] OR hyperalges* OR allodyni* OR hyperesthesi*.

Biosis. Variability in indexing required combing three hedges:

- Hedge 1 (title search): ((opiate* OR opioid* OR heroin OR fentanyl OR morphine) AND (antianalges* OR allodyni* OR hyperesthesi* OR hyperalg*)) NOT (antihyperalges* OR "anti hyperalges*"));
- Hedge 2 (subject search): hyperalgesia AND drug-induced;
- Hedge 3 (subject search): ((hyperalgesia AND (opiate* OR opioid*)).

PsycInfo. A simple search using a single and fairly broad hedge was sufficient:

- Hedge: hyperalgesia AND (kw: Opiate* Or kw: Opioid*).

Results

The search retrieved 869 citations. Based on the preestablished criteria that only peer-reviewed original articles published in English were considered for this review, a total of 213 citations were excluded (123 meeting abstracts, 24 letters, 46 reviews, 3 meeting notes, 9 book chapters, 5 articles not in English, 3 patents). Of the remaining 656 articles, 139 were included in this review, because they reported data relevant for the discussion of hyperalgesia associated with the exogenous administration of opioids (OIH). Most of the other 517 articles were excluded because they reported opioid-mediated antinociceptive and antihyperalgesic effects. Other articles were excluded because they reported data obtained in nonmammalian species (lizards), hyperalgesia as a consequence of abstinence from endogenous opioids, or antianalgesic rather than hyperalgesic treatment effects (attenuation of analgesic effects rather than increased sensitivity to pain).

The 139 articles included in this review were supplemented by an additional 41 publications. These 41 articles were added because they were either identified by the authors as containing relevant data when they reviewed references cited in retrieved manuscripts, or these articles provided important background information indirectly related to OIH. Specifically, 18 manuscripts provided additional data relevant for the discussion of hyperalgesia associated with the exogenous administration of opioids (2 manuscripts in nonmammal species but of particular interest), 7 articles reported analgesic effects in the context of opioid-antagonist administration, 8 articles documented mechanisms potentially related to OIH but without testing for the expression of OIH, 7 manuscripts were reviews of topics pertinent to the discussion of OIH, and 1 reference referred to a diagnostic guidebook. The 157 articles reporting OIH in the context of exogenous opioid administration consist of 120 animal and 37 human studies.

OIH during Maintenance and Withdrawal

Human Studies

Brief Historical Perspective. For more than a century, clinical reports have listed hyperesthesia or an increased sensitivity to pain as one of the symptoms associated with opioid withdrawal. In an essay dating back to 1880, Rossbach wrote, "[W] hen dependence on opioids finally becomes an illness of itself, opposite effects like restlessness, sleep disturbance, hyperesthesia, neuralgia and irritability become manifest."[6] Six decades later, Himmelsbach gave a comprehensive description of the opioid abstinence syndrome and stated that "aching referred to the bones, joints, and muscles is probably the most common symptom of withdrawal."[7] Today, pain symptoms are part of the criteria used for diagnosing opioid withdrawal.[8] Although strictly observational in nature, these clinical reports provide early cues for a significant alteration of pain modulating neuronal systems as a consequence of opioid therapy.

Recent Evidence. During the last decade, several clinical scientists became interested in exploring OIH as a consequence of withdrawal and/or maintenance therapy. In contrast to early work in the field of addiction, recent studies focused on OIH in the context of pain management. The renewed interest in OIH was triggered by dozens of animal studies conducted since the early 1970s suggesting that administration of opioids paradoxically may increase the sensitivity to pain and potentially may aggravate preexisting pain. This quite disturbing

Table 1. Studies in Former Opioid Addicts Maintained on Methadone

Reference No.	Study Population (n)	Methadone		Pain			Remarks
		Daily dose (mg)*	Duration (mo)*	Test	Threshold	Tolerance	
11	43 patients receiving methadone; 26 patients not receiving methadone	—	—	CPP	—	42% ↓ †	Similar findings in current and former cocaine users
15	42 patients; 16 controls	0.7 ± 025 (mg/kg)	3–56	PP	ND	—	
14	18 patients; 10 controls	7.5–130	6–120	EP	ND‡	—	
10	60 patients; 60 controls	66 ± 20	>1	CPP	—	53% ↓ ‡	
13	18 patients; 18 controls	66 ± 21	>1	CPP	—	56% ↓ ‡	
12	16 patients; 16 controls	62 ± 6	4–120	CPP EP	43% ↓ § ND	74% ↓ § 15% ↓	At peak plasma concentration, no hyperalgesia for EP and 57% ↓ for CPP
9	4 patients; 4 controls	81 ± 25	9–96	CPP EP	34% ↓ § ND	76% ↓ § ND	At peak plasma concentration, 56% ↓ for CPP

* Mean ± SD or range. † Time of testing relative to time of drug intake not specified. ‡ Measurements obtained within 2 h of drug administration. § Measurements obtained at trough plasma concentrations.

— = no data available; ↓ = decrease compared with controls; CPP = cold pressure pain evoked by ice-water immersion of hand; EP = electrically induced pain at earlobe; ND = no difference; PP = blunt pressure pain evoked on middle phalanx of digit.

prospect triggered a series of controlled clinical trials examining expression and potential clinical impact of OIH in humans.

Evidence so far suggests that OIH does develop in humans and may have important clinical implications. Data supporting this notion has been collected in three distinct experimental settings: (1) in former opioid addicts maintained on methadone, (2) in patients undergoing surgery, and (3) in human volunteers tested in experimental pain paradigms. These studies are discussed in more detail in the following paragraphs.

Former Opioid Addicts Maintained on Methadone. Different clinical investigators have measured pain sensitivity in former opioid addicts with aid of the cold pressor test and an electrical and/or a pressure pain model.[9–15] Results of these studies are summarized in table 1 and suggest that former opioid addicts maintained on a stable dose of methadone are more sensitive to cold pressor pain than former opioid addicts not maintained on methadone or healthy controls.[9–13] Hyperalgesia to electrical stimulation was less pronounced or not detectable at all, suggesting that OIH develops differentially for different types of pain.[9,12,14] Similarly, hyperalgesia to mechanical pressure was not detected.[15] It is noteworthy that the two studies reporting negative results for electrically and mechanically evoked pain measured the pain threshold, which is less sensitive than the pain tolerance for detecting OIH.[9,12]

Findings in former opioid addicts maintained on methadone are compatible with the concept that hyperalgesia was caused by chronic opioid therapy. However, the cited studies were cross-sectional rather than prospective in design and do not allow establishing a cause-and-effect relationship. It can not be excluded that former opioid addicts receiving methadone maintenance seemed to be relatively hyperalgesic because increased pain sensitivity may predispose to both becoming an addict and requiring methadone to prevent relapse after detoxification. The fact that current users of both substances, an opioid or cocaine, are more sensitive to cold pressor pain than former users of either drug is compatible with this latter view.[11]

Patients Undergoing Surgery. Two controlled studies reported aggravated postoperative pain despite increased postoperative opioid consumption in patients receiving a high rather than a low systemic opioid dose during surgery.[16,17] Similarly, a study of women undergoing cesarean section under spinal anesthesia documented increased postoperative opioid consumption if intrathecal opioids rather than saline placebo was injected before the surgery.[18] In contrast, a fourth study failed to detect increased pain or exaggerated opioid consumption in the postoperative period if patients had received a high rather than a low systemic opioid dose during surgery.[19] This study explored the same opioid analgesic in a similar patient population as Guignard *et al.*,[16] who reported positive findings. However, the intraoperative opioid dose administered to patients in the high-dose group was approximately 3.4 times higher in the study by Guignard *et al.* (infusion rate and duration), suggesting dose dependency of the observed phenomenon (table 2).[17–19]

The finding of increased postoperative pain and postoperative opioid consumption in patients receiving a high rather than a low intraoperative opioid dose is compatible with the view that OIH developed in these patients. Alternatively, these patients may have experienced acute tolerance to analgesic opioid effects. Although it is tempting to speculate that increased postoperative pain despite augmented opioid consumption points toward OIH, no firm conclusions can be drawn. Differentiation between OIH and tolerance requires a

Table 2. Studies in Patients Undergoing Surgery

		Intraoperative Data		Postoperative Data (High *vs.* Low Intraoperative Opioid Dose)		
Reference No.	Surgery	Opioid	Dose	Opioid Use	Pain	Remarks
18	Cesarean section	Fentanyl IT	0 *vs.* 25 μg	60% ↑	ND	n = 60; 23-h observation
17	Hysterectomy	Fentanyl IV	1 *vs.* 22 μg/kg	120% ↑	30% ↑	n = 60; 16-h observation
16	Colectomy	Remifentanil IV	0.1 *vs.* 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 260 min	85% ↑	50% ↑	n = 50; 24-h observation
19	Gynecologic	Remifentanil IV	0.1 *vs.* 0.23 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 100 min	ND	ND	n = 60; 24-h observation

IT = intrathecal; IV = intravenous; ND = not different.

method directly assessing pain sensitivity. Implementation of such a method into a clinical trial is difficult and has not yet been attempted.

Experimental Pain Studies in Human Volunteers. Two sets of experiments have been performed to document OIH in human volunteers. A first set explored the effect of a short-term opioid infusion on an experimental skin lesion rendered hyperalgesic before starting the drug infusion.[20–23] A second set explored the effects of opioid antagonist precipitated withdrawal on cold pressor pain in volunteers made acutely dependent on opioids.[24]

Several investigators observed aggravation of preexisting mechanical hyperalgesia after a 30- to 90-min infusion with the ultra–short-acting opioid agonist remifentanil. Aggravation was reflected by a 1.4- to 2.2-fold enlargement of the hyperalgesic skin area compared with preinfusion measurements, and the magnitude of this effect was related directly to the infusion duration and the opioid dose.[20–22,25] Aggravation of preexisting hyperalgesia was observed up to 4 h after stopping the remifentanil infusion, but was no longer evident when assessed on the subsequent day.[21] These changes are consistent with an expanded area of secondary hyperalgesia thought to be the result of enhanced nociceptive signal processing at the level of the spinal cord. Two studies also assessed the effect of remifentanil exposure on heat pain sensitivity.[20,21] Contrasting with results obtained in hyperalgesic skin, heat pain sensitivity in normal skin was not different before and after remifentanil exposure, suggesting that OIH develops differentially for different types of pain. Two studies documented that coadministration of ketamine abolished remifentanil-induced aggravation of preexisting hyperalgesia, thereby implying an *N*-methyl-D-aspartate (NMDA) receptor-dependent underlying mechanism.[20,22] Finally, one report suggested that coadministration of the α-2-receptor agonist clonidine attenuated remifentanil-induced aggravation of preexisting hyperalgesia.[22]

A single study examined pain sensitivity to cold pressor pain in a model of acute physical opioid dependence in a small number of human volunteers. Two to 4 h after a single injection of morphine or hydromorphone, withdrawal was precipitated with the intravenous administration of the opioid antagonist naloxone. Subjective and objective signs of withdrawal became evident in all subjects and were accompanied by a significantly increased sensitivity to cold pressor pain.[24,26]

Finally, a single study reported hyperalgesia to pressure-evoked pain after a short-term infusion of remifentanil in volunteers.[27] However, these investigators exposed volunteers to significantly higher nociceptive input during remifentanil than during saline placebo administration. It can not be excluded that postinfusion hyperalgesia resulted from more intense noxious stimulation during the remifentanil infusion rather than the opioid administration itself.

In summary, studies in human volunteers involving the short-term administration of opioids provide the only currently available direct evidence for the existence of OIH in humans using models of secondary hyperalgesia and cold pressor pain.

Small and Anecdotal Reports. Our search also revealed a series of isolated reports perhaps consistent with OIH in patients. In the first, a patient underwent three separate withdrawal episodes while being evaluated and treated for chronic back and radicular pain with an intrathecal morphine pump.[28] Withdrawal signs and symptoms included fever, vomiting, diarrhea, disturbed sense of smell, and ataxia. Painful paresthesias to brush on all four extremities also were noted. In the second study, investigators compared the analgesic effects of morphine between human volunteers and pain patients on chronic opioid therapy. This provided the first quantitative evidence for OIH.[29] The authors observed that study patients undergoing withdrawal had a significantly lower tolerance to heat-evoked pain (outside the 95% confidence interval) compared with healthy volunteers. Last, a single report by Seymour *et al.*[30] described enhanced pain after third molar extraction in patients given regular doses of dihydrocodeine after surgery, although other reports documented modest analgesic effectiveness of dihydrocodeine for postoperative pain.[31]

Table 3. Animal Studies Reporting Opioid-induced Hyperalgesia during Maintenance and Withdrawal

Investigator(s), yr	Reference	Animal	Route	Drug	Nociceptive Test	Mechanism(s) Explored
Aley and Levine, 1995	50	Rat	ID	DAMGO	Mechanical	
Aley and Levine, 1997	51	Rat	ID	DAMGO	Mechanical	AC, calcium, PKC
Aley and Levine, 1997	52	Rat	ID	DAMGO	Mechanical	PKC
Aley and Levine, 1997	53	Rat	ID	DAMGO	Mechanical	
Arts *et al.*, 1991	54	Mouse	ICV	Morphine	Thermal	Dynorphin
Bederson *et al.*, 1990	142	Rat	IV	Morphine	Thermal	RVM (on cell/off cell activity)
Bie *et al.*, 2003	143	Rat	IV	Morphine	Thermal	NRM (α1-adrenergic receptor)
Bie, 2003	144	Rat	IP	Morphine	Thermal	NRM (κ-opioid receptor)
Burdin *et al.*, 1992	145	Rat	PAG	Morphine	Electrical	PAG (opioid modulation)
Celerier *et al.*, 1999	38	Rat	SC	Morphine Fentanyl	Mechanical	NMDA receptor
Celerier *et al.*, 2000	43	Rat	SC	Fentanyl	Mechanical	NMDA receptor
Celerier *et al.*, 2001	37	Rat	SC	Heroin	Mechanical	NMDA receptor
Celerier *et al.*, 2004	39	Mouse	SC	Fentanyl	Mechanical Chemical	PKCγ
Christensen and Kayser, 2000	146	Rat	SC	Morphine	Mechanical	
Colpaert *et al.*, 2002	147	Rat	SC	Morphine	Mechanical	
Crain and Shen, 2004	136	Rat	SC	Morphine	Thermal	Neuraminidase/GM1 ganglioside
Davies *et al.*, 2003	49	Mouse	SC	Morphine	Mechanical	
Doerr and Kristal, 1991	148	Rat	IP	Morphine	Thermal	Amniotic fluid
Dunbar and Pulai, 1998	60	Rat	IT	Morphine	Thermal	NMDA receptor
Dunbar *et al.*, 2000	65	Rat	IT	Morphine	Thermal	Cyclooxygenase
Dunbar and Karamian, 2003	100	Rat	IT	Morphine	Thermal	EAA release, NMDA receptor
Ekblom *et al.*, 1993	149	Rat	IV	Morphine	Thermal	
Galeotti *et al.*, 2002	150	Mouse	Oral	Morphine	Thermal	Caffeine, indomethacin, prochlorperazine
Gardell *et al.*, 2002	76	Rat	SC	Morphine	Mechanical Thermal	Dynorphin
Grilly *et al.*, 1981	151	Rat	SC	Morphine	Electrical	
Grilly *et al.*, 1986	152	Rat	SC	Morphine	Electrical	
Harris *et al.*, 2004	153	Rat	IP	Morphine	Thermal	
Heinzen and Pollack, 2004	154	Rat	IV	Morphine	Electrical	NOS
Hendrie, 1985	137	Rat	Oral	Morphine	Thermal	Adrenocorticotropin
Hendrie, 1989	155	Mouse	IP	Morphine	Thermal	Endogenous opioid system
Hoffmann *et al.*, 1998	156	Rat	SC	Morphine	Thermal	Genetic factors
Ibuki *et al.*, 1997	45	Rat	IT	Morphine	Thermal	NMDA receptor, EAA
Johnston *et al.*, 2004	66	Rat	IT	Morphine	Thermal	Cytokines
Kang *et al.*, 2002	157	Rat		Fentanyl	Thermal Mechanical	Cyclooxygenase activity
Kaplan and Fields, 1991	158	Rat	RVM, IV	Morphine	Thermal	RVM
Kayan and Mitchell, 1968	159	Cat	SC	Morphine	Electrical	
Kayan *et al.*, 1971	32	Rat	SC	Morphine	Thermal	
Kest *et al.*, 2002	160	Mouse	SC	Morphine	Thermal	Genetic factors
Khasar *et al.*, 1995	55	Rat	ID	DAMGO	Thermal	AC
Kim *et al.*, 1990	161	Rat	IV	Morphine	Thermal	
Kim and Siegel, 2001	162	Rat	IV	Morphine	Thermal	Cholecystokinin
Kissin *et al.*, 2000	163	Rat	IV	Alfentanil	Mechanical	NMDA receptor
Lane *et al.*, 2004	164	Rat	PAG	Morphine	Thermal	PAG
Larcher *et al.*, 1998	165	Rat	SC	Heroin	Mechanical	NMDA receptor
Laulin *et al.*, 1999	40	Rat	SC	Heroin	Mechanical	NMDA receptor
Laulin *et al.*, 2002	42	Rat	SC	Fentanyl	Mechanical	NMDA receptor
Li *et al.*, 2001	36	Rat	SC	Morphine	Thermal, mechanical, incision	Endogenous opioid system
Li *et al.*, 2001	46	Mouse	SC	Morphine Fentanyl	Thermal, mechanical, chemical	NMDA, NOS and HO receptors
Li and Clark, 2002	35	Mouse	SC	Morphine	Thermal, mechanical, IT neurotransmitters	Glutamate, substance P
Liang *et al.*, 2003	73	Mouse	SC	Morphine	Thermal, mechanical	HO system
Manning *et al.*, 1996	166	Rat	SC	Morphine	Thermal	NMDA receptor
Mao *et al.*, 1994	48	Rat	IT	Morphine	Thermal	NMDA receptor, non-NMDA glutamate receptor, PKC

(*continued*)

Table 3. (continued)

Investigator(s), yr	Reference	Animal	Route	Drug	Nociceptive Test	Mechanism(s) Explored
Mao *et al.*, 2002	62	Rat	IT	Morphine	Thermal	Glutamate transporters, NMDA receptor
McNally and Akil, 2002	167	Rat	SC	Morphine	Thermal	Corticotropin-releasing hormone
Milne *et al.*, 1985	168	Rat	SC	Morphine	Thermal	
Ohnishi *et al.*, 1990	169	Mouse	SC	Morphine	Chemical	Calcium ion channel
Plesan *et al.*, 1999	170	Rat	SC	Morphine	Thermal	NMDA receptor
Raghavendra *et al.*, 2002	171	Rat	SC	Morphine	Thermal, mechanical	Glia/cytokines
Raghavendra *et al.*, 2003	75	Rat	SC	Morphine	Thermal, mechanical	Glia/cytokines
Raghavendra *et al.*, 2004	172	Rat	SC	Morphine	Thermal, mechanical	Glia/cytokines
Rivat *et al.*, 2002	44	Rat	SC	Fentanyl	Chemical	NMDA receptor
Salimov *et al.*, 1993	173	Mouse	SC	Morphine	Thermal	Alcohol deprivation
Schmidt and Way, 1980	174	Mouse	SC	Morphine	Thermal	Calcium
Shen and Crain, 2001	175	Mouse	SC	Morphine	Thermal	Cholera toxin
Sweitzer *et al.*, 2004	176	Mouse	SC	Morphine	Thermal, mechanical	
Sweitzer *et al.*, 2004	71	Mouse	SC	Morphine	Thermal	PKC
Tilson *et al.*, 1973	33	Rat	IP	Morphine	Electrical	
Tislon and Reech, 1974	177	Rat	SC	Morphine	Electrical	p-chlorophenylalanine
Vanderah *et al.*, 2000	64	Rat	IT	DAMGO	Thermal, mechanical	Dynorphin
Vanderah *et al.*, 2001	47	Rat	SC	Morphine	Thermal, mechanical	RVM
VonVoigtlander and Lewis, 1983	34	Mouse	SC	Morphine, pentazocine, ethylketocyclazocine, nalbuphine, butorphanol	Chemical	
Welin *et al.*, 1994	178	Rat	SC	Morphine	Mechanical	
Wilcox *et al.*, 1979	179	Rat	SC	Morphine	Electrical	
Yu *et al.*, 1997	180	Rat	IT	Morphine	Thermal, mechanical	
Zeitz *et al.*, 2001	70	Mouse	SC	Morphine	Chemical	PKC

AC = adenylate cyclase; DAMGO = Tyr-D-Ala-Gly-(me) Phe-Gly-ol; EAA = excitatory amino acids; HO = heme oxygenase; ICV = intracerebroventricular; ID = intradermal; IP = intraperitoneal; IT = intrathecal; IV = intravenous; NMDA = *N*-methyl-D-aspartate; NOS = nitric oxide synthase; NRM = nucleus raphe magnus; PAG = periaqueductal gray; PKC = phosphokinase C; RVM = rostral ventral medulla; SC = subcutaneous.

Animal Studies

Early Studies: OIH as a Measure of Physical Dependence. For more than three decades, it has been recognized that systemic administration of opioids to rodents can lead to a hyperalgesic response during withdrawal. Early studies documented that such hyperalgesia can be observed after precipitating withdrawal with the injection of an opioid antagonist as well as during spontaneous withdrawal after cessation of opioid administration.[32–34] The objective of these studies was to examine whether the hyperalgesic response was useful as a quantitative measure of opioid dependence. They did not emphasize the potential impact of OIH on pain management. This not only may reflect the primary research focus of the investigators on questions relating to addiction rather than pain management, but also may reflect a more restricted medical use of opioids for the treatment of chronic pain at that time.

The Mechanistic Exploration of OIH. More recent investigations have focused on OIH as a phenomenon relevant to clinical pain management. Many animal studies describing various aspects of the pharmacology, biochemistry, and functional neuroanatomy of this phenomenon were identified in our literature search. The phenomenon of OIH as it is studied during consistent opioid dosing or after abrupt discontinuation of opioid administration can be described in terms of several dimensions, including the nociceptive modality rendered hyperalgesic, the time course of hyperalgesia, the opioid receptor system implicated, and the neuroanatomical structures and signaling pathways involved. Table 3 provides a comprehensive listing of all studies describing OIH in rodent model systems. Excluded from this table are studies specifically addressing the phenomenon of associative hyperalgesia and studies examining hyperalgesia in the context of administering κ-opioid receptor agonists. These types of hyperalgesia reflect special entities and are addressed in separate sections of this review.

Nociceptive Methods. The increased pain sensitivity induced by exposure to opioids has been demonstrated in many different nociceptive assays. Table 3 lists these methods separately for each study. Although all assays using heat, mechanical stimuli, or chemical irritants relied on the activation of peripheral nociceptors, there was a single study demonstrating OIH after nociceptive stimulation at the level of the spinal cord *via* intrathecal neurotransmitter injections.[35] Examining the data of all

these studies suggests variable susceptibility of different pain signaling pathways to express OIH. Probably best documented is a greater susceptibility of pathways activated by mechanical (punctuated pressure) rather than thermal (heat) noxious stimuli.

Few studies have attempted to go beyond assays using brief noxious stimuli to better mimic clinical pain. Virtually lacking are investigations examining the potential impact of OIH in models of chronic pain. One study used a hind paw incision, a model of postsurgical pain. Animals chronically treated with morphine experienced much more marked hyperalgesia in response to the hind paw incision than opioid-naïve animals.[36] Findings of this study fit well with human data suggesting that patients receiving a high rather than a low intraoperative opioid dose experience increased pain after surgery despite higher postoperative opioid consumption.[16–18]

Time Course. Two fundamental patterns characterizing the onset and resolution of OIH can be distinguished. The first is observed after the acute administration of an opioid, that is, the systemic administration of one to four relatively high opioid doses within 1 h. Morphine, heroin, and fentanyl have been administered acutely to mice and rats and evoked a consistent, biphasic, and dose-dependent response. Intense antinociceptive effects were followed by a 2- to 3-h period of mechanical hyperalgesia.[37–42] However, one of these studies demonstrated prolonged hyperalgesia that lasted up to 5days after a very high dose of fentanyl.[43] A second experiment administering a similarly high dose of fentanyl before injecting carrageenan into the hind paw demonstrated that hyperalgesia associated with hind paw inflammation was prolonged from 2 to 10 days.[44] Thus acute opioid administration typically has evoked a transient hyperalgesic response lasting for hours, except for some instances of prolonged hyperalgesia lasting for days. The duration of acute OIH clearly is related to the opioid dose.

More commonly investigators have exposed animals to opioids on a more chronic time course (3–12 days) *via* repeated subcutaneous injections, implantation of subcutaneous opioid containing pellets or pumps, or intermittent administration or continuous infusions through indwelling intrathecal catheters. If animals were given opioids by continuous techniques, antinociception typically was measurable for the first day, which was followed by a loss of this effect or even by a hyperalgesic state during ongoing drug administration.[36,45–47] Animals given repeated systemic or intrathecal boluses of opioids developed progressive hyperalgesia to thermal or mechanical stimuli over the course of several days.[37,48] Where studied, the time course of resolution of OIH was similar to the time course of its development.[36,37,46,49]

Of particular interest is a study by Celerier *et al.*[37] documenting that animals with normal noxious sensitivity after recovering from OIH expressed recurrent and robust hyperalgesia if challenged with a single bolus of either drug, an opioid agonist or antagonist. These findings have two important implications. First, animals apparently recovered from OIH remained sensitized to the hyperalgesic effects of opioids. Second, this sensitization most likely was opposed by an endogenous opioidergic system, because the injection of an opioid antagonist unmasked hyperalgesia. This implies that OIH resolved because of upregulated inhibitory pathways opposing activity of sensitized excitatory pathways rather than the desensitization of excitatory pathways. According to this concept, resolution of OIH occurred at a new equilibrium of high neuronal activity between excitatory and inhibitory pathways (fig. 1). It is conceivable that an equilibrium achieved at a high level of neuronal activity is prone to derangements, which in a clinical context may translate into increased vulnerability to pain.

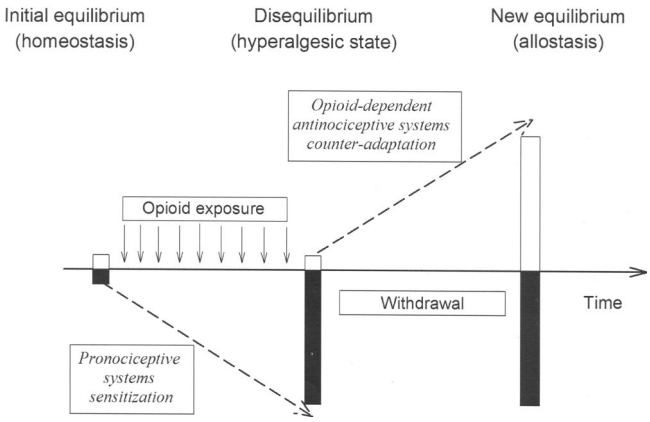

Fig. 1. A model of the neuroadaptive changes underlying expression and recovery of opioid-induced hyperalgesia (OIH) has been suggested by Celerier *et al.*[37] Antinociceptive (*white bars*) and pronociceptive (*black bars*) systems are in balance at a low level of neuronal activity before the exposure to opioids. Pronociceptive systems become upregulated as a result of opioid exposure, which is reflected by the development of OIH. Upregulation of antinociceptive systems is associated with the discontinuation of opioid exposure, which results in the offset of OIH. However, recovery from OIH is the result of a new equilibrium between pronociceptive and antinociceptive systems that occurs at high level of neuronal activity. The high-level balance between pronociceptive and antinociceptive systems may be prone to derangements, which in a clinical context may build the basis for a long-term vulnerability to pain. From Celerier *et al.*[37]; used with permission, copyright 2001 by the Society for Neuroscience.

Site of Action and Signaling Systems. Studies examining OIH can be characterized by the route of opioid administration. Because drugs are distributed differently after peripheral, intrathecal, or systemic administration, interpretation can be made about potential mechanisms underlying observed OIH. This section of the manuscript summarizes studies investigating signaling systems mediating OIH because anatomical site and signaling systems often have been explored within the same set of experiments. Figure 2 provides a diagram summarizing the neuroanatomical sites implicated in the expression of OIH.

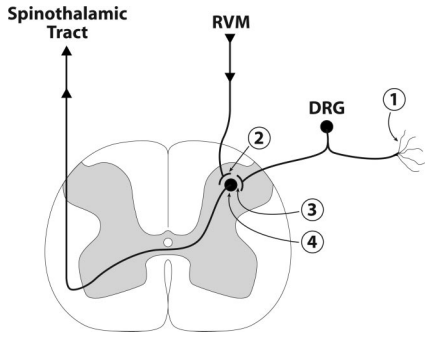

Fig. 2. Neuroanatomical sites and mechanisms implicated in the development of opioid-induced hyperalgesia during maintenance therapy and withdrawal. (*1*) Sensitization of peripheral nerve endings. (*2*) Enhanced descending facilitation of nociceptive signal transmission. (*3*) Enhanced production and release as well as diminished reuptake of nociceptive neurotransmitters. (*4*) Sensitization of second-order neurons to nociceptive neurotransmitters. Figure 2 does not illustrate all potential mechanisms underlying opioid-induced hyperalgesia, but rather depicts those that have been more commonly studied. DRG = dorsal root ganglion; RVM = rostral ventral medulla.

Peripheral administration. Opioids have been administered locally in very small volumes to rodent hind paw tissue. In a series of studies, it was demonstrated that the repeated local injection of the selective μ-opioid agonist Tyr-D-Ala-Gly-(me) Phe-Gly-ol (DAMGO) followed by the local administration of the opioid antagonist naloxone caused mechanical hyperalgesia.[50–55] This hyperalgesic state seemed to be dependent on protein kinase C activity as well as the activation of guanosine triphosphate binding proteins.[51,55]

Spinal administration. Mao *et al.*[48] conducted one of the earliest and most complete studies examining the role of the spinal cord in the genesis of OIH. Rats receiving intrathecal morphine for 8 days developed thermal hyperalgesia in association with antinociceptive tolerance, suggesting similar underlying mechanisms. The excitatory amino acid (EAA) neurotransmitter and receptor system was implicated because coadministration of the NMDA receptor antagonist MK-801 or the non-NMDA EAA-receptor antagonist 6-cyano-7-nitroquinoxaline-2,3-dione with intrathecal morphine fully or partially blocked the development of OIH and tolerance. A critical role of the intracellular messenger phosphokinase C (PKC) for developing OIH and tolerance was suggested by the fact that both phenomena were prevented by the PKC inhibitor GM1 ganglioside. Studies in a cultured neuronal cell line also suggested a modulating role of GM1 ganglioside in opioid-related neuroplasticity.[56] Mao *et al.*[57–59] demonstrated that the EAA receptor and neurotransmitter systems not only are relevant for hyperalgesia observed in conjunction with opioid administration, but also for hyperalgesia associated with chronic pain states.

Dunbar *et al.*[60] demonstrated independently that NMDA receptor antagonists reduce thermal hyperalgesia caused by intrathecal morphine administration. An increased content of EAA in spinal cord tissue has been verified directly in the context of chronic intrathecal morphine administration.[61] An increased availability of spinal EAA may be caused in part by a decreased activity of spinal glutamate transport systems associated with intrathecal opioid administration.[62] Spinal injection of the EAA glutamate but also of the neurokinin-1 agonist substance P in mice chronically exposed to morphine evoked an exaggerated pain response.[46] Others have demonstrated increased expression of several primary neurotransmitters in dorsal root ganglion neurons when chronically exposed to opioids.[63] Therefore, OIH has been linked to enhanced EAA availability and receptor sensitivity in spinal cord tissue, although other neurotransmitter systems may play a role as well.

Vanderah *et al.*[64] demonstrated that chronic intrathecal administration of the selective μ-opioid receptor agonist DAMGO enhanced spinal expression of dynorphin and suggested that the release of dynorphin was a critical step in propagating OIH. Spinal prostaglandins may be of some importance, because intrathecal administration of the cyclooxygenase inhibitor ibuprofen reversed hyperalgesia associated with opioid antagonist precipitated withdrawal.[65] Finally, spinal cytokines (interleukin 1β) and chemokines (fractalkine) may be relevant for the development of OIH.[66] The role of neuronal systems other than the EAA system and likely interactions between relevant neuronal systems in the expression of OIH are not yet well understood and need further clarification.

Experiments discussed so far used behavioral data to support a role of the spinal cord in the genesis of OIH. However, studies using c-fos protein immunocytochemistry to quantify neuronal activity have been consistent with the view that chronic exposure to morphine can sensitize neurons in the dorsal horn of the spinal cord. Opioid antagonists precipitated not only physical signs of withdrawal in rats chronically exposed to morphine, but also increased c-fos expression in sensory neurons of the spinal cord.[67,68] Injection of noxious formalin into the hind paw also resulted in an accentuated expression of c-fos in the spinal cord if rats had been chronically treated with morphine.[69] Li *et al.*[35] found a similarly enhanced expression of spinal c-fos in response to noxious mechanical stimulation if mice had been chronically exposed to morphine.

Systemic administration. The systemic delivery of opioids has been used most often to study OIH in animals. Much of the work centered on the EAA system, and the NMDA receptor in particular. Results are consistent with those obtained after intrathecal opioid administration. The systemic administration of the NMDA receptor antagonist MK-801, or ketamine, reversed opioid-induced thermal and mechanical hyperalgesia after acute (one injection or multiple injections on a single day) and chronic opioid administration (5 days continuous-

ly).[37,38,40–44,46] A role for the intracellular messenger PKC has been suggested by several groups. Administration of an opioid evoked OIH in wild-type mice but not in mice lacking the PKC-γ gene.[39,70] Also, Sweitzer *et al.* used selective PKC antagonists to demonstrate a role for both PKC-γ and PKC-ε for the expression of hyperalgesia during morphine withdrawal in rat pups.[71]

Other mechanisms have been implicated in OIH. Blocking the monoxide signaling systems heme oxygenase and nitric oxide synthase reversed OIH in mice chronically treated with morphine.[46] Similar to the EAA-system, both of the monoxide signaling systems also have been implicated in opioid tolerance, and the link between NMDA receptor activation and enhanced NOS activity supporting opioid tolerance has received significant attention.[72–74] Both the heme oxygenase and nitric oxide synthase systems are also involved in modulating chronic pain states, again suggesting that similar pathways mediate hyperalgesia observed in OIH and chronic pain. Although probably underappreciated for their roles in nociceptive neurotransmission, glial cells in the spinal cord become activated and produce enhanced levels of cytokines in rats rendered hyperalgesic with systemic morphine treatment.[75]

One set of studies suggested involvement of the brainstem in OIH.[47,76] Experiments used stereotactic injections of local anesthetics into the rostral ventromedial medulla or surgical lesioning of the dorsolateral funiculus to demonstrate that descending pain facilitating pathways play a role in the genesis of OIH. These pathways may trigger the release of dynorphin and calcitonin gene-related peptide at the level of the spinal cord. Considering the results of all the studies examining different anatomical sites and structures for their involvement in OIH, it is most likely that relevant changes occur at multiple levels of the nervous system, including the brainstem nuclei, spinal cord neurons, glia, and primary afferent neurons.

It should be recognized that the doses of morphine used in the aforementioned studies were generally far higher than those used in the management of pain in humans. Also, the period of exposure generally was quite short compared with common human scenarios. This raises the possibility that the mechanisms responsible for rodent OIH are different to some extent from those responsible for the phenomena in humans.

Opioid Receptor Subtypes. Many different μ-opioid receptor agonists elicit OIH. Most investigators administered morphine, but, as summarized in table 3, others explored opioids included heroin, fentanyl, DAMGO, pentazocine, nalbuphine, and butorphanol. Some of these compounds, like fentanyl and DAMGO, show selectivity for the μ-opioid receptor, whereas others are less selective for various opioid receptor subtypes. However, CXBK mice, a strain expressing μ-opioid receptors at a very low density, did not develop OIH in a protocol rendering wild-type mice hyperalgesic.[46] This suggests that the μ-opioid receptor system plays a relevant role in the development of OIH.

Exogenous administration or enhanced endogenous release of κ-opioid receptor agonists can result in both hyperalgesic and antinociceptive effects.[77] Factors determining the net effect of κ-agonist administration are complex, incompletely understood, and likely include the site of drug administration and the nociceptive method tested. Given the scope of this review, studies predominantly reporting on the hyperalgesic effects of κ-agonist are briefly discussed in the next paragraph.

Intrathecal lumbar injections of κ-agonists resulted in thermal and mechanical hyperalgesia and aggravated allodynia in dogs, guinea pigs, and rats tested in models of acute and chronic pain.[78–80] Microinjections of κ-agonists into the rat brain stem caused heat hyperalgesia at the mesencephalic tegmentum but antinociception at the lower medulla.[81] Blocking the endogenous κ-agonist dynorphin at the level of the mesencephalic tegmentum enhanced antinociception, suggesting that tonic nociceptive facilitation mediated by κ-receptor originates from this site.[82,83] A role for κ-receptor–mediated medullary hyperalgesia also was suggested by experiments injecting κ-agonist into the forth ventricle of rats.[84] Finally, a single study reported heat hyperalgesia after the peripheral, subcutaneous administration of dynorphin in rats.[85]

Contrary to the biphasic, analgesic-hyperalgesic temporal response observed after administering μ-opioid agonists, the response elicited by κ-opioid agonists seems to be monophasic, that is, either analgesic or hyperalgesic. Although the μ-opioid receptor is a likely candidate for triggering events leading to OIH, it is entirely possible that κ-opioid receptors play a role in the manifestation of OIH. The increased expression and release of spinal dynorphin during chronic exposure to μ-opioid agonists recently has been cited as a mechanism supporting OIH in rats.[64,76]

Associative Hyperalgesia. Although most of the work investigating mechanisms supporting OIH has been biochemical in its orientation, several laboratories have focused on learning and conditioning as factors contributing to the expression of OIH. These studies were conducted pursuant to the hypothesis that animals associate opioid injections and opioid effects with environmental cues. As a consequence of such association, animals express a conditioned drug response that is triggered by environmental cues and typically antagonizes the original opioid effect. According to this concept, OIH in the setting of repetitive dosing can be viewed as a conditioned drug response opposing antinociceptive opioid effects. Although reasonable consensus exists about the role of a conditioned drug response in the development of antinociceptive opioid tolerance, it is less clear whether a conditioned drug response con-

tributes to the expression of OIH. Data from several studies support this concept.[86–92] However, other studies found no evidence for the development of associative hyperalgesia.[93–96] Several investigators pointed out that the specific drug administration algorithm and nociceptive assay may be decisive factors determining whether associative hyperalgesia is expressed.[86,97,98] Mechanisms underlying associative hyperalgesia are poorly understood, although one study suggested that NMDA receptors may mediate it.[99]

Based on existing animal data, it remains controversial whether an associative hyperalgesic component significantly contributes to the expression of OIH. In fact, most studies exploring OIH were not designed to clarify this question because they neither systematically excluded nor intentionally provided environmental clues to control for an associative component.

OIH versus *Tolerance to Analgesic Effects.* Exposure to opioids can result in a need to increase the dose over time to maintain a desired analgesic effect. Typically, this has been attributed to the development of tolerance. However, dose escalation can also be expected as a result of OIH. Pharmacologically, tolerance is characterized by a loss of drug potency or a right-shift of the dose *versus* effect relationship, while OIH is characterized by increased pain sensitivity or a downward-shift of the dose *versus* effect relationship. Figure 3 illustrates why both of these pharmacologically distinct phenomena share the same net effect on dose requirements. Mechanistically, tolerance reflects a desensitization of antinociceptive pathways to opioids, whereas hyperalgesia involves a sensitization of pronociceptive pathways. Such a distinction is not trivial and becomes relevant when attempting to overcome a loss of treatment effect. Tolerance may be addressed by increasing the opioid dose, whereas the same intervention may result in aggravated pain in case of OIH. Furthermore, some of the mechanisms underlying the two phenomena may be distinct and amenable to different preventive or therapeutic strategies.

Tolerance and OIH can be demonstrated and distinguished in animal behavioral studies by measuring baseline pain sensitivity and antinociceptive potency of an opioid over time. In a clinical setting, distinguishing the two phenomena is much more challenging and often is impossible. The assumption that the two conditions are likely to coexist is probably safe, because both involve stimulation of opioid receptors and share some neurotransmitter and receptor systems, including dynorphin, PKC, NMDA receptors, nitric oxide synthase, hemoxygenase, and others. However, two sets of observations suggest that OIH and tolerance may not contribute in strict proportion to a loss of treatment effect or the need for dose escalation. First, intermittent administration of the opioid-receptor antagonist naloxone during ongoing, intrathecal administration of morphine in rats aggravated

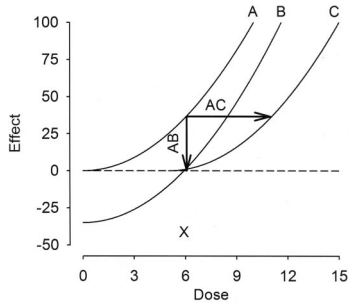

Fig. 3. Tolerance and opioid-induced hyperalgesia (OIH) are pharmacologically distinct phenomena that share the same net effect on dose requirements. Either condition necessitates dose escalation for maintaining a certain drug effect. If tolerance is expressed, decreased drug potency is reflected by a right-shift of the dose *versus* effect relationship (AC). If OIH is expressed, increased pain sensitivity is reflected by a downward shift of the dose *versus* effect relationship (AB). Both, tolerance, or OIH result in a decreased effectiveness of a given drug dose (X). From Carroll *et al.*[102]; used with permission from The American Society of Regional Anesthesia and Pain Medicine, copyright 2004 by Elsevier, Inc.

OIH, whereas the degree of opioid tolerance remained unaffected.[100] Second, experiments using repeated heroin administration in rats suggested that there was only an apparent loss of antinociceptive potency over time, which was no longer present when accounting for changes in baseline pain sensitivity. In other words, these experiments documented a lowered noxious threshold to mechanical stimulation with repeated heroin injections but maintained antinociceptive potency of heroin when considering relative rather than absolute changes of the mechanical pain threshold in response to drug administration.[37] Although OIH and tolerance may share certain mechanistic components, the relative expression of both phenomena may vary depending on the opioid treatment protocol and the nociceptive assay used.

Considerations and Recommendations

Above, we addressed OIH as it has been most commonly explored in laboratory and clinical studies. With respect to rodent studies, many investigators using a variety of opioids, dosing schedules, routes of administration, and nociceptive paradigms have demonstrated hyperalgesia between opioid doses and during withdrawal. Studies in higher mammals are virtually lacking, thus creating uncertainty about how generalizable these results may be. The available human data are far more limited in terms of the types of opioids administered, dosing schedules, and nociceptive paradigms used, although the results are compatible with the rodent findings. It is also important to recognize that most of the human studies provide only indirect evidence for OIH in clinically relevant settings. The few human studies suggesting a cause-and-effect relationship only demonstrated an aggravation of preexisting hyperalgesia by opioids.

Table 4. Case Reports Documenting High-dose, Opioid-induced Allodynia/Hyperalgesia

Reference	Opioid	Route	Dose	Hyperalgesia (n)	Remarks
104	M	PO, IM, IV	60–300 mg/d PO; 150–960 mg/d IM; 20 g/d IV	Generalized allodynia, myocloni (1)	n = 4; cancer pain; substituting morphine with methadone, sufentanil, or ketobemidone reversed allodynia
105	M	IV	175–200 mg/h	Generalized allodynia (5), aggravated neuralgia (3), myocloni (4)	n = 8; cancer pain (described in detail, n = 2), dose escalation aggravated allodynia
106	M	IT	37.5 mg/h	Spontaneous pain, allodynia not reported	n = 1; cancer pain, 50-fold reduction of IT morphine resolved pain aggravation
107	M	IT	80 mg/d	Spontaneous pain and allodynia in dermatomes S5–T5, myocloni	n = 1; cancer pain, primary pain T4–T7, dose reduction to 50 mg/d reduced allodynia
108	M	IV	600 mg/h	Generalized allodynia, myocloni	n = 1; cancer pain, substituting morphine with methadone reversed allodynia
109	M	PO, IT	400 mg/d IV; 48 mg/d IT	Generalized or lumbosacral segmental allodynia, myocloni (1)	n = 3; cancer and nonmalignant pain (described in detail, n = 2), dose reduction or substituting morphine with sufentanil, fentanyl, or methadone reversed allodynia
110	M	IV	105 mg/h	Generalized allodynia	n = 1; cancer pain in infant, reduction of morphine resolved allodynia
111	M	IT	0.2 and 0.5 mg bolus	Allodynia in dermatomes T6–T7	n = 1; central pain after spinal injury, administration of naloxone did not reverse hyperalgesia
112	M/MET	IV/PO	200/75 mg/d; 90/90 mg/d	Generalized allodynia	n = 2; cancer pain, switching second patient to methadone did not reverse hyperalgesia

IT = intrathecal; IV = intravenous; M = morphine; Met = methadone; PO = per oral.

Based on the available evidence, we need to give serious consideration to the possibility that OIH is a significant consequence of opioid therapy in humans. Paradoxically, the aggressive treatment of pain with opioids may predispose patients to greater levels of pain at later times. For example, patients chronically consuming opioids experience increased levels of postoperative pain despite consuming larger amounts of postoperative pain medications.[101,102] In addition, there seems to be a prevailing belief that patients currently or formerly using opioids display much heightened pain responses to minor procedures like venipuncture. Conceivably, the long-term use of opioids also may exacerbate rather than ameliorate chronic pain. The possibility of OIH limiting the usefulness of opioids emphasizes the value of alternative methods of pain control.

OIH with Dose Escalation and Ultra-high Doses

Human Studies

Severe allodynia, that is, pain evoked by stimuli, such as touch, that normally are not painful, is a rare complication in patients treated for intractable pain with high and escalating opioid doses.[103] Nine reports document allodynia in 22 patients (table 4). In eight patients, allodynia was accompanied by myocloni. Taken together, these reports provide evidence that systemic or neuraxial administration of large doses of morphine can produce a generalized tenderness of skin and soft tissue that makes patients hurt when touched or gently moved. Escalating the morphine dose in patients already suffering from opioid-induced allodynia typically aggravated the symptoms.[104–106] Reducing the morphine dose or substituting for it with an alternative opioid (fentanyl, sufentanil, methadone, ketobemidone) alleviated or abolished observed allodynia.[104,107–110]

A few reports are not entirely consistent with the general characteristics of high-dose, opioid-induced allodynia as outlined in the previous paragraph. Allodynia after typical rather than very high morphine doses was reported in two patients.[104,111] One patient experienced central pain and segmental allodynia after intrathecal morphine administration. It is possible that some forms of central pain are particularly sensitive to excitatory opioid effects. The second patient had cancer-related

back pain and, for reasons currently unclear, experienced generalized allodynia after a dose of oral morphine. Second, allodynia was reported in two patients receiving escalating doses of methadone in combination with morphine.[112] The relative contribution of methadone for producing allodynia remains uncertain, particularly when considering reports suggesting that substituting morphine with methadone can abolish high-dose, morphine-induced allodynia.[104,108,109] It should be noted that the possibility of spinal granulomas surrounding the intrathecal catheters used to administer opioids in some patients contributing to the observed segmental hyperalgesia cannot be excluded.

Animal Studies

Animal studies documented that administration of a high opioid dose can evoke an allodynic/hyperalgesic state and shed some light on potential underlying mechanisms. Rats receiving intrathecal morphine at a dose 10 times higher than that required to produce antinociception displayed a biting and scratching behavior and an extreme aversion to touch at dermatomes in close proximity to the subarachnoid injection site.[113–115] A role for the opioid-receptor system in mediating this allodynic/hyperalgesic state is unlikely because the phenomenon was (1) not reversed by opioid-receptor antagonists, (2) not produced by all opioid agonists tested at a high dose, (3) evoked in a nonstereospecific fashion by various enantiomers, and (4) not cross-tolerant with effects known to be mediated by opioid receptors.[113–117]

An intrathecal injection of strychnine produced an allodynic/hyperalgesic state quite similar to that observed after administering a high opioid dose.[114] Strychnine depresses glycinergic neuronal inhibition and electrophysiological evidence obtained in single-cell recordings of the rodent spinal cord indicates that high opioid concentrations can act similarly.[118,119] Intrathecal injection of glycine dose-dependently attenuated allodynia evoked by a high opioid dose, further pointing toward impaired glycinergic inhibitory control as an underlying mechanism.[117] Recent evidence suggests that the excitatory phenomena observed in conjunction with a high opioid dose are mediated by the NMDA receptor system.[116,117]

Considerations and Recommendations

For practical reasons, it is important to consider work suggesting that not all opioids produce an allodynic/hyperalgesic state when given at high doses.[115] Yaksh *et al.*[115] explored 33 opioid-related alkaloids in rats and concluded that opioids need the following structural characteristics to produce an allodynic/hyperalgesic state: (1) phenantrene structure, (2) hydrogen at position 14, (3) ether bond, (4) one or no methyl group on the nitrogen, and (5) free 3-OH position or glucuronide/sulfate conjugate in this position. Available clinical data are consistent with the suggestion of Yaksh *et al*. Convincing clinical evidence for the development of high-dose, opioid-induced allodynia/hyperalgesia exists only for the phenantrene morphine (table 4). Switching patients to the piperidine derivatives fentanyl or sufentanil attenuated or abolished such allodynia/hyperalgesia.[104,109] In this context, two apparently contradictory case reports are worth mentioning. The first report describes the occurrence of acute hyperalgesia in a patient receiving a 50-fold overdose of intravenous fentanyl.[120] This report needs to be interpreted carefully, because the portrayed patient was confused and unresponsive to verbal commands at the time of showing signs of motor hyperactivity in response to touch and noise. It is questionable whether observed behavior truly reflects presence of allodynia/hyperalgesia. The second report describes a patient with radiating neuropathic pain in her left leg as a result of chronic arachnoiditis who experienced aggravated spontaneous burning pain in both legs after intrathecal injection of sufentanil.[121] However, this patient did not experience measurable allodynia or hyperalgesia, making the report of unclear relevance to OIH.

In summary, administration of very high doses of certain opioids can produce allodynia and possibly hyperalgesia on rare clinical occasions. The allodynic/hyperalgesic state is not reversed by opioid antagonists and can become aggravated when the dose of the causative opioid agonist is further escalated. As soon as a high-dose, opioid-induced allodynic/hyperalgesic state is suspected, dose reduction of the causative agent and/or substitution of the causative agent with an opioid agonist less likely to cause such symptoms are appropriate next steps aiming at attenuating or eliminating these symptoms. In this regard, experimental evidence backed by limited clinical data suggests that switching from a phenantrene (*e.g.*, morphine) to a piperidine derivative (*e.g.*, fentanyl or sufentanil) is a valid strategy.

OIH with Ultra-low Doses

Human Studies

Although several laboratories performed animal studies to explore whether ultra-low opioid doses exert hyperalgesic effects, very little experimental work has been carried out in humans. A single anecdotal report dating back to the early 1940s was identified and describes the inadvertent finding of a dose-dependent biphasic response to morphine in 7 of 57 studied former addicts. These seven patients became mildly hyperalgesic to heat pain at the lowest morphine dose, but experienced analgesia at higher doses.[122]

However, some human studies attempted to exploit the idea that an ultra-low opioid dose causes excitatory or hyperalgesic effects, which typically are overshadowed by inhibitory effects exerted by higher opioid

doses. These studies tested the reverse concept, that is, whether an ultra-low dose of an opioid antagonist selectively could block excitatory opioid effects and, as a consequence, augment analgesic opioid effects obtained with higher and clinically used doses. Early clinical studies in humans indeed provide some support for the idea that opioid antagonists may exert analgesic effects at low doses, while aggravating pain at higher doses.[123] Two studies in patients undergoing hysterectomy suggested that coadministration of a very low dose of an opioid antagonist reduced postoperative opioid consumption or postoperative pain.[124,125] However, subsequent studies in patients undergoing surgery could not confirm these findings, and it remains controversial whether coadministration of ultra-low doses of an opioid antagonist with an opioid agonist augments opioid analgesia.[126,127]

Animal Studies

The administration of μ-opioid receptor agonists at doses far below those predicted to be effective caused a hyperalgesic response in animals. Kayser *et al.*[128] measured the effects of systemic morphine in arthritic rats when administered a dose approximately 1000-fold lower than that typically used to study antinociceptive effects and demonstrated a paradoxically enhanced sensitivity to noxious pressure in the arthritic paw. Similar results were obtained by Crain *et al.*[129] using mice and a thermal nociceptive test. In a paradigm measuring cardiovascular reactivity under anesthesia, a very low dose of the μ-opioid receptor agonist sufentanil aggravated the hemodynamic response to noxious stimuli, further suggesting that systemic subanalgesic opioid doses may cause hyperalgesia.[130] Finally, the opioid etorphine injected locally caused hyperalgesia at very low doses, but evoked an antinociceptive effect at higher doses.[131] Both effects were sensitive to antagonists, suggesting that both were mediated by opioid receptors.

Shen and Crain[132] suggested that the naloxone-reversible hyperalgesic effects of ultra-low dose morphine may be the result of bimodal effects on dorsal root ganglion opioid receptors. According to this theory, opioid receptors trigger an excitatory signaling cascade when exposed to very low opioid agonist concentrations but activate inhibitory pathways when exposed to higher agonist concentrations. This concept is supported by the observation that very low opioid antagonist concentrations produced antinociceptive effects, whereas higher antagonist concentrations caused hyperalgesia.[133,134] The antinociceptive effects observed at very low opioid antagonist concentrations are likely mediated by opioid receptors, because they showed cross-tolerance to the antinociceptive effects evoked by higher concentrations of an opioid agonist.[135] At a molecular level, GM1-ganglioside has been implicated in mediating these excitatory opioid effects.[136]

Considerations and Recommendations

At this point, significant evidence in the animal literature suggests that rodents exposed to very low opioid doses show signs of hyperalgesia, whereas larger doses produce antinociceptive effects. No controlled studies were identified that directly examined whether very low opioid doses cause hyperalgesia in humans. Studies in humans providing some indirect evidence for an hyperalgesic effect of very low opioid doses explored the reversed hypothesis, that is, whether very low doses of an opioid antagonists would provide enhanced postoperative pain control. However, results of these studies are conflicting.

The concept that ultra low doses of opioids cause hyperalgesia may have some relevance to OIH as observed during periods of abstinence (see above). Presumably, very low opioid concentrations may still be present in experiments testing animals and humans during abstinence. A single report documenting that naloxone reversed hyperalgesia as observed during opioid abstinence in mice is compatible with this idea.[137] However, naloxone enhanced the degree of OIH displayed by rats in other paradigms.[37] These latter studies are in line with the many studies using naloxone to precipitate opioid withdrawal and OIH. Although we cannot exclude some contribution of low opioid concentrations to OIH during periods of abstinence, it is unlikely that this is a predominant mechanism.

The fundamental capacity of the opioid receptor system to elicit hyperalgesia is especially apparent in species inert to antinociceptive opioid effects. Such species, including the fowl and the mole-rat, display a monotonic, naloxone-reversible hyperalgesic response to thermal and chemical stimuli after opioid administration.[138–141] Thus, the overall effect of a given opioid dose is likely the composite response resulting from activation of opioid-dependent pronociceptive and antinociceptive systems.

General Implications and Future Directions

Administration of opioids typically results in analgesia. However, the opioid receptor system signals and modulates a multitude of effects, and under certain conditions mediates hyperalgesia rather than analgesia. In this systematic review, we divided opioid-induced hyperalgesia into three major categories based on the opioid dose and further subdivided these categories by distinguishing various types of pain as well as route and pattern of opioid administration. It can be reasonably concluded from the available literature that opioidergic mechanisms can counteract analgesia and enhance pain sensitivity. Such mechanisms have been identified as originating in afferent neurons, in spinal cord tissue, and in supraspinal centers of the central nervous system. Al-

though opioids have enjoyed widespread use in the management of acute and cancer-related pain for many decades, the increasingly popular use of opioids for alleviating chronic, nonmalignant pain stresses the importance of gaining a thorough understanding of potential limitations of the clinical usefulness of these drugs.

It is clear from our systematic review of the literature that OIH in the context of maintenance therapy and periods of withdrawal or abstinence has received the most attention. This is not particularly surprising, because OIH in these settings may be clinically most relevant for a large number of patients. Particularly concerning is the possibility that chronic pain and pain associated with interventional procedures could be worsened by virtue of ongoing and possibly even acute opioid therapy.

The body of laboratory data using behavioral assays is robust, although human studies in this area are far less numerous. The animal studies predominantly provide evidence for sensitization to acute noxious stimuli after acute and chronic opioid dosing. Lacking are animal studies examining OIH in models of chronic pain. Human studies have used patients and volunteers. Patient data provide evidence for aggravation of postoperative pain in the setting of acute and chronic opioid administration. Increased sensitivity to acute experimental pain also was seen in patients receiving methadone maintenance therapy. Most data from human volunteer studies demonstrates exacerbation of secondary hyperalgesia after short-term administration of short-acting opioids. Lacking are prospective studies exploring the possible role of OIH in exacerbating clinical pain states.

We believe that there are two primary areas on which to focus future studies:

1. Mechanisms of OIH. Existing data suggest that peripheral, spinal cord, and higher central nervous system structures may be involved in OIH, but many specifics are missing from our understanding. Such topics include the sensitization of primary afferents, the overall understanding of the neurotransmitter systems involved, the participating intracellular second messenger systems, and the genetic susceptibility to OIH. Ultimately, these mechanistic studies will need to be integrated into a model accounting for the likely complex interactions. Such a model would be useful in developing strategies to optimize opioid therapy.
2. Clinical studies. Existing human data generally support the existence of OIH in a few specific settings. Future studies will need to clarify the conditions under which OIH is expressed and its clinical significance. Such studies would include evaluating the impact of OIH on our ability to control chronic pain with opioids, exploring whether OIH may facilitate the development of chronic pain, developing opioid administration algorithms minimizing OIH, identifying patients at particular risk for developing OIH, and evaluating approaches for reducing OIH after it is established.

As for ultra-high opioid doses, a series of case reports indicates that certain opioids can produce allodynia and hyperalgesia particularly during rapid dose escalation. This condition is not reversed by administration of an opioid antagonist, but would be expected to respond to opioid dose reduction or rotation from a phenantrene (*e.g.*, morphine) to a piperidine opioid derivative (*e.g.*, fentanyl). From the currently available literature, there are no clear mechanistic commonalities between the hyperalgesia experienced during rapid opioid dose escalation and that experienced during opioid maintenance or withdrawal. Although some animal studies exist, there are no human studies prospectively exploring pain sensitization in humans during rapid opioid titration.

Although it has been observed that very low opioid doses can cause hyperalgesia in rodents, the human data are conflicting, and direct evidence for the existence of this condition in humans is lacking. Mechanistically, we do not at present have sufficient information to (1) determine in which clinical situations the phenomena may be relevant and (2) design clinical strategies to avoid any negative impact on pain control that this form of hyperalgesia might have. Prospective human studies clearly are required.

It needs to be recognized that our method of literature search does impose some limitations on the forgoing discussion. Specifically, our search algorithm was designed to identify studies that measured OIH as a primary endpoint. It is likely that studies reporting OIH as an incidental finding also were identified by the search. Although studies measuring OIH as a primary endpoint and reporting negative results likely were captured as well, studies providing incidental data suggesting absence of OIH might have been missed.

In summary, clinicians need to be aware of the possibility that opioid therapy, particularly if aggressive in nature, may cause heightened pain sensitivity and may aggravate preexisting pain. It would seem reasonable to discuss with patients the possible adverse impact of OIH when initiating opioid therapy. The disappearance of opioid treatment effects, particularly if coupled with the unexplained expansion of pain complaints, may signal the expression of OIH. In this setting, the use of alternative analgesics and detoxification from opioids may need to be considered. Specific recommendations for the management of patients at risk for OIH have been made by Carroll *et al.*[102] Although these recommendations were made in the context of perioperative pain control, many of them would be applicable to the management of chronic pain patients receiving opioid therapy. Some of the relevant approaches would include the use of multimodal analgesia, using caution when rapidly

titrating opioids, and avoiding periods of relative opioid abstinence. As our appreciation of the relevance of OIH improves, more recommendations may become available.

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