Opioid-induced Hyperalgesia in Humans

Molecular Mechanisms and Clinical Considerations

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Abstract: Opioid-induced hyperalgesia (OIH) is most broadly defined as a state of nociceptive sensitization caused by exposure to opioids. The state is characterized by a paradoxical response whereby a patient receiving opioids for the treatment of pain may actually become more sensitive to certain painful stimuli. The type of pain experienced may or may not be different from the original underlying painful condition. Although the precise molecular mechanism is not yet understood, it is generally thought to result from neuroplastic changes in the peripheral and central nervous systems that lead to sensitization of pronociceptive pathways. OIH seems to be a distinct, definable, and characteristic phenomenon that may explain loss of opioid efficacy in some cases. Clinicians should suspect expression of OIH when opioid treatment effect seems to wane in the absence of disease progression, particularly if found in the context of unexplained pain reports or diffuse allodynia unassociated with the pain as previously observed. This review highlights the important mechanistic underpinnings and clinical ramifications of OIH and discusses future research directions and the latest clinical evidence for modulation of this potentially troublesome clinical phenomenon.

Key Words: opioid-induced hyperalgesia, opioid adverse effects, opioid-related disorders/complications, animals, humans

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Ancient Sumerian writings found on clay tablets from Nippur show that opioid medications have been used for thousands of years to treat pain and to "ease the harshness of life."[1] Today, they are widely recognized as a primary treatment for moderate to severe pain.[2] These medications have most commonly been used for the treatment of acute and cancer-related pain. However, recent evidence suggests that opioid medications may also be useful for the treatment of chronic noncancer pain, at least in the short term.[3–14]

Perhaps because of this new evidence, opioid medications have been increasingly prescribed by primary care physicians and other patient care providers for chronic painful conditions.[15,16] Indeed, opioids are among the most common medications prescribed by physicians in the United States[17] and accounted for 235 million prescriptions in the year 2004.[18]

One of the principal factors that differentiate the use of opioids for the treatment of pain concerns the duration of intended use. For example, opioid analgesia after surgical procedures often occurs in the time frame of several days to weeks. Opioids use for cancer-related pain can be more sustained, though clinical remission of disease or death owing to disease often limits the duration of opioid treatment. On the other hand, opioids used for chronically painful conditions like osteoarthritis and back pain may need to be prescribed for decades. It is for this category of prolonged use that the available pool of efficacy and side effect data seem furthest from our clinical practice.

Despite the growing use of these medications for chronic noncancer pain, concerns remain about physical dependence, addiction, adverse side effects, and the need for dose escalation to overcome apparent analgesic tolerance in some patients. Unfortunately, there is a dearth of quality prospective clinical evidence that directly addresses factors that may influence the long-term efficacy of opioids in treating chronic pain. Recent evidence suggests that opioids are responsible for yet another problem that may potentially limit their usefulness over time, opioid-induced hyperalgesia (OIH). The focus of this review is to highlight important aspects of our current understanding of this entity with respect to its mechanistic underpinnings and clinical ramifications. Previously published reviews are available that detail various aspects of the biochemistry and neurobiology of OIH.[19–22]

DEFINITION OF OIH

OIH is most broadly defined as a state of nociceptive sensitization caused by exposure to opioids. The state is characterized by a paradoxical response

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whereby a patient receiving opioids for the treatment of pain may actually become more sensitive to pain. This increased sensitivity to pain is a new, unique entity that is distinct from the patient's original underlying painful condition. In clinical settings, OIH may represent one of many reasons for declining levels of analgesia while receiving opioids or a worsening pain syndrome. Another manifestation might be the experience of excessive pain after an otherwise straightforward surgical procedure. This phenomenon is thought to result from neuroplastic changes in the central nervous system (CNS) and peripheral nervous system leading to sensitization of pronociceptive pathways. There exist a wide variety of settings in which OIH can be observed as presented below.

OIH VERSUS TOLERANCE TO ANALGESIC EFFECTS

A common clinical observation in patients receiving opioid medication for the treatment of pain is the need to increase the dose over time in some patients to maintain adequate analgesia. This observation is commonly attributed to the development of tolerance to the analgesic effects of opioids. However, the loss of analgesic efficacy can also be the result of OIH. It is important to note that OIH and analgesic tolerance are 2 distinct pharmacologic phenomena that can result in similar net effects on opioid dose requirements.

For illustrative purposes, we have constructed a hypothetical diagram showing changes that might occur after chronic opioid use, which are indicative of analgesic tolerance and OIH (Fig. 1). The figure represents a hypothetical experiment where an acute opioid infusion is used to detect changes in the analgesic dose-experimental pain-response curve that occur as a result of chronic opioid exposure. As shown in Figure 1A, a patient with OIH owing to chronic opioid exposure experiences increased pain or has enhanced pain sensitivity even in the setting of low serum opioid levels, reflected by a downward shift in the dose-response curve. OIH, as shown in Figure 1A, is uniquely characterized by a decrease in pain tolerance (y-axis) at baseline (eg, before the start of the opioid infusion), compared with opioid-naive individuals. It should be noted that this curve reflects a situation where the effects of OIH can be overcome by increased opioid doses. This observation is consistent with a central or peripheral sensitization of pronociceptive pathways that is thought to underlie the mechanism of OIH. In contrast, Figure 1B illustrates the development of analgesic tolerance, characterized by a rightward shift of the dose-response curve that is consistent with habituation or desensitization of anti-nociceptive pathways mediated by opioid medications. Both OIH and analgesic tolerance result in an observed decrease in opioid effectiveness for a given dose of medication. These figures also demonstrate that it could be difficult in some clinical settings to determine if a patient was developing OIH, tolerance, or both to opioids. Quantitative sensory testing of pain and analgesic sensitivity before and after initiating chronic opioid therapy may help elucidate this diagnostic dilemma.

ANALGESIC PARADOX OF DOSE ESCALATION

The observation that 2 pharmacologically distinct mechanisms may have similar net effects on opioid dose escalation over time has important clinical implications.

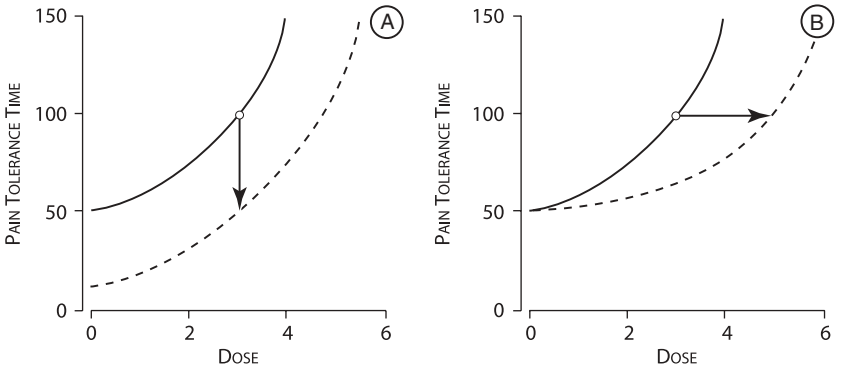

FIGURE 1. Alterations in the opioid dose-response relationship with chronic opioid administration. We present a hypothetical experiment where an acute opioid infusion is used to detect changes in the analgesic dose-experimental pain response curve that occur as a result of chronic opioid exposure. This diagram shows changes in analgesic response (eg, cold pressor tolerance time) as a function of analgesic dose (eg, target plasma remifentanil concentration), measured using human experimental pain techniques (eg, cold pressor test). The responses of opioid-naive patients to such an experiment are shown as solid lines. A, In OIH, the dose-response curve of the chronic opioid user (dashed line) is shifted downward and the patient experiences increased pain to noxious stimuli at baseline (shown as decreased cold pressor tolerance time before the onset of opioid infusion). This figure illustrates the situation where OIH can be effectively counteracted by the analgesic effect of increased opioid doses. B, In analgesic tolerance, the slope of the dose-response curve of the chronic opioid user (dashed line) becomes attenuated and rightward shifted; however, there is no significant change in pain sensitivity at baseline (shown as an identical analgesic response in opioid-naive and chronic opioid users when analgesic dose is zero). OIH indicates opioid-induced hyperalgesia.

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In the case of analgesic tolerance, desensitization of opioid antinociceptive pathways over time can be addressed by simply increasing the opioid dose. However, in patients with OIH, this maneuver will paradoxically aggravate the problem and worsen the patient's underlying pain. In clinical practice, it may be difficult to distinguish these 2 phenomena because the observed dose escalation may be a manifestation of pharmacologically distinct and dimorphic etiologies involving desensitization of antinociceptive or sensitization of pronociceptive pathways. Further complicating the picture is that even chronic forms of pain will naturally wax and wane and the underlying disease causing chronic pain may progress over time.

OIH VERSUS OPIOID DOSAGE

It is perhaps useful from a clinical if not mechanistic standpoint to consider OIH in 3 different settings. As reviewed in detail elsewhere, OIH is seen in both humans and in animal models in the settings of very low-dose opioid administration, during maintenance dosing, and when doses are extremely high.[19] Because most of the experimental and clinical data concern the situation where opioid doses are relatively stable or are oscillating in a manner consistent with standard therapeutic approaches, we first present the human and animal data related to these scenarios. We will then proceed on to consider the other forms of OIH.

OIH–OCCURRENCE UNDER COMMON THERAPEUTIC CONDITIONS

Human Evidence

Clinical reports of hyperalgesia associated with opioid use span more than 100 years, as noted by Rossbach[23] in 1880, "[W]hen dependence on opioids finally becomes an illness of itself, opposite effects like restlessness, sleep disturbance, hyperesthesia, neuralgia and irritability become manifest." Over the past decade, several observational, cross-sectional, and prospective controlled trials have examined the expression and potential clinical significance of OIH in humans. These studies have been conducted using several distinct cohorts and methodologies: (1) former opioid addicts (OAs) on methadone maintenance therapy, (2) perioperative exposure to opioids in patients undergoing surgery, (3) healthy human volunteers after acute opioid exposure using human experimental pain testing, and more recently (4) a prospective observational study in opioid-naive pain patients undergoing initiation of chronic opioid therapy.

Former OAs on Methadone Maintenance Therapy

A number of studies have examined pain sensitivity in OAs maintained on methadone using cold pressor, electrical, and pressure pain models.[24–30] These studies show a modality-specific increased sensitivity to cold pressor pain in these patients, compared with matched or healthy controls.[24–28] In contrast, hyperalgesia to electrical pain was weak or absent as was hyperalgesia in mechanically evoked pain models.[24,28–30] Other investigators studying healthy human volunteers were also unable to show development of OIH in thermal pain models.[31,32] These results suggest that OIH develops differently for various types of pain.[24,28,29]

Pud et al[33] recently conducted a study of cold pressor testing in a cohort of OAs presenting for a 4-week inpatient detoxification program. Cold pressor pain measurements were taken on admission and 7 and 28 days thereafter. Interestingly, in contrast to previous studies, the authors found increased latency to the onset of pain and decreased visual analog scale pain scores for peak pain in the OA group, compared with healthy controls. However, they did find a significant decrease ($\sim$50%) in cold pressor tolerance in the OA group compared with controls that is consistent with earlier findings by other investigators.[24–28] The authors could not readily explain the mixed finding of increased cold pressor latency and hypoalgesia in the setting of decreased cold pressor tolerance and putative hyperalgesia in the OA group. The authors postulate that pain avoidance behavior[34,35] and markedly low frustration levels[36] may cause addicts to initially deny the feeling of pain. However, when denial becomes impossible, their tendency to overreact[37] causes them to very quickly terminate the stimulus. Therefore, it may not be so much the intensity of pain as it may be the aversive character or unpleasantness of pain that becomes exaggerated in these patients. This may also explain why OIH is much more prominent in the cold pressor test than in models of acute heat and electrical pain. The latter pain models cause significantly less pronounced negative affect than the cold pressor test at similar levels of pain intensity.[38]

The Pud study also offers some insight into the reversibility of OIH in this population. The authors did not see a significant change in pain sensitivity over time during the 4 weeks of opioid abstinence. This is in contrast to work by Compton[25] and Hay et al[39] who found higher pain tolerance and decreased pain sensitivity in OAs who were abstinent for 6 months to 1 year compared with current opioid users or controls. These results suggest that OIH in this patient population may be reversible to some extent, but requires a long period of opioid abstinence.

Taken as a whole, these studies provide observations that are compatible with the hypothesis that OIH is caused by chronic opioid exposure. It is important to understand the limitations of these studies. The cross-sectional or retrospective nature of these studies (ie, the cohort was already chronically exposed to opioids) precludes establishing a firm causal relationship between opioid use and development of OIH. In addition, unique properties of the OA population may confound pain measurements in these patients. Finally, another limitation of these studies is the possibility that increased pain sensitivity may intrinsically predispose people to become OAs and require methadone to prevent relapse after detoxification. This hypothesis is supported by the

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observation that current users of opioid or cocaine are more sensitive to cold pressor pain than former users of either drug.[25]

Perioperative Exposure to Opioids

A small number of clinical studies have looked at OIH in the setting of acute perioperative opioid exposure. Two prospective controlled clinical studies have reported increased postoperative pain despite increased postoperative opioid use in patients who received high doses of intraoperative opioids.[40,41] A separate study of women undergoing cesarean section found that the intraoperative exposure to intrathecal fentanyl also leads to a similar postoperative finding of increased postoperative opioid consumption without improved analgesia, compared with women who received placebo intrathecal saline injections.[42] More recently, a study by Joly et al[43] directly measured the development of secondary wound hyperalgesia after acute intraoperative opioid exposure. The authors found that high-dose intraoperative exposure to the potent, ultrashort-acting μ-opioid agonist remifentanil increased peri-incisional wound allodynia and hyperalgesia measured by von Frey hairs compared with low-dose intraoperative remifentanil in patients undergoing major abdominal surgery.

These findings are contrasted by other studies that did not show an effect of intraoperative opioid dose on postoperative pain sensitivity. Cortinez et al[44] did not find increased pain or postoperative opioid consumption after high-dose intraoperative remifentanil exposure in patients undergoing elective gynecologic surgery. A more recent study by Lee et al[45] also failed to see a significant difference in postoperative pain or opioid consumption in patients who received intraoperative remifentanil compared with 70% nitrous oxide, after colorectal surgery. Finally, Hansen et al[46] also failed to see a sustained significant difference in postoperative pain or opioid consumption in patients who received intraoperative remifentanil compared with saline infusion, after major abdominal surgery. Although the authors of this study did find a significant increase in visual analog scale score in the remifentanil group compared with placebo during the immediate postoperative period that is suggestive of OIH, this difference was no longer significant 2 hours after surgery or during the remainder of the 24-hour observation period. The failure to observe an effect of intraoperative opioid exposure on postoperative pain and opioid consumption in these studies may be because of lower total intraoperative opioid exposure in the cases of the Cortinez and Lee studies when compared with the positive results of Guignard et al,[41] suggesting a dose-dependent effect of opioids on the development of OIH.

These observations provide mixed support for a hypothesis of development of OIH after acute perioperative opioid exposure. Importantly, these observations only provide indirect evidence in support of this phenomenon. As noted previously in this review, the need for dose escalation to maintain analgesia can be owing to the development of analgesic tolerance, OIH, or simultaneous expression of both phenomena. No causal relationship between acute perioperative opioid exposure and development of OIH can be established without direct measurement of pain sensitivity. Although Joly et al[43] have successfully implemented quantitative assessment of pain into a clinical study of OIH and postoperative pain, further work incorporating these methodologies into high quality prospective trials will be needed to further characterize the expression and clinical significance of OIH after acute opioid exposure in the perioperative setting.

Acute Opioid Exposure in Healthy Volunteers Using Experimental Pain Methods

Several studies have examined the development of OIH in humans after acute short-term exposure to opioids. Multiple investigators have found aggravation of experimentally induced hyperalgesic skin lesions after short-term infusion of remifentanil. Angst et al[32] and Koppert et al[47–49] found significant enlargement of the area of mechanical hyperalgesia induced by transdermal electrical stimulation after 30 to 90 minutes of exposure to remifentanil. Using the heat-capsaicin–rekindling model, Hood et al[31] found a similar aggravation of hyperalgesia after 60 to 100-minute remifentanil infusions. This aggravated hyperalgesia was observed up to 4 hours after remifentanil exposure was discontinued and was absent when assessed on the following day. Aggravation of pressure-evoked pain after short-term remifentanil infusion in a single study of healthy volunteers has also been reported, though unequal nociceptive input during remifentanil and control infusions may account for the observed postinfusion hyperalgesia.[50] Finally, Compton et al found increased sensitivity to cold pressor pain in a small cohort of healthy human volunteers following precipitated opioid withdrawal after induction of acute physical opioid dependence.[51,52] Taken together, these findings provide direct evidence for development of OIH in humans using models of secondary hyperalgesia and cold pressor pain.

Prospective Observational Study in Chronic Pain Patients

Although the studies cited above provide useful information, they are somewhat limited by their cross-sectional rather than prospective study design, failure to distinguish tolerance from hyperalgesia, or by their use of short-term rather than the long-term opioid exposure that is typical when opioids are used for the treatment of chronic pain. Recently, Chu et al[53] attempted to overcome some of these shortcomings by conducting the first prospective observational study documenting the development of OIH in opioid-naive chronic pain patients.

Patients with moderate to severe chronic low back pain were prospectively assessed for both analgesic tolerance and hyperalgesia after 1 month of oral morphine therapy using tonic cold (cold pressor) and phasic heat experimental pain models. The study found significant hyperalgesia and analgesic tolerance in the

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cold but not heat pain models. This modality-specific response suggests that certain types of pain are more likely to be aggravated by OIH than others. Indeed, human experimental pain studies by Doverty et al[28] showed more pronounced hyperalgesia in the cold pressor model than a model of electrical pain in methadone maintenance patients compared with matched controls. Angst et al[32] and Hood et al[31] also failed to show hyperalgesia to heat pain in the setting of aggravated mechanical hyperalgesia after cessation of acute remifentanil infusion in healthy human volunteers. There are, however, several limitations of this study. The study cohort reflects a very small sample size, and there was no placebo group or blinding of participants and the investigators to the treatment. Despite these limitations, this preliminary study is the first to prospectively document development of OIH in opioid-naive chronic pain patients and suggests that the phenomenon can occur within 4 weeks after exposure to moderate doses (median dose 75 mg/d) of morphine.

Animal Data

More than 90 publications are available describing OIH in various animal models. The majority of these have been tabulated and presented in a recent publication.[19] Out of these efforts has emerged a model for OIH that considers this process to be neurobiologically multifactorial. In fact, it seems that, in general, neurobiologic systems that respond to opioids acutely in such a manner as to provide analgesia may change over time in such a way as to enhance nociception, especially in the setting of declining opioid doses. A diagram of several of the best investigated sites of such plasticity is provided as Figure 2. The mechanisms relevant to each site of plasticity are probably unique.

Peripheral Effects

The first site of plasticity evaluated in animals as contributing to OIH involves the terminals of primary afferent neurons. Because it was recognized that μ-opioid receptors are expressed on both the central and peripheral terminals of primary afferent neurons, it was considered possible that the peripheral injection of selective opioid agonists could cause functional changes in the neurons. In a series of investigations, the selective μ-opioid agonist [d-Ala2, NMe-Phe4, Gly-ol5-enkephalin (DAMGO)] was injected in microliter volumes into the skin of the hind paws of rats.[54–58] Although these injections were associated with antinociception acutely, repeated injection was associated with tolerance and mechanical hyperalgesia which was interpreted as a sign of ''local'' physical dependence. This ability to cause tolerance and hyperalgesia was not limited to opioid receptors as adenosine A1 and A2 agonists lead to similar findings.[57] Further studies revealed roles for protein kinase C (PKC) and adenylate cyclase in modulating this phenomenon.[55,56] Thus it is not required that drugs reach the CNS in order for some degree of hyperalgesia to emerge from repeated drug administration.

In a later set of studies, Liang et al[59] used contemporary genetic mapping techniques to associate the β2-adrenergic receptor (β2-AR) with OIH after repeated morphine administration to mice. In studies designed to confirm the association, it was observed that the local hind paw administration of selective β2-AR antagonists reduced the thermal and mechanical manifestations of OIH whereas the local administration of β2-AR agonists actually enhanced nociceptive sensitization.

Spinal Effects

Spinal cord plasticity underlying OIH has been demonstrated after both the intraspinal and systemic

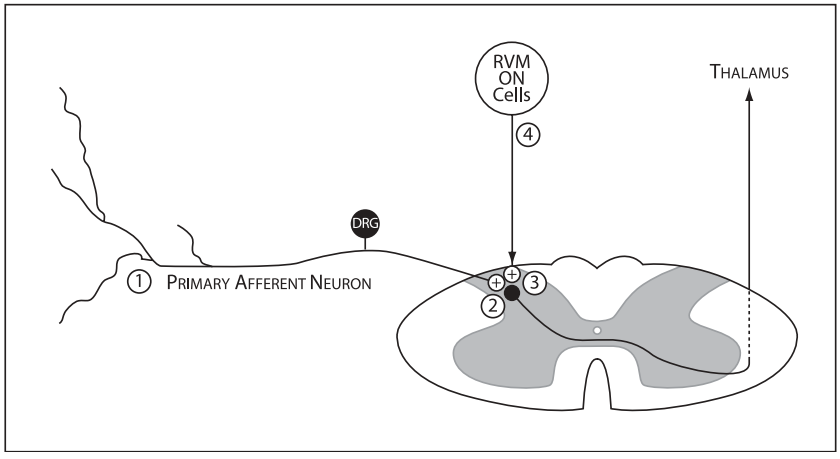

FIGURE 2. Possible molecular mechanisms for opioid-induced hyperalgesia. Some mechanisms that have been studied include (1) sensitization of primary afferent neurons, (2) enhanced production and release of excitatory neurotransmitters and diminished reuptake of neurotransmitters, (3) sensitization of second order neurons to excitatory neurotransmitters, and (4) neuroplastic changes in the rostral ventromedial medulla that may increase descending facilitation via ''on-cells'' leading to up-regulation of spinal dynorphin and enhanced primary afferent neurotransmitter release and pain.

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administration of opioids. One of the first studies in this area involved the daily bolus administration of intrathecal morphine to rats for more than 1 week.[60] At both 8 and 10 days after initiation of treatment, the animals were observed to display thermal hyperalgesia. The authors went on to make observations largely confirmed by subsequent investigators that *N*-methyl-D-aspartate (NMDA) and non-NMDA excitatory amino acid receptors and also PKC mediate this phenomenon. Dunbar and Pulai[61] added to these early observations by showing that if intrathecal morphine was infused in a continuous manner that the degree of OIH which developed was smaller than if bolus administration with intermittent abstinence was employed. Spinal blockade of the NMDA receptor again reduced OIH.

Though potentially not involving the spinal cord exclusively, other groups have shown that the same systems operate to support OIH after systemic opioid administration. For example, the administration of the NMDA receptor blockers MK-801 or ketamine reduce or reverse OIH owing to the chronic (days) systemic administration of opioids to rats and mice.[62–69] Likewise, animals lacking the gene for PKC-γ did not develop OIH normally after systemic opioid administration.[70] The PKC observations were further supported by the work of Sweitzer et al[71] who used primarily pharmacologic tools to show that PKC isoforms participated in OIH as studied in rat pups.

Since the time of the early observations, more spinal receptor systems have been explored in the setting of OIH. For example, the enhanced production and release of spinal dynorphin seems to support OIH.[72] Likewise, investigators have implicated spinal cyclooxygenase (COX) as the injection of ibuprofen intrathecally reduced OIH.[73] Spinal cytokines like interleukin-1β and chemokines like fractalkine have been implicated as well.[74] The latter observations connect OIH with the emerging appreciation of spinal inflammation as participating in many abnormal pain syndromes. More recently, Vera-Portocarrero et al[75] provided an elegant series of studies in which substance P (SP) conjugated to saporin was used as an intrathecal neurotoxin to ablate neurokinin-1 receptor expressing cells in the spinal cord. This maneuver prevented the normally observed morphine-induced sensitization in rats. These investigators further discovered that the serotonin 5-HT3 receptor, which participates in a spinal-supraspinal-spinal loop to maintain nociceptive sensitization, needed to be active for OIH to be manifest.

Regardless of the pharmacologic basis for spinal sensitization by opioids, additional biochemical and behavioral observations suggest that the dorsal horn of the spinal cord is central to many of the mechanisms converging to support OIH. In mice treated for several days to induce OIH, the intrathecal injection of SP or glutamate lead to greatly enhanced nociceptive behaviors when compared with saline treated mice.[76] In addition, neuronal activation in the spinal cord dorsal horn (as indexed by Fos expression) was far greater in the morphine treated animals after intrathecal SP or glutamate injection, suggesting that spinal cord neurons are sensitized to nociceptive neurotransmitters after chronic morphine treatment.[76] It is important to note that chronic morphine treatment causes the increased expression of the nociceptive neurotransmitters SP and calcitonin gene-related peptide.[77] Moreover, chronic opioid administration leads to decreased expression of the spinal glutamate transporters excitatory amino acid carrier 1 and glutamate/aspartate transporter. Thus, excitatory amino acids once released linger in the synapse for a sustained period.[78]

Supraspinal Effects

Though the majority of the work carried out in exploring the mechanistic basis of OIH has involved the spinal cord and peripheral neurons, there is growing appreciation that higher CNS centers may participate in supporting this and other forms of abnormal pain sensitivity through enhanced descending facilitation to the spinal cord dorsal horn. The focus of this work has been the rostral ventromedial medulla (RVM). Microinjection of local anesthetic to stop neuronal discharge from this structure or lesioning of the dorsolateral funiculus, which carries descending nerve fibers from the RVM, prevents or reverses not only OIH but also tolerance to opioids.[79,80] Work pursuant to these observations suggested that cholecystokinin released in the RVM and acting through cholecystokinin-2 receptors might activate the RVM and support the descending influences.[81]

Opioid Distribution

All of the mechanisms present to this point have involved pharmacodynamic mechanisms. Indeed, little evidence has emerged over the years for pharmacokinetic factors governing phenomena like opioid tolerance or hyperalgesia. Recent results have caused us to reappraise this situation. After measuring the degree of thermal sensitization developing after 4 days of morphine treatment in 16 inbred strains of mice, Liang et al[82] used an in silico haplotypic genetic mapping strategy to identify genes linked to the thermal OIH trait. The most strongly linked gene was that coding for the P-glycoprotein drug transporter. This relatively nonselective drug transporter was known to be able to control brain levels of opioids including morphine by mediating the efflux of the drug across the blood brain barrier.[83] Confirmatory studies showed that inhibition of P-glycoprotein eliminated OIH as did genetic deletion of the *abcb1a/b* genes coding for P-glycoprotein transporters in mice. Finally, brain levels of morphine were inversely statistically correlated with the development of OIH in the inbred strains. Thus, drug distribution and pharmacodynamic issues need to be considered in understanding OIH.

OIH–VERY LOW OPIOID DOSES

A limited amount of direct human data directly support the notion that low opioid doses cause

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hyperalgesia. In fact, one of the only studies to examine this question demonstrated biphasic effects of morphine in a subset of former OAs given morphine.[84] However, more recent investigations have approached the question from another angle and have shown that the inclusion of very low doses of opioid antagonists reduce postoperative opioid consumption.[85,86] These findings have not been reproduced by all investigators.[87,88]

The animal data are more complete. For example, Kayser et al[89] demonstrated that a dose of morphine approximately 1/1000th the systemic analgesic dose heightened nociceptive sensitization in arthritic rats. Later, investigators using cultures of dorsal root ganglion neurons determined that low morphine concentrations rendered the neurons sensitized.[90] These authors felt that initially activated excitatory pathways gave way to analgesia ones as the concentration of opioid increased. This theory is supported by other studies demonstrating that very low doses of naloxone can provide analgesia whereas much larger doses cause the expected hyperalgesia.[91,92] It should be noted that virtually all available studies suggest that this low-dose OIH effect is mediated through opioid receptors as opposed to being due to a toxic effect of the drugs employed.

It is unclear in what clinical settings low-dose OIH might become relevant. As mentioned above, the data for this form of hyperalgesia contributing to postoperative pain are at this point equivocal. It might be considered, however, that during opioid detoxification or taper, plasma opioid or active opioid metabolite levels will eventually pass through very low concentrations. Increased pain late in the course of opioid taper might be supported by this mechanism.

OIH–VERY HIGH OPIOID DOSES

On the other side of the dose spectrum is OIH as observed when very large doses of opioids are provided or the doses of opioids are rapidly rising. Although this phenomenon has not been studied in prospective fashion in large populations, many case reports or series exist (Table 1). The majority of these reports involve the systemic or intrathecal administration of morphine, raising the possibility that metabolites, such as morphine-3-glucuronide that is known to cause neuroexcitation, could contribute to hyperalgesia.[93–95] In this setting, many patients develop both increased pain at the sites of ongoing pain as well as allodynia or even myoclonus.[96–98] Opioid rotation or substitution of a different opioid generally reduced the symptoms sharply.[97,99–102]

Animal studies have reproduced these findings. Several studies using rats demonstrated that the intrathecal injection of opioids at doses 10 times or more than those typically employed in analgesic studies evoked segmental nocifensive behaviors.[113–115] Contrary to the low-dose OIH phenomenon, however, high-dose OIH does not seem to be mediated by opioid receptors.[113–117] Two of the key pieces of information leading to this conclusion are that opioid antagonists do not efficiently reduce this type of OIH, and the stereospecificity of high-dose OIH does not fit the specificity for binding to opioid receptors.

Two nonopioid receptor systems may contribute to these effects. The first is glycine. The intrathecal injection of glycine dose-dependently reversed the allodynia caused by the intrathecal administration of high doses of morphine.[117] These effects were compatible with the excitatory and allodynia-producing effects of intrathecal strychnine.[115] It is not clear whether these effects are mediated through the glycine binding site on the NMDA receptor or perhaps some other site.[117] Additional studies have focused on the spinal cord NMDA receptor system as mediating the hyperalgesia and allodynic effects of large doses of morphine. For example, the NMDA receptor antagonist (NMDARA) MK-801 reduced the allodynia caused by the intrathecal injection of morphine in rats.[116]

As opposed to the low-dose opioid OIH phenomenon, high-dose opioid OIH is an uncommon, but problematic, clinical phenomenon. Real-life clinical situations do not always suggest OIH as the only possible cause of the accelerating pain symptoms. Considerable clinical confidence is required to reduce opioid doses in patients experiencing large amounts of pain. For this reason, one of the maneuvers commonly recommended when faced with this uncertain situation is to rotate the opioid.[19,99,101–103] In fact, methadone seems to have particular efficacy in reducing high-dose opioid OIH.[97,101,103] This may be owing to methadone's weak NMDA receptor blocking properties.[118]

MODULATION OF OIH WITH MULTIMODAL THERAPIES

Although the precise molecular mechanisms responsible for the development of OIH are just beginning to be understood, preclinical models implicate the glutaminergic system and pathologic activation of NMDA receptors in the development of central sensitization. Consequently, clinical work in attenuating or preventing the expression of OIH has primarily focused on manipulation of the glutaminergic system, either through direct or through indirect modulation of the NMDA receptor (Table 2). Although few studies have looked directly at the modulation of OIH in humans, growing preclinical and clinical evidence suggest a role for biochemical modulation of OIH with adjuvant therapies, specifically NMDARAs, α_2-agonists, and COX-2 inhibitors (Table 3). The evidence in support of these drug targets will be discussed in the subsequent sections. However, the clinical efficacy and significance of these approaches still need to be studied in large prospective clinical trials.

Human Evidence for NMDA Receptor Modulation of OIH

The NMDA receptor is comprised of several different subunits (NR1, NR2A-D, and sometimes NR3A/B) that are differentially expressed in various

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TABLE 1. Case Reports Documenting High-dose, Opioid-induced Allodynia/Hyperalgesia

Reference	Opioid	Route	Dose	Hyperalgesia (N)	Remarks
Sjogren et al[97]	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 M with MET, SF, or ketobemidone reversed allodynia
Sjogren et al[96]	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
Wilson et al[98]	M	IT	37.5 mg/h	Spontaneous pain, allodynia not reported	N = 1; cancer pain, 50-fold reduction of IT M resolved pain aggravation
De Conno et al[99]	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
Lawlor et al[103]	M	IV	600 mg/h	Generalized allodynia, myocloni	N = 1; cancer pain, substituting M with MET reversed allodynia
Sjogren et al[101]	M	PO, IT	400-mg/d IV; 48-mg/d IT	Generalized or lumbosacral segmental allodynia, myocloni (1)	N = 3; cancer and noncancer pain (described in detail, N = 2), dose reduction or substituting M with SF, gentanyl, or MET reversed allodynia
Heger et al[102]	M	IV	105 mg/h	Generalized allodynia	N = 1; cancer pain in infant, reduction of M resolved allodynia
Parisod et al[104]	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
Mercadante et al[105]	M/MET	IV/PO	200/75 mg/d; 90/90 mg/d	Generalized allodynia	N = 2; cancer pain, switching second patient to MET did not reverse hyperalgesia
Devulder[106]	SF	IT	25-50 mg/d	Generalized allodynia of the lower body	N = 1; left lumbosciatic pain after failed back surgery, cessation of SF resolved allodynia
Mercadante et al[107]	F	TD	12 mg/d (5 patches, 100 mcg/h)	Generalized allodynia, myocloni	N = 1; cancer pain, switching to MET resolved allodynia
Guntz et al[108]	F/RF	TD/IV	1.8-mg/d F (1 patch, 75 mcg/h) and 6.3-mg RF intraoperatively over 5 h	Severe postoperative pain. Aggravation of pain with M bolus	N = 1; postoperative pain, administration of ketamine and removal of F patch dramatically reduced pain
Axelrod and Reville[109]	F/HM	TD/IV	12-mg/d F (5 patches, 100 mcg/h), HM 24 mg/h	Spontaneous pain	N = 1; cancer pain, switching to MET resulted in adequate pain control
Ackerman[110]	M/HM	IT	18-mg/d M111	Pain poorly controlled on high doses IT opioid, no myocloni or allodynia[111]	N = 1; lumbar back pain, tapering of IT opioid and substitution with anticonvulsant, TCA and NSAIDS improved pain control
Chung et al[112]	HM	IV	1890 mg/d	Aggravation of pain, myocloni, confusion, hallucinations	N = 1; cancer pain, switching to MET resulted in resolution of myocloni and resolution of pain

F indicates fentanyl; HM, hydromorphone; IT, intrathecal; IV, intravenous, M, morphine, MET, methadone; NSAIDS, nonsteroidal anti-inflammatory drugs; PO, per oral; RF, remifentanil; SF, sufentanil; TCA, tricyclic antidepressants; TD, transdermal.

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TABLE 2. Selected Studies Investigating Pharmacologic Modulation of Opioid-induced Hyperalgesia or Analgesic Tolerance in Humans

Reference	Model	Drug	Route	Target	Outcome Measure	Remarks
Dudgeon et al[119]	Cancer pain treated with morphine	DM	PO	NMDA	PS, OC	N = 65; no effect detected
Galer et al[120]	Chronic noncancer pain treated with morphine	DM	PO	NMDA	PS, OC	N = 829; no effect detected
Joly et al[43]	Remifentanil-induced postoperative hyperalgesia	K	IV	NMDA	PPH, OC	N = 75; small dose K prevents remifentanil-induced postoperative hyperalgesia
Angst et al[32]	Remifentanil-induced postinfusion aggravation of hyperalgesia (IDES model)	K	IV	NMDA	PPH	N = 10; K abolished remifentanil-induced aggravation of preexisting hyperalgesia
Koppert et al[49]	Remifentanil-induced post-infusion aggravation of hyperalgesia (IDES model)	K, C	IV	NMDA	PPH	N = 13; K abolished and C significantly attenuated remifentanil-induced aggravation of preexisting hyperalgesia
Luginbuhl et al[50]	Remifentanil-induced hyperalgesia	K	IV	NMDA	EP, PP	N = 14; no effect detected
Troster et al[47]	Remifentanil-induced post-infusion aggravation of hyperalgesia (IDES model)	PC	PO	COX-2	PPH	N = 15; preventative administration of PC reduced postinfusion hyperalgesia
Singler et al[121]	Remifentanil-induced aggravation of hyperalgesia (IDES model)	PR	IV	?NMDA or $GABA_A$[122–124]	PPH	N = 15; PR attenuates and delays development of postinfusion antianalgesia, but aggravates hyperalgesia

C indicates clonidine; COX-2, cyclooxygenase-2 enzyme; DM, dextromethorphan; EP, electrical pain; K, ketamine; IDES, intradermal electrical stimulation; OC, opioid consumption; PC, parecoxib; PP, pressure pain; PPH, pin-prick hyperalgesia assessed by von Frey hair; PR, propofol; PS, self-reported pain score.
? indicates possible target, the exact mechanism is not clear.

regions of the brain and during development.[125] The subunit expression of individual NMDA receptors can affect their binding sensitivity to neuromodulators and function.[143] Alternative splicing of these subunits further diversifies receptor expression.[144] The varied and ubiquitous expression of NMDA receptors throughout the CNS can create challenges in targeting pathologic activation of NMDA receptors while still permitting normal physiologic activation to occur. Indeed, side effects associated with first generation NMDARAs, such as ketamine and dextromethorphan, have limited their clinical utility in some patients precisely because of this reason.

Ketamine

Well known as a dissociative anesthetic, ketamine was developed for clinical use in the 1960s. It uniquely provides rapid hypnosis and analgesia while maintaining cardiovascular function with minimal depression of respiratory drive and airway muscle activity and tone.[145,146] A relatively high incidence of psychotomimetic effects, especially when used as a sole anesthetic agent, have limited its clinical use as an anesthetic agent in recent times.[147]

Although it binds to many different receptor sites, ketamine is known to be an uncompetitive antagonist of the phencyclidine binding site of the NMDA receptor, where its primary anesthetic effects are thought to occur.[148] Recently, several studies have examined the use of ketamine in low subanesthetic doses in conjunction with opioid medications in an attempt to attenuate the expression of OIH or analgesic tolerance, largely because of its NMDARA properties.

Meta-analysis of studies examining perioperative low-dose ketamine in conjunction with opioid administration found a small improvement in postoperative pain scores and delayed time to first analgesic request that were not clinically significant.[149] However, perioperative ketamine did reduce postoperative opioid consumption by 30%, but did not reduce opioid-associated side effects, except for nausea and vomiting,[150] and was not found to be a significant adjuvant to opioid administered by patient-controlled analgesia devices.[151] Despite these findings, 2 studies have shown marked reduction in postoperative wound hyperalgesia with perioperative ketamine administration consistent with attenuation of central sensitization.[134,152] Although the effect of ketamine on postoperative wound hyperalgesia is not related to OIH per se, it does suggest a role for ketamine in attenuating the expression of other conditions associated with central sensitization, such as OIH.

A recent qualitative systematic review by Bell et al[153] identified 4 randomized controlled trials of a total of 57 patients, examining the use of ketamine as an adjuvant to opioid therapy for cancer pain. They did not find sufficient evidence to support the conclusion that ketamine improves the effectiveness of opioid therapy in cancer pain.

Where ketamine has found significant benefit is in patients who require large amounts of opioid medications

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TABLE 3. Possible Drugs for Modulation of Opioid-induced Hyperalgesia in Humans

Drug Class	Site of Action	Prototype Drugs
High affinity noncompetitive NMDA receptor antagonists	NMDA receptor	MK-801[125] Phencyclidine[125]
Low-moderate affinity, open-channel noncompetitive NMDA receptor antagonists	NMDA receptor	Amantidine[126,127] CHF3381[128–130] Dextromethorphan[120,131] Ketamine[49,50,66–68,132–135] Memantine[125] Neramexane[136,137] Zenvia[138]
NR2B antagonists	NMDA receptor, NR2B subunit	Ifenprodil[139] Traxoprodil Mesylate[140,141] RGH-896[142]
COX-2 inhibitors	Cyclooxygenase-2 enzyme	Parecoxib[47]
Opioid agonist and NMDA receptor antagonist	NMDA receptor	Methadone[109,118] Ketobemidone[97]
α_2 agonist	α2 adrenergic receptor	Dexmedetomidine Clonidine[49]

COX-2 indicates cyclooxygenase-2; NMDA, *N*-methyl-D-aspartate.

or exhibit some degree of opioid tolerance.[133,154,155] Human experimental pain studies have also directly shown that administration of *S*-ketamine abolishes remifentanil-induced aggravation of hyperalgesia induced by intradermal electrical stimulation.[32,49] Joly et al[43] have recently corroborated these findings in the postsurgical patient population.

In summary, there is some evidence to show that perioperative administration of low-dose ketamine may modulate the expression of OIH or analgesic tolerance and that it reduces postoperative wound hyperalgesia after acute intraoperative opioid exposure. These findings are consistent with the hypothesis that its NMDA receptor antagonism modulates changes in antinociceptive and pronociceptive systems. However, the clinical significance of these benefits still needs to be demonstrated in larger prospective studies.

Methadone and Opioid Switching

Methadone has been shown to have weak NMDA receptor antagonism.[118] Perhaps because of this property, many case reports have shown that clinicians chose to switch patients to this opioid when OIH is suspected, such as when high doses of other opioid agents fail to improve or even aggravate chronic pain. Indeed, 6 published reports in the literature have shown that opioid rotation to methadone significantly improved or resolved suspected OIH.[97,101,103,107,109,112]

Methadone offers several advantages for opioid switching or rotation, including incomplete cross-tolerance with opioid receptors and NMDA receptor antagonism.[109,156] The conversion to methadone from other opioids is complex and the judicious use of lower conversion ratios may be indicated when patients are on high opioid doses. Vigilance for signs of methadone toxicity, including Torsades de Points, is indicated when high doses are administered.

It should be noted that methadone exposure has been linked to increased pain states in observational and cross-sectional studies of former OAs maintained on methadone.[24–28] Therefore, opioid switching to methadone should be undertaken with the understanding that it may have an intrinsic ability to activate pronociceptive pathways, despite its NMDARA properties. Indeed, 1 case report has shown aggravation of OIH with methadone and failure of methadone to reverse OIH.[105] However, these observations may have been confounded by development of renal failure and accumulation of morphine-3-glucuronide metabolites, which have been shown to produce neuroexcitatory and antianalgesic effects in some studies.[157,158]

Dextramethorphan

Dextramethorphan is a noncompetitive NMDARA typically used as a cough suppressant. There have been a number of studies indirectly examining the ability of dextromethorphan to attenuate or prevent expression of OIH or analgesic tolerance in patients on opioid therapy. Although these studies will not be reviewed here in their entirety, 1 recent study bears mentioning. In perhaps the largest clinical study of dextromethorphan and opioids to date, Galer et al[120] conducted 3 large randomized, double-blinded, placebo-controlled multicenter trials of MorphiDex (morphine and dextromethorphan mixture in a 1:1 ratio) in 829 patients with chronic noncancer pain. These patients were observed for 3 months and various indirect measures of opioid tolerance or hyperalgesia were taken, including mean change in average daily pain intensity from baseline to last 7 days on treatment and percentage change in daily morphine use from baseline to last 30 days on treatment. It might be inferred that analgesic superiority of MorphiDex or reduced morphine requirements needed to treat pain when coadministered with dextromethorphan might result from modulation of OIH or tolerance. The study did not find any significant difference between MorphiDex and morphine alone in these outcome measures. The lack of treatment effect is discordant with results in some

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TABLE 4. Ongoing Prospective Clinical Trials Examining Opioid-induced Hyperalgesia in Humans*

Study Title	Study Type and Design	Study Population	Study Information
Hyperalgesia in methadone patients: can it be treated? Dextromethorphan, gabapentin, and oxycodone to treat opioid-induced hyperalgesia	Study type: interventional. Design: randomized, double-blinded, placebo controlled, parallel assignment	Methadone maintenance patients, age 18-55 y, DSM-IV criteria for opioid dependence, taking stable dose of methadone for 6 wk before study entry	Primary outcome measures: pain response day 1436. Cold pressor, electrical stimulation. Observation period: 5 wk Start date: July 2003 Total enrollment goal: 300 Study information: PI: Margaret Compton Clinical trials identifier: NCT00218374
Opiate-induced tolerance and hyperalgesia in pain patients	Study type: interventional. Design: randomized, double-blinded, placebo controlled, single assignment	Chronic back pain patients, age 18-70 y, opioid-naive (or < 4 vicodin equivalent/d), candidate for opioid therapy	Primary outcome measure: change in pain response (cold pressor) at 1 mo compared with baseline measurement Observation period: 1 mo Start date: October 2005 Total enrollment goal: 160 PI: Larry Chu Clinical trials identifier: NCT00246532
Fentanyl ultralow doses effects on the nociceptive threshold: towards a simple pharmacologic test able to predict pain vulnerability, postoperative hyperalgesia development risk	Study type: interventional. Design: treatment, randomized, double-blinded, placebo controlled, cross-over assignment	Healthy adult male volunteers, age 18-40 y, weight 60-85 kg, ASA I Group assignment: "operated" (history of perioperative opioid exposure), "healthy" (no history of surgery)	Primary outcome measure: pain tolerance Total enrollment goal: 48 Start date: March 2007 PI: Philippe Richebe Clinical trials identifier: NCT00454259
A GCRC study: a comparison of the addiction liability of hydrocodone and sustained release morphine	Study type: interventional. Design: randomized, double-blinded, placebo controlled, cross-over assignment	Chronic pain patients, taking > 80 mg morphine equivalent/d, referred to pain or substance abuse clinic for self-escalation of opioids	Outcome measure: cold pressor testing for opioid-induced hyperalgesia Demonstrate that opioid-induced hyperalgesia differs among prescription opioids Total enrollment goal: 12 Start date: November 2005 PI: Barth L. Wilsey Clinical trials identifier: NCT00314340
RAPIP study: clinical trial on remifentanil for analgesia and sedation of ventilated neonates and infants	Study type: interventional. Design: randomized, double-blinded, active control, parallel assignment	Ventilated term newborns and infants (≤60 d), expected duration of ventilation between 12and 96 h	Outcome measure: occurrence of hyperalgesia after opioid infusion evaluated by cutaneous flexor reflex with von Frey hairs Total enrollment goal: 20 Start date: November 2006 PI: Bernhard Roth Clinical trials identifier: NCT00419601

*On the basis of *http://www.clinicaltrials.gov* accessed on May 27, 2007.
ASA I indicates American Society of Anesthesiologist physical classification status I; DSM-IV, diagnostic and statistical manual of mental disorders, 4th edition; GCRC, general clinical research center; PI, Principal Investigator.

animal studies and early clinical trials[159–161] and may be the result of insufficient dextromethorphan dose. Further clinical studies will need to be conducted to elucidate these findings.

Future Work in NMDA Receptor Modulation

Recently, new strategies for attenuating or inhibiting pathologic activation of NMDA receptors and their resulting excitotoxicity as a target for neuroprotection have been proposed.[162] To develop NMDARAs with clinically acceptable side effect profiles, it has been proposed that a drug must block excessive or pathologic activation of NMDAR while leaving normal receptor function intact. Open-channel NMDAR blockers provide this function because the antagonists enter the ion channel only when it is in an open or activated state. Therefore, this type of drug will be most active during excessive receptor activation and exhibit significantly less blockade of normal physiologic NMDAR activation.[162–167]

Chen et al[164] have also shown that off-rate from channel block is another important determinant of clinical tolerability of NMDARAs.[165] If a drug binds with too high an affinity or remains in the channel for too

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long, it can accumulate in the channel and progressively block critical normal cellular functions.[125] A drug with low affinity and too short a dwell time would not function well as a receptor antagonist. Therefore, it has been proposed that subsequent generations of NMDARAs should be low-affinity, open-channel blockers with relatively fast off-rates to prevent excessive receptor activation in pathologic states while not substantially interfering with normal synaptic transmission. The prototype drug with these properties is memantine (MEM).[125]

MEM (1-amino-3,5-dimethyl-adamantane) is a derivative of the anti-influenza agent amantadine and has been used to treat various neurologic disorders for more than 20 years.[168] The drug is clinically well tolerated by patients when used for the treatment of Alzheimer disease[169,170] and for prolonged periods of time.[171] MEM has been shown to reduce hyperalgesia in animal models.[172–174] There is also clinical evidence for the use of MEM in the treatment of pathologic pain states. A recent case series reported results of MEM therapy in 6 patients with 1 upper extremity affected by complex regional pain syndrome after injury. The authors found improvement in pain, motor, and autonomic changes and also functional magnetic resonance imaging-documented changes in the somatosensory cortex reflecting cortical reorganization comparable with the unaffected limb after 6 months of MEM therapy.[175] Other studies of human immunodeficiency virus-induced peripheral neuropathy,[176] postherpetic neuralgia,[177,178] and phantom limb[179] pain found that although the drug was well tolerated, it did not significantly improve pain. These mixed findings may be owing to dose-dependent effects or simply reflect varying efficacy with different types of neuropathic pain. Recently, another moderate-affinity uncompetitive NMDA antagonist, neramexane, has shown analgesic properties in human experimental pain models of neurogenic hyperalgesia.[136] CHF3381, a low-affinity NMDA and reversible monoamine oxidase-A inhibitor has also been shown to attenuate secondary hyperalgesia in human experimental pain models.[128]

There has been significant interest in another therapeutic target for NMDAR modulation, the development of antagonists for the NR2B subunit.[180] NMDA receptors with NR2B subunits have been localized to primary afferent neurons[181] and the dorsal horn of the spinal cord.[140] Therefore, specific targeting of these subunits may allow suppression of pathologic NMDA activation involving nociceptive pathways, while still allowing normal physiologic functioning in other areas of the CNS to occur. This approach may allow development of clinically tolerated drugs with more acceptable side effect profiles by specifically targeting nociceptive pathways. Ifenprodil is a prototype drug of this category,[139] though other drugs such as RGH-896 are in phase IIB clinical trials for neuropathic pain.[142] The clinical utility and tolerability of these agents for neuropathic pain and modulation of OIH and analgesic tolerance remain to be studied.

Propofol

Recent evidence suggests propofol may have some modulatory effect on OIH, possibly through interactions with γ-aminobutyric acid ($GABA_A$) receptors at the supraspinal level.[121,182] Specifically, propofol was shown to have analgesic effects at subhypnotic doses, and it delayed the onset of antianalgesia after remifentanil infusion in a small clinical study of healthy human volunteers.[121] However, it actually aggravated postremifentanil infusion secondary hyperalgesia in the intradermal electrical stimulation pain model, suggesting a facilitation of pronociceptive pathways, possibly through modulation of descending inhibition by receptor binding to the $GABA_A$ ionophore.[182] The clinical significance of these findings, especially in higher dosages used in the intraoperative setting, remains to be studied.

COX-2 Inhibitors

As we have already discussed, OIH is thought to be because of the sensitization of pronociceptive pathways in the CNS through various mechanisms of which NMDA receptors have been largely implicated. Interestingly, prostaglandins have also been shown to modulate nociceptive processing[183] and are able to stimulate the release of the excitatory amino acid glutamate in spinal cord dorsal horns.[184] COX inhibitors have also been shown to antagonize NMDA receptor function in the CNS[185,186] and to attenuate development of opioid tolerance in animals.[187,188] Therefore, it is reasonable to hypothesize that inhibition of prostaglandin synthesis in the spinal cord may attenuate or inhibit expression of OIH by modulating NMDA receptor function.

Indeed, recent evidence suggests a role for COX-2 inhibitors in the modulation of OIH in humans. Troster et al[47] found attenuation of remifentanil-induced aggravation of hyperalgesia skin produced in an intradermal electrical stimulation model. Importantly, the authors note that they only observed this effect when the COX-2 inhibitor parecoxib was administered before opioid exposure and not when infused concurrently with opioid. It is also significant to note that parecoxib did not return hyperalgesic levels to that of baseline controls in a manner that had been previously observed with the NMDARA *S*-ketamine.[32,49] These findings suggest a possible role for prostaglandins in sensitizing nociceptive systems before pathologic activation, and that although OIH is modulated by COX-2 activity, it probably has less important role than NMDA receptor system, at least in human experimental pain models after acute opioid exposure.

α_2-receptor Agonists

A small number of studies have examined the role of α_2-receptor agonists in modulating OIH. Koppert et al found that the NMDARA *S*-ketamine, when coadministered during acute opioid exposure, abolished opioid-induced postinfusion secondary hyperalgesia, but had no effect on postinfusion antianalgesia. In this same setting,

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the α_2 agonist clonidine attenuated opioid-induced postinfusion antianalgesia and abolished opioid-induced postinfusion secondary hyperalgesia. These data suggest a possible role for α_2 agonists in OIH modulation.

In contrast to these results, a study by Quartilho et al[189] found that a single injection of clonidine produced transient antinociception with delayed thermal hypersensitivity after 24 to 30 hours in rats. These effects were prevented with coadministration of the α_2 antagonist idazoxan. However, it should be noted that Davies et al[190] did not see hyperalgesia after cessation of chronic administration of the α_2 agonist dexmedetomidine in mice.

In summary, animal studies provide mixed evidence for the ability of α_2 agonists to directly cause hyperalgesia whereas human studies provide direct evidence in support of the ability for these drugs to attenuate expression of OIH in human experimental pain models after acute opioid exposure. Further studies will be needed to evaluate the use of these drugs to modulate OIH, particularly in the area of postoperative pain management, which has already shown some interest in the use of these medications to improve analgesia and decrease wound hyperalgesia.[191]

CONCLUSION

Existing clinical data generally support the development of OIH in a few specific settings such as former OAs receiving methadone maintenance therapy or after acute remifentanil exposure in human volunteer and postsurgical pain cohorts. To date, only 1 observational study in a small series of 6 patients has prospectively documented the development of OIH in opioid-naive chronic pain patients after 1 month of oral morphine therapy using quantitative sensory pain measurements.[53] Future studies will need to further explore the conditions under which OIH is expressed through high quality prospective trials that directly document the development of OIH using appropriate assessments of pain sensitivity and clarify its clinical significance. It is also important to understand the impact of OIH in the acute postsurgical setting and on the management of chronic pain with opioids, to determine if it may contribute to the development of chronic pain, to develop algorithms or diagnostic tests to allow us to identify patients at risk for developing OIH, and to determine if its expression can be attenuated or even reversed through pharmacologic modulation.

Already, it seems several ongoing prospective clinical trials are attempting to address these issues (Table 4). An ongoing National Institutes of Health-funded randomized, double-blinded placebo-controlled clinical trial by Chu and colleagues[53] is designed to directly measure the development of OIH or tolerance in patients with chronic back pain after 1 month of oral morphine therapy using cold pressor and phasic heat pain models. This work is an extension of a previously published small observational study that validated the methodology used in this larger trial. RAPIP, an ongoing randomized double-blinded active controlled study by Roth and colleagues,[9] is designed to look at the occurrence of hyperalgesia as a secondary outcome measure in ventilated term newborns and infants ($\leq$60 d) after remifentanil infusion as evaluated by cutaneous flexor reflex measurements with von Frey hairs. A randomized double-blinded placebo-controlled crossover study by Wilsey (Table 4) is looking at differences in the expression of OIH between sustained release morphine and hydrocodone in chronic pain patients referred to pain or substance abuse clinics for self-escalation of opioids as evaluated by cold pressor pain testing. In an attempt to clinically correlate preclinical observations of ultralow-dose opioid exposure and hyperalgesia,[89,90] Fentanyl Ultra Low Dose, a randomized double-blinded placebo-controlled study by Richebe (Table 4) will examine the role of ultralow doses of opioid in altering experimentally measured nociceptive thresholds in healthy human volunteers. Interestingly, the study also plans to examine the correlation of previous history of opioid exposure and pain with the development of nociceptive changes as a possible predictive test to identify patients at risk for postoperative hyperalgesia. Finally, Compton is looking at the treatment or reversibility of OIH in former OAs on methadone maintenance therapy in a 5-week randomized double-blinded placebo-controlled study of dextromethorphan, gabapentin, and oxycodone as evaluated by cold pressor and electrical stimulation pain models.

In summary, clinicians need to be vigilant for the possibility that opioid therapy may sensitize pronociceptive pathways and may impair treatment of pain or even aggravate preexisting pain, particularly if aggressively escalated or dosed (Table 1). It would seem reasonable to discuss the possible adverse impact of OIH with patients initiating opioid therapy. Clinicians should suspect expression of OIH when opioid treatment effect seems to wane in the absence of disease progression, particularly if found in the context of unexplained pain reports or diffuse allodynia unassociated with the site of injury.

Reasonable approaches to modulate expression of OIH in patients at risk or suspected of having OIH include reduction of opioid dose or careful opioid titration, opioid rotation, avoiding periods of relative opioid abstinence and withdrawal, or instituting multimodal analgesia with adjuvant therapies such as nonsteroidal anti-inflammatory drugs, COX-2 inhibitors, NMDARAs, and regional or neuraxial anesthetic techniques where appropriate. Recently, Miaskowski et al[192] have questioned the adequacy of scheduled opioid dosing in the treatment of chronic pain when compared with "as needed" dosing regimens. Indeed, the authors found that patients randomized to scheduled opioid dosing received 12.4 times more opioid than the "as needed" group, yet did not demonstrate improved analgesic efficacy as measured by Verbal Pain Score over time and duration of pain. It is possible that higher opioid doses associated with scheduled opioid dosing may lead to greater expression of OIH or analgesic tolerance. Further work

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is needed to determine if alternative dosing regimens can improve opioid efficacy by modulating expression of OIH or analgesic tolerance. Our understanding of OIH is only beginning. Ongoing and future human studies will help to further elucidate the clinical implications of OIH and hopefully lead to new ways to attenuate or even reverse expression of this potentially troublesome clinical phenomenon.

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