Research Article

The Evidence for Opioid-Induced Hyperalgesia Today

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Abstract

Hyperalgesia is an increased response to painful sensation. Opioid-induced hyperalgesia occurs after sustained opioid exposure and/or following abrupt cessation of opioid. At the cellular level, adenylyl cyclase superactivation and elevated cAMP levels lead to PKA-mediated enhanced neurotransmitter release. Spinal glutamate, substance P, and CGRP enhance pain through NMDA, NK-1, and CGRP receptors respectively. Non-opioid receptor mediated OIH may be caused by M3G activation of TLR4. In controlled human experiments OIH is evident to cold pain, but less consistently found with pain caused by other modalities such as heat, electricity, or pressure. Hyperalgesia detected in response to cold pain can be reduced by the NMDA antagonist ketamine. Patients on methadone maintenance also show an increased sensitivity to nociception between doses. Multi-modal analgesia may be the best strategy for treatment of OIH in the clinical setting.

Keywords: Hyperalgesia; Opioid; Nociception; Ketamine

Introduction

Nearly all clinicians know that when they prescribe opioid medications to treat their patient's pain, they are balancing against the risk of tolerance and addiction, overdose and death. What they know less about is that high-dose opioids, as an intra-operative infusion or as an oral home dose, could make the pain worse under certain conditions. This latter situation is called Opioid-Induced Hyperalgesia (OIH) and is defined as an increased response to a painful stimulus caused by exposure to opioids. The paradox of potentially doing harm when trying to provide relief is antithetical to a clinician's sworn oath, so if real, must be recognized and avoided.

Is OIH real in humans, and if it is real, is it relevant? After 3 decades of research, the question is still being asked [1]. Since the early observation that patients on morphine had a lower threshold for pain [2,3], *in vitro* cell studies and *in vivo* animal studies have proceeded to uncover the potential mechanisms. Case reports and clinical studies of OIH are appearing with increased frequency. Models to empirically measure OIH in humans have been developed, and are used to detect hyperalgesia in these controlled situations. Still, what is its relevance in the clinic?

Clinically OIH may occur with chronic oral opioid consumption or after intra-operative intravenous infusions of opioid. In methadone maintained populations the threshold for pain sensation is decreased. After remifentanil infusions, post-operative hyperalgesia is presumed due to increased pain scores and opioid requirement. In either scenario, what are the clinician's options? Withholding pain-relieving opioids is not the complete answer, but opioid-sparing techniques may be at least part of it.

It seems more obvious that the chronically treated patient may be subject to a relatively increased disservice by the prescription of opioids compared to the surgical patient that is given an intra-operative infusion. If methadone-maintained patients are more sensitive to pain, preventing ongoing suffering or managing perioperative pain becomes a challenge. Compare this to the patient exposed intra-operatively to a remifentanil infusion who is requiring more morphine in the recovery room. A transient increased use of morphine to become comfortable seems to be an appropriate measure and trade-off for preventing intra-operative severe surgical pain, especially if there are no long-term downsides. On the other hand, if there are options that can prevent hyperalgesia and also provide equal relief from pain then we are obligated to use them.

This review provides an overview of the evidence for OIH. First, *in vitro* cell models and *in vivo* animal models are reviewed followed by up-to-date evidence from human trials. Reference tables were created to show all human trials published to date. Several good reviews have been published on this topic that deal with the potential mechanisms in great depth [4,5]. This review emphasizes the evidence for OIH in humans in order to serve as a reference for clinicians.

Background

Hyperalgesia is an increased response to a painful stimulus. The injured organism is more sensitive to pain and thereby is encouraged to guard against further injury while the healing occurs. Chronic pain is the pathological extension of allodynia or hyperalgesia beyond the normal healing period.

The establishment of hyperalgesia is known to have a central mechanism. Peripheral injury may directly damage nerve and surrounding tissue inducing the release of an inflammatory milieu that facilitates transmission of pain. Continual pain stimulus results in plastic changes in the dorsal horn of the spinal cord that decrease the threshold to pain sensation for surrounding neural inputs. Descending pain-inhibiting pathways are themselves inhibited. Over time, as the wound heals and the barrage of peripheral pain stimuli decreases, hyperalgesia lessens and disappears. On the other hand, a continuous exogenous stimulus may cause hyperalgesia to persist. Continued delivery of exogenous opioids induces downstream mechanisms that result in opioid tolerance and hyperalgesia.

***In vitro* studies of the cellular mechanism of opioid-**

induced hyperalgesia

In vitro studies of OIH have used mammalian cell cultures or acute tissue preparations to reveal several potential underlying mechanisms (Table 1). Prolonged opioid exposure causes changes in opioid-receptor mediated, and opioid-receptor independent downstream second messenger systems that may persist beyond the duration of opioid exposure. Mechanisms underlying hyperalgesia may involve both primary neurons as well as changes in glia. We first look at the opioid receptor-mediated mechanisms.

μ-Opioid receptor mechanisms

Opioid receptors concentrate in peripheral nociceptive fibers that synapse centrally upon spinal dorsal horn neurons, and in pathways descending from the rostral ventral medial medulla to the spinal cord [6,7]. When exogenous opioids activate opioid receptors, a cascade of changes in down-stream second messenger systems leads to decreased neuronal transmission of pain (Figure 1A). Opioid receptors belong to the class of seven- transmembrane domain G-protein coupled inhibitory receptors, so when opioid ligand binds to the receptor they, in turn, activate Gi/o which dissociates into its α and β/γ subunits [8]. Gi/o α inhibits adenylyl cyclase (AC) activity, downstream levels of cyclic adenosine monophosphate (cAMP) are reduced, and protein kinase activity is reduced [9]. Potassium channels are made more permeable while calcium channels become less permeable, causing presynaptic terminals to hyperpolarize and decreasing the release of glutamate and substance P [7,10-12]. Postsynaptic terminals are also hyperpolarized resulting in decreased neuronal excitability and reduced signal transduction [7]. With respect to pain signal sensitivity and transmission, the neuronal cell becomes quiescent.
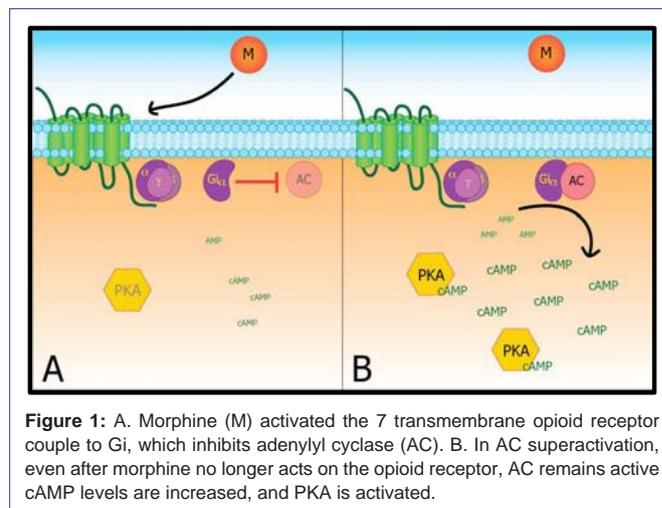
In chronic opioid exposure, *in vitro* studies show the situation is nearly reversed (Figure 1B). Chronic opioid activation of μ-, δ-, or κ- receptors transfected into neuronal cell types leads to Raf-1 mediated phosphorylation of AC [13]. Raf-1 phosphorylation of AC increases its activity [14], a process now commonly called AC "super activation" [15]. This leads to increased cAMP production and augmentation of protein kinase A (PKA), which in turn enhances the release of pain neurotransmitters such as calcitonin gene-related peptide [16-18]. Calcitonin gene-related peptide release may also be augmented by sustained morphine-induced AC sensitivity to excitatory pathways, such as prostaglandin E2 (PGE2) coupled to Gs [19].

Under short-term opioid exposure, the capsaicin and noxious heat sensitive transient receptor potential vanilloid 1 (TRPV1) voltage-gated ion channel is inhibited in the presence of low cAMP levels [20]. After sustained morphine exposure labeling of TRPV1 in the DRG is increased [21].

In this activated state, cellular signaling of pain is restored, and

Table 1: *In vitro* models used to study opioid/induced hyperalgesia.

Model	Representative References
Chinese hamster ovary (CHO) cells	[9,13]
Dissociated dorsal root ganglion (DRG) of rat	[10,12,16-18,20,24]
African green monkey kidney COS-7 cells	[15]
Premotor cardiac parasympathetic nucleus ambiguous neurons of rat	[11]
Human embryonic kidney 293 (HEK-293) cells	[14,20,25]

Figure 1: A. Morphine (M) activated the 7 transmembrane opioid receptor couple to Gi, which inhibits adenylyl cyclase (AC). B. In AC superactivation, even after morphine no longer acts on the opioid receptor, AC remains active cAMP levels are increased, and PKA is activated.

it now requires increased doses of opioid to reinstitute the quiescent state. When opioids are stopped, either through washout or blocked, AC supersensitization persists and synaptic strength is facilitated in a process called opioid withdrawal long-term potentiation (LTP) [22,23]. Persistent AC supersensitization and opioid withdrawal LTP may underlie OIH.

Opioid receptor-independent mechanism

Opioid receptor independent mechanisms of OIH exist. Morphine-3-glucuronide (M3G), a liver metabolite of morphine, increases neuronal excitability via Toll-like receptors (TLR) [24,25]. Morphine activation of TLR4, concentrated in spinal microglia, causes the release of interleukin-1, and tumor necrosis factor (TNF-α) [25]. Toll-like receptor antagonists have been identified as possible treatments for alleviation of glial sustained hyperalgesia [26,27]. Suppression of inhibition by glia on lamina I neurons of the spinal dorsal horn may contribute to enhanced transmission and decreased threshold in these neurons during hyperalgesic states [28]. Ferrini showed prolonged exposure to morphine activated the purinoceptor, P2X4R, in microglia and caused the release of brain-derived neurotrophic factor (BDNF) [28]. Block of BDNF receptor, tropomyosin related kinase B (TrkB), signaling prevented OIH and OIH was absent in mice lacking BDNF in microglia [28]. Morphine may also cause hyperalgesia independent of the μ-opioid receptor or M3G [29]. The complete story of morphine-induced hyperalgesia is not yet clear.

In vivo studies of opioid-induced hyperalgesia

Animal tests: In animals, experimental protocols to induce OIH consist of oral, subcutaneous (S.C), intravenous, intraperitoneal, or intrathecal injection of opioid [30]. Repetitive, continuous, or intermittent opioid dosing protocols can induce hyperalgesia after discontinuation or precipitated withdrawal by opioid receptor antagonists [31]. After prolonged high doses of opioid periods of hyperalgesia can last hours to days [30,32].

Hyperalgesia is measured by mechanical, thermal, or electrical nociceptive tests (Table 2). With OIH the withdrawal thresholds are reduced and withdrawal and response latencies are shorter for these tests. For a thorough list of animal studies of OIH see table 3 in Angst

Table 2: *In vivo* models used to study opioid/ induced hyperalgesia.

Modality	Model	Description	References
Mechanical pressure pain	Withdrawal threshold	Calibrated von Frey filaments are applied to the hind foot and the smallest filament that elicits a withdrawal response is considered to be the withdrawal threshold.	[57]
	Paw pressure withdrawal or vocalization tests	The threshold to paw withdrawal is measured while a pressure pad is applied to the metacarpal of the toe.	[63]
Thermal pain	Tail flick test	Radiant heat is applied to the tail or the tail is placed in hot water which causes the animal to flick its tail out of the way. The Time to withdrawal of the tail is measured as the withdrawal latency.	[36,38, 43,48]
	Paw withdrawal test	Radiant heat is applied under the animal's foot. The Time to withdrawal is measured. This test is more sensitive than the tail flick test.	[38]
Electrical pain	Hot plate test	An animal is placed on a hot plate of variable temperature. When the animal licks its feet, or jumps off the plate the response latency is recorded.	[34,37]
	Electrical shock tail vocalization test	The threshold to vocalization is measured with electrode delivered current to the tail.	[36]

and Clark [30].

Peripheral delivery: In early animal investigations it was reported that repeated peripheral administration of morphine to guinea pigs caused hyperesthesia once the analgesia had worn off [33]. Kayan and Mitchell reported a decreased threshold to thermal hot plate test after repeated injection of morphine S.C. [34].

Central delivery: By injecting opiate intrathecally, the direct effects of centrally mediated analgesia and hyperalgesia are measured. While investigating the effects of spinal opioid pain relief, it was discovered that high doses of intrathecal morphine paradoxically caused hypersensitivity in rats [35-37]. The effect was reproduced by injection of morphine-3-glucuronide (M3G), indicating that both opioid receptor dependent and independent mechanisms of hyperalgesia exist [37].

Excitatory amino acid signaling in the spinal cord may be responsible for OIH just as it is for hyperalgesia and central sensitization due to peripheral nerve injury, chronic inflammation, and neuropathic pain [38-40]. Following 8 days of intrathecal morphine injection, rats developed tolerance and hyperalgesia measured by tail- flick and foot withdrawal tests. The hyperalgesia was prevented and reversed by intrathecal injection of dizocilpine, also known as MK 801, an N-methyl-D-aspartate (NMDA) receptor antagonist [38]. Single subcutaneous doses of heroin decreased pain threshold in rats which was blocked by NMDA antagonists MK 801 [41] and ketamine [31]. Fentanyl-induced hyperalgesia was also blocked by pretreatment with ketamine [32,42]. L-methadone caused thermal hyperalgesia, while the racemic isomer d-methadone prevented it, perhaps through its action on the NMDA receptor [43]. On the other hand, in one small study of methadone-induced thermal hyperalgesia memantine, a weaker NMDA antagonist than ketamine, failed to alter the nociceptive threshold [44]. Repeated morphine

administration reduced spinal glutamate transporter, GLT-1, which is responsible for clearance of glutamate [45]. The beta-lactam antibiotic, ceftriaxone, inhibited OIH by up regulating GLT-1 [45]. NMDA receptor messenger RNA (mRNA) expression decreased during sub acute exposure to morphine, but returned to baseline with chronic treatment [46]. Ketamine co-administration prevented this effect on NMDA receptor mRNA expression [46]. Glycogen synthase kinase-3β (GSK-3β) modulates NMDA receptor trafficking. Inhibition of GSK-3β prevented remifentanil-induced hyperalgesia [47]. Enhanced glutamatergic signaling in the central nervous system is triggered by opioid exposure and measurable in behavioral tests of hyperalgesia, consistent with the aforementioned *in vitro* studies [36].

Excitability of nociceptive pathways in OIH extends beyond glutamatergic signaling systems. Neurokinin 1 (NK-1) cells are expressed in lamina I of the spinal dorsal horn and project to supraspinal areas that mediate pain processing [48]. Activated ascending NK-1 receptor expressing cells signal descending facilitation via serotonergic projections to the dorsal horn [49]. Opioid-induced hyperalgesia is characterized by an increase in spinal dynorphin [50], substance P [50,51] and calcitonin gene-related peptide (CGRP) levels [49,51]. Substance P activates NK-1 receptors and causes internalization similar to what occurs in the spinal cord during chronic inflammation [51]. When injected intrathecally, substance P induced pain, while dynorphin antiserum prevented morphine-induced abnormal pain [50]. Ablation of NK-1 expressing cells prevented morphine-induced thermal hyperalgesia, FOS expression, and the up regulation of dynorphin [48]. Intrathecal injection of anti-inflammatory cyclooxygenase inhibitors blocked glutamate- and substance P-induced hyperalgesia [52]. Similarly intrathecal ibuprofen reversed hyperalgesia during opioid withdrawal [53]. Descending facilitation and OIH are blocked by serotonin antagonists, ondansetron and granisetron [48,49,51,54,55]. The excitatory state described in *in vitro* studies of OIH is supported by *in vivo* characterization of neuronal ascending and descending nociceptive signaling pathways.

While it is generally accepted now that OIH involves excitation of nociceptive pathways, there is still limited insight into the second messenger systems. Tumati extended their *in vitro* studies of the role of PKA through small interfering RNA (siRNA) knockdown of spinal PKA [56] *in vivo*. Knockdown attenuated sustained morphine-induced thermal hyperalgesia indicating that OIH is mediated by spinal PKA and cAMP mechanisms [56]. The downstream effects of opioid receptor activation also depend on protein kinase C (PKC) [40]. Intrathecal injection of the ganglioside GM1, a PKC inhibitor, along with morphine prevented OIH [38]. Fentanyl-induced hyperalgesia was prevented in knock-out mice lacking PKCγ gene [57]. Pretreatment of rats with intrathecal chelerythrine, a PKC inhibitor also prevented OIH [58].

The TRPV1 channel is inhibited by µ-opioid receptor mediated decreases in cAMP [20]. During opioid withdrawal, uncovered AC superactivation and elevated cAMP increased capsaicin-induced TRPV1 activity [20]. Subcutaneous morphine in TRPV1 wild-type mice produced thermal and tactile hypersensitivity but not in TRPV1 knockout mice [59]. This is consistent with *in vitro* studies mentioned above (Figure 1).

Opioid receptor independent mechanisms of OIH may exist. The

morphine metabolite, M3G, is inactive at opioid receptors, yet is able to cause hyperalgesia [36,37,59]. M3G caused hyperalgesia without analgesia in opioid-receptor knockout mice [60]. Opioid–induced increases in spinal dynorphin may bind to bradykinin receptors and induce hyperalgesia. Sufentanil-induced hyperalgesia was found in wild-type but not bradykinin receptor (B2R) knockout mice [61].

Gabapentin and pregabalin act on the α2δ subunit of voltage gated calcium channels and are effective in the management of neuropathic pain, a modality involving central sensitization [62]. Intraperitoneal and intrathecal gabapentin dose dependently prevented a decrease in pain threshold in the paw pressure test after fentanyl-induced hyperalgesia [55,63,64]. Gabapentin acted synergistically to prevent OIH when combined with ketamine [42].

Genetic Susceptibility

Different rodent strains show differences in their susceptibility to OIH suggesting a genetic role. Spontaneously hypertensive rats (SHR) were more likely to develop hyperalgesia to hot plate test during morphine administration [65]. New genetic haplotype mapping techniques have identified variants of the beta- receptor and the P-glycoprotein transporter up-regulated in OIH that predispose certain animal strains to hyperalgesia [54,66,67]. Morphine induced-hyperalgesia was more pronounced, occurred earlier, and persisted longer in female, compared to male, Sprague-Dawley rats [68,69]. During morphine-induced hyperalgesia epigenetic regulation through histone acetylation seems to maintain and prolong the duration of hyperalgesia [70].

In summary, behavioral animal studies have provided insight into multiple mechanisms by which opioids may induce hyperalgesia. Centrally, the mechanism is NMDA dependent. Opioid-induced hyperalgesia is characterized by enhancement of nociceptive signaling via ascending and descending pathways in the spinal cord. Animal studies agree with cell models, that there are both PKA and PKC contributions to OIH. *In vivo* studies introduced the possibility that genetic variance plays a role in mammalian susceptibility to OIH.

Human studies of opioid-induced hyperalgesia

Clinically, hyperalgesia has been recognized for over a century [2,3]. With the introduction of several newer opioid agonists into clinical practice, a different propensity toward hyperalgesia has been noticed. Most of the early observational studies, case reports, and clinical trials of hyperalgesia involved patients on methadone or remifentanil (Table 3), opioid agonists of very different pharmacokinetic and dynamic properties. Remifentanil is an ultra-short acting opioid analgesic commonly used as an intra-operative infusion. Remifentanil-induced opioid hyperalgesia occurs after the infusion has been stopped in the recovery room and thereafter. Methadone, on the other hand, is prescribed as a maintenance medication in lieu of opioids of abuse. Early observational research showed that patients on chronic methadone may be more sensitive to pain [71-73]. Clinical studies of OIH look at its expression under these 2 relative conditions: in the immediate post-surgical phase following intra-operative infusions of opioids, or during chronic oral consumption. Our search found 21 clinical studies of remifentanil-induced hyperalgesia (Table 3), 10 studies of hyperalgesia in patients on methadone, and 10 remaining studies of other opioids (Table 3), not including case reports.

Hyperalgesia during remifentanil withdrawal

Hyperalgesia in the period after remifentanil infusion is the most frequently tested model for studying OIH in humans. Unfortunately most studies are underpowered, testing methods differ, and outcomes are inconsistent. In a series of small, randomized, controlled trials volunteers underwent remifentanil infusion under experimental conditions [74-80]. In two studies remifentanil hyperalgesia was evaluated by testing the expansion of a localized area of hyperalgesia created with heat and capsaicin [74,77]. Post-infusion painscores measured by visual analog scale (VAS) were increased to heat pain using a thermode [75] and the measured area of hyperalgesia was increased up to 4 hours after infusion [74,77]. Area of hyperalgesia was also expanded after remifentanil infusion in a model using transcutaneous electrical stimulation to create a region of hyperalgesia [75,78-84]. In 2 of these studies pain intensity scores were not significantly different from controls [79,81] but were significant in 3 studies [80,82,83].

Prospective studies of surgical patients where remifentanil was used have enrolled more patients and consistently shown increased post-operative pain [85-87]. Only Guignard et al. [85] and Lee et al. [87] found an increase in post-operative morphine consumption.

Hyperalgesia in patients on methadone

Prospective trials analyzed pain tolerance in opioid addicted patients transitioned to methadone maintenance, or patients with chronic pain on methadone (Table 4). In most trials methadone users were less tolerant of cold pain during the cold pressor test than nonusers [71,72,88-93] but in Pud et al. threshold to cold pain was increased [94]. No hyperalgesia to mechanical pain tests was found in patients on methadone [92,95]. Two underpowered studies found methadone maintained patients to be less tolerant but have unchanged pain detection thresholds to electrical stimuli [72,95], while another showed increased threshold to electrical pain [92]. Methadone-induced hyperalgesia is poorly supported. Most of the evidence for it comes from too few investigating groups with conflicting outcomes.

Hyperalgesia reports with other opioids

Of the remaining published studies of OIH, 2 are prospective, randomized, double-blinded, and placebo-controlled trials (Table 5) [75,96]. The first trial was done in a crossover format involving 12 patients exposed to an alfentanil infusion [76]. The area of focal hyperalgesia induced by transcutaneous electrical stimulation was measured before and after alfentanil infusion and found to be insignificant. Chu et al. performed a preliminary observational trial of patients with chronic low back pain and showed that after 1- month of oral morphine, pain threshold and tolerance to cold, but not heat, pain were reduced [97]. The follow-up controlled trial randomized 102 chronic low back pain patients to 1- month of morphine treatment versus placebo, and then evaluated hyperalgesia after remifentanil infusion [96]. No difference was found between groups for cold or heat pain. On the other hand, one study found that decreased heat pain threshold and exacerbated temporal summation of the second pain may be characteristic quantitative sensory test (QST) changes in

Table 3: Clinical Research Trials of Opioid-Induced Hyperalgesia with Remifentanil.

Reference	Model	Study Design	Opioid	Route	Outcome Measure	Details, Results
[85]	remifentanil infusion for major abdominal surgery	randomized, controlled,	remifentanil	IV	postop VAS and morphine consumption	n=50, high intraop remifentanil dose caused increased postop VAS and morphine consumption
[74]	remifentanil infusion; heat and capsaicin-induced hyperalgesia (punctate hyperalgesia with von Frey), thermode induced heat pain	Double-blinded, placebo-controlled	remifentanil	IV	VAS, area of punctate hyperalgesia	n=14, post-remifentanil infusion VAS was increased to heat pain, area of hyperalgesia was increased compared to placebo, but not compared to pre-remi baseline
[75]	remifentanil infusion vs. remi+ketamine; IM needle stim, transcutaneous electrical stim, pressure pain	randomized, double-blind, placebo-controlled, crossover	remifentanil	IV	pain threshold, pain tolerance	n=12, post-remifentanil infusion patients have lower tolerance to pressure pain not prevented with ketamine, none or increased tolerance to electrical stim
[78]	remifentanil infusion; transcutaneous electrical stim-induced hyperalgesia (punctate hyperalgesia with von Frey)	randomized, double-blind, placebo-controlled	remifentanil	IV	area of punctate hyperalgesia	n=13, male, post-remifentanil infusion area of punctate hyperalgesia expanded, but not post ketamine or clonidine infusion
[77]	remifentanil infusion; heat and capsaicin induced hyperalgesia (punctate hyperalgesia with von Frey)		remifentanil	IV	area of punctate hyperalgesia	n=10, post-remifentanil infusion area of punctate hyperalgesia expanded at 4 hours
[81]	remifentanil infusion; transcutaneous electrical stim-induced hyperalgesia (punctate hyperalgesia with von Frey), transdermal electrode stim	randomized, double-blind, placebo-controlled, cross over	remifentanil	IV	NRS, area of punctate hyperalgesia	n=13, post-saline control slightly expanded area of hyperalgesia but not NRS, whereas post-remifentanil infusion area of hyperalgesia greatly expanded but not NRS; post-naloxone infusion expanded area of hyperalgesia but by less
[79]	remifentanil infusion; transcutaneous electrical stim-induced hyperalgesia (punctate hyperalgesia with probe), thermode induced heat pain	randomized, double-blind, placebo-controlled, cross-over	remifentanil	IV	VAS, area of punctate hyperalgesia	n=X, post remifentanil infusion area of punctate hyperalgesia expanded, but no increase in VAS with heat pain; post-ketamine+remi infusion abolished expansion of hyperalgesia
[68]	major abdominal surgery randomized to remifentanil at low dose, large dose, or large dose + ketamine; mechanical pain threshold to von Frey filament, pressure pain threshold	randomized, controlled	remifentanil	IV	VAS, NRS, pain threshold, 48- hr morphine consumption, time-to-first morphine	n=75 (25 patients per group), post large dose remi infusion tactile pain threshold was less at 24 and 48 hrs. No diff in pressure pain thresholds. No diff in VAS and NRS. No diff in time to first morphine needed in PACU nor total PACU consumption, but 48-hr consumption was sig. greater in large dose remi.
[86]	major abdominal surgery randomized to remifentanil infusion or placebo while under general plus epidural anesthesia	randomized, double-blind, placebo-controlled	remifentanil	IV	VAS, 24-hr morphine consumption	n=50, post remifentanil infusion patients had higher VAS, but no difference in 24 hour PCA morphine consumption
[105]	pediatric patients undergoing surgical correction of idiopathic scoliosis under remifentanil infusion or IV morphine	prospective, randomized, double-blind	remifentanil, morphine	IV	NRS, 24-hr morphine consumption	n=30 (15 remi, 15 morphine), 24-hr morphine consumption was sig. more in the remifentanil group. There were no differences in NRS.
[80]	remifentanil infusion; transcutaneous electrical stim-induced hyperalgesia (punctate hyperalgesia with von Frey)	randomized, double-blind, placebo-controlled, cross-over	remifentanil	IV	NRS, area of punctate hyperalgesia	n=15, male, post remifentanil infusion area of punctate hyperalgesia expanded and NRS pain intensity increased; pre-remi infusion parecoxib diminished remi- induced area of hyperalgesia, but parallel administered parecoxib did not
[82]	remifentanil infusion; transcutaneous electrical stim-induced hyperalgesia (punctate hyperalgesia with von Frey)	randomized, double-blind, placebo-controlled, cross-over	remifentanil	IV	NRS, area of punctate hyperalgesia	n=15, post remi area of punctate hyperalgesia expanded and NRS increased; post-propofol infusion did not expand area of hyperalgesia or cause increased NRS; propofol co-admin weakened but did not prevent post-remi hyperalgesia
[104]	pediatric patients for surgical correction of idiopathic scoliosis under remi infusion +/ pre-remi injection of IV morphine	randomized, double-blind, placebo-controlled	remifentanil	IV	NRS, 24-hr morphine consumption	n=40 (18 in morphine+remi, 19 in remi group) no difference in morphine consumption or NRS scores between groups
[19]	breast cancer surgical patients under high vs. low remifentanil infusion with either sevoflurane or propofol	randomized, blinded, controlled	remifentanil	IV	VAS, 24-hr morphine consumption	n=214 (female, 50 in each group), morphine consumption was higher in sevo +high remi group compared to sevo+low remi, and both propofol groups. VAS was also higher in the sevo+high remi group vs. all other groups
[83]	remifentanil infusion; transcutaneous electrical stim-induced hyperalgesia (punctate hyperalgesia with von Frey), CPT	randomized, double-blind, placebo-controlled, cross-over	remifentanil	IV	NRS, area of punctate hyperalgesia	n=16, male, post remi area of punctate hyperalgesia expanded and NRS increased; pretreatment with parecoxib or ketorolac decreased area of post-remi hyperalgesia, effect of parecoxib was greater than ketorolac; NRS after remi infusion was increased and not prevented by parecoxib or ketorolac

[87]	Robot-assisted laparoscopic prostatectomy under remifentanil infusion; remi+magnesium injection to incision site vs. remi+saline injection vs. no remi+saline injection	randomized, placebo- controlled	remifentanil	IV	VAS, time-to-post-op requirement of opioid, total post-op opioid requirement	n=75 (25 remi+mag, 25 remi+saline, 25 des+saline), time to first analgesic was longer in the mag. and des. groups, VAS was lower in mag. and des. groups for 24 hrs, total opioid consumption was lower in mag. and des groups.
[99]	Laparoscopic gynecological surgery under sevoflurane and remifentanil infusion with or without ketamine	cohort, controlled (not controlled to evaluate remifentanil)	remifentanil	IV	VAS, post-op morphine requirement	n=40 (female. 20 remi+ketamine, 20 remi only), VAS was lower in the ketamine treated group up to 3 hours post op, PCA morphine consumption was reduced in the ketamine group up to 2 hours post-op
[42]	elective open septorhinoplasty surgery under propofol general anesthesia with remifentanil infusion +/ N$_2$O; mechanical pain threshold with von Frey filament	randomized, double-blind, controlled (not controlled to evaluate remifentanil)	remifentanil	IV	VAS, post-op morphine requirement, mechanical pain threshold	n=50 (25 with N$_2$O, 25 with O$_2$ as control), post remifentanil no difference in VAS or morphine consumption with or without N$_2$O intraop. N$_2$O group had lower post op mechanical pain threshold at 12-18 hours but not at 2 hours
[103]	remifentanil infusion; thermode induced heat pain, mechanical hyperalgesia with punctate probes	crossover, placebo-controlled, blinded	remifentanil	IV	VAS	n=33 (10 excluded), no sig. difference in VAS to heat or punctate pain
[84]	remifentanil infusion in patients +/- propranolol; transcutaneous electrical stim-induced hyperalgesia (punctate hyperalgesia with von Frey), heat pain	randomized, double-blind, placebo-controlled, crossover	remifentanil	IV	area of punctate hyperalgesia, pain threshold, pain tolerance	n=10, post remifentanil infusion area of punctate, but not thermal, hyperalgesia greatly expanded. Punctate hyperalgesia was prevented post remi+propranolol infusion.
[87]	intraop remifentanil with dexmedetomidine or placebo in laparoscopic assisted vaginal hysterectomy patients; mechanical hyperalgesia with von Frey	randomized, placebo-controlled	remifentanil	IV	pain threshold, pain tolerance, VAS, morphine consumption	n=90 (30 placebo+remi, 30 placebo+high remi, 30+dex+high remi), post-remi infusion pain threshold was lower in placebo+high remi group, VAS and morphine requirement were also higher post op in placebo+high remi group; dex group showed no hyperalgesia

Abbreviations: ADP: Acute opioid physical Dependence Protocol; BPI: Brief Pain Inventory; CES: Cutaneous Electrical Stimulus of earlobe; CPT: Cold Pressor Test; NPS: Numeric Pain Score; NRS: Numeric Rating Scale; TD: Transdermal; VAS: Visual Analog Scale

subjects with chronic opioid therapy [40].

Translational trials

Cellular and animal models of OIH suggest that chronic opioid exposure can result in paradoxical neuronal excitation mediated by the NMDA receptor and many second messenger systems. Ketamine and dextromethorphan are NMDA antagonists studied in the context of OIH in human trails [75,76,78,79,98,99]. In a randomized crossover trial Koppert et al reported decreased area of punctate hyperalgesia after ketamine infusion [76], supported by 2 subsequent trials [78,79]. In another randomized crossover study Luginbuhl et al reported a lower tolerance to pressure pain after remifentanil infusion that was not prevented by ketamine [75]. In methadone maintained patients there was no difference in pain threshold or tolerance to cold in those taking dextromethorphan versus placebo [98].

Cyclooxygenase inhibitors may reduce hyperalgesia via reduction in PGE2 activity on the NMDA receptor of astrocytes and spinal cord dorsal horn neurons [80]. In a randomized controlled trial, parecoxib given before remifentanil infusion, but not during, reduced the area of punctate hyperalgesia [80]. Parecoxib was more effective that ketorolac in reducing the area of hyperalgesia after remifentanil [83]. Reznikov compared the treatment of 224 patients with chronic pain over 3 months using opioids or non-steroidal anti- inflammatory medications and found no difference in pain intensity to mechanical or heat pain [100].

Discussion

Although originally OIH was detected by astute clinicians observing hyperesthesia in their patients, controlled human studies are far from clear and the evidence for OIH is strongest and most consistent in cellular and animal models. The phenomenon of persistent AC superactivation by opioids, and subsequent neuronal excitation may be the underlying mechanism of OIH, as far as it has been shown to occur in rodents. Discovery that NMDA antagonists prevent OIH has led to human trials using ketamine to antagonize remifentanil- induced hyperalgesia. This is a practical first step as both medications are commonly used intra-operatively; however, the dissociative side effects of ketamine limit its use in other realms. Gabapentin and pregabalin are also used frequently for the treatment of chronic pain and occasionally in the perioperative setting. Their action at α2δ receptors to inhibit calcium channels decreases hyperalgesia in rodents [42,55,64] and potentially in humans [101]. Adrenergic antagonists clonidine, dexmedetomidine, and propranolol may have promise against hyperalgesia both in the operating room and the clinic [78,84,87]. Medications that target second messenger systems involved in OIH have yet to be employed in clinical trials.

The relevance of mild transient hyperalgesia that may occur after remifentanil infusions in the operation room has been questioned [1,102]. In practice, remifentanil is rarely used alone, and due to its short duration of action most practitioners add a long-acting opioid to treat pain in the recovery room. In neurosurgical and orthopedic surgeries that require motor and sensory evoked potential monitoring, remifentanil and propofol combination is common. Propofol too, may reduce hyperalgesia caused by remifentanil [84]. Quantitative sensory tests to detect hyperalgesia in controlled experiments may not be comparable to the perioperative setting. After remifentanil infusions most studies show hyperalgesia to cold but questionably to heat, electrical, and pressure pain [75,79,96,103]. Postoperatively, hyperalgesia has been presumed given an increase in 24-hour opioid consumption despite conflicting or insignificant pain intensity scores [87,104,105].

Table 4: Clinical Research Trials of Opioid-Induced Hyperalgesia with Methadone.

Reference	Model	Study Design	Opioid	Route	Outcome Measure	Details, Results
[71]	methadone maintained heroin dependent; CPT		methadone	PO	pain threshold	pain threshold lower in drug free ex-addicts and methadone maintained patients compared to controls
[73]	heroin users on methadone maintenance; mechanical pressure test	cohort, match controlled	l-methadone	PO	pain threshold	n=42, pain threshold and tolerance similar to controls at time of plasma trough
[89]	Methadone-maintained opioid abusers response to hydromorphone; CPT	cohort, placebo-controlled, 2-way factorial, mixed model	methadone maintained, hydromorphone tested	PO	pain tolerance before and after hydromorphone	n=120 (60 methadone, 60 controls), methadone maintained patients less tolerant than controls, no sig. difference with hydromorphone analgesia vs. NSAID
[95]	Methadone-maintained patients; CES, CPT	cohort, match controlled	methadone	PO	pain threshold, pain tolerance	n=32 (16 methadone, 16 controls), methadone-maintained are less tolerant to electrical stim and cold pain, but have lower threshold to cold pain only
[72]	Methadone-maintained heroin users; CES, CPT	cohort	methadone maintained, morphine tested	IV	pain threshold, pain tolerance	n=8 (4 methadone/morphine, 4 controls), methadone patients have lower threshold and tolerance to CPT pain, no difference in threshold but lower tolerance for CES pain
[90]	Opioid-maintained former opiate addicts, CPT	cohort	methadone, buprenorphine	PO	pain tolerance	n=54 (18 methadone, 18 buprenorphine, 18 control), methadone and buprenorphine maintained patients are equally less tolerant
[60]	opioid dependent patients on methadone maintenance on once daily doses (11-45mg, 46-80mg, 81-115mg) compared to controls; CPT, CES	Double-blind, placebo controlled, crossover	methadone	PO	pain threshold, pain tolerance	n=28 (18 methadone maintained, 10 control), pain threshold and tolerance increased in controls with morphine, but did not on methadone maintained patients
[94]	heroin or methadone addicted patients compared to healthy non-addicts, CPT	cohort, controlled	heroin, methadone	IV, PO	VAS, pain threshold, pain tolerance	n= (60 opioid addicts, 70 controls), opioid addicts had lower VAS, *increased* threshold but decreased tolerance
[98]	methadone maintained patients treated with dextromethophan or placebo; CPT, CES	Double-blind, placebo-controlled	methadone	PO	pain threshold, pain tolerance	n=40 (18 dex, 22 placebo), no difference in pain threshold or tolerance between dex patients and placebo
[44]	methadone maintained patients for dependence compared to patients with chronic pain on methadone or morphine; mechanical pain threshold with von Frey filament, CPT, CES	Observational	methadone, morphine	PO	pain threshold, pain tolerance	n=?, no difference between treated groups, but all treated groups (methadone or morphine) showed lower threshold and decreased tolerance to cold pain. There was no hyperalgesia to electrical pain.
[101]	methadone maintained individuals treated with gabapentin vs placebo; CPT	randomized, placebo-controlled	methadone	PO	pain threshold, pain tolerance	n=26 (10 gabapentin, 16 placebo), patients on gabapentin had increased threshold and increased tolerance to cold pain
[91]	heroin addicts randomized to methadone or buprenorphine treatment with matched drug-free controls; pain measured at trough and peak opioid plasma levels using CPT, electrical stimulation	randomized, match-controlled	methadone, buprenorphine	PO	pain threshold, pain tolerance	n=82 (11 methadone, 64 buprenorphine, 21 controls), baseline threshold and tolerance to cold were less in heroin-dependent group, hyperalgesia increased at trough in both methadone and buprenorphine groups.
[92]	Opioid-dependent subjects (methadone or buprenorphine); CPT, CES, mechanical pressure test, ischemic pain test	open design, cohort, controlled	methadone, buprenorphine	PO	pain threshold, pain tolerance	n=32 (8 on methadone, 8 on buprenorphine, 16 matched controls), pain threshold and tolerance were reduced in both methadone and buprenorphine groups; electrical pain thresholds increased in opioid groups but with no change in tolerance; no differences in ischemic or mechanical pain tests
[93]	male, heroin or methadone addicts, former addicts, drug-naïve; CPT	Observational	heroin, methadone	PO	pain threshold, pain tolerance	n=143 (50 heroin or methadone, 43 former addicts, 50 controls), active users show decreased pain threshold and tolerance while former addicts do not

Abbreviations: ADP: Acute opioid physical Dependence Protocol; BPI: Brief Pain Inventory; CES: Cutaneous Electrical Stimulus of earlobe; CPT: Cold Pressor Test; NPS: Numeric Pain Score; NRS: Numeric Rating Scale; TD: Transdermal; VAS: Visual Analog Scale

Table 5: Clinical Research Trials of Opioid-Induced Hyperalgesia with Other Opioids.

Reference	Model	Study Design	Opioid	Route	Outcome Measure	Details, Results
[88]	opiate vs. cocaine abusers; CPT	Quasi-experimental	opioid	PO	pain tolerance	n=122, male, pain intolerance correlated with opioid use
[31]	intraop high and low dose fentanyl infusion for TAH		fentanyl	IV	postop VAS and fentanyl consumption	n=60, female, higher intraop fentanyl caused increased postop VAS and fentanyl consumption
[76]	alfentanil infusion, transcutaneous electrical stim-induced hyperalgesia (punctate hyperalgesia with von Frey)	randomized, double-blind, placebo-controlled, crossover	alfentanil	IV	NRS, area of punctate hyperalgesia	n=12, post-alfentanil infusion patients showed a trend (insig) toward increased area of hyperalgesia but baseline NRS, whereas post-ketamine (sig) or lidocaine (insig) infusion caused reduced area of hyperalgesia
[90]	ADP protocol with IM morphine, IV morphine, hydromorphone, CPT	Quasi-experimental placebo-controlled crossover	morphine, hydromorphone	IM, IV	pain threshold, pain tolerance	n=4, male, IM and IV morphine and IV hydromorphone lowered pain threshold and tolerance following naloxone-induced withdrawal (ADP protocol)
[100]	chronic non-malignant pain or cancer-related pain patients on opioids for 3+ months vs. NSAIDS; mechanical pain threshold with von Frey filament, mechanical pain threshold, heat pain threshold, suprathreshold heat pain NPS	cohort, tester blind, controlled	opioid	PO	NPS, pain threshold	n=224 (142 on opioid, 82 non-opioid), no difference in pain threshold, no difference in NPS in suprathreshold heat pain
[97]	chronic low back pain patients on oral morphine; CPT, heat pain	prospective, observational	morphine	PO	pain threshold, pain tolerance	n=6, 1-month oral morphine lowered pain threshold and tolerance to CPT, but not to heat
[25]	chronic non-malignant pain or cancer-related pain patients on chronic opioids compared to patients with chronic nonmalignant pain on chronic non-opioid analgesia; CPT	cohort	opioid (oxycodone, morphine, tramadol, propoxyphene, fentanyl, codeine)	PO	NPS, pain threshold, pain tolerance	n=110 (73 opioid treated group, 37 non-opioid treated control), chronic opioid treated group showed no decreased threshold, no difference in pain tolerance, and no difference in pain intensity.
[101]	chronic pain patients on opioids undergoing outpatient opioid tapering; heat pain	prospective, cohort	opioid (reported morphine equiv. dose)	PO	NRS	n=109, baseline opioid using patients showed decreased threshold to pain, tapering of opioid resulted in decreased heat pain compared to baseline
[84]	chronic low back pain tested post-remifentanil infusion, then treated for 1 month morphine vs. placebo and retested post-remi infusion; CPT, heat pain	randomized, double-blind, placebo-controlled	Sustained-release morphine	PO	pain threshold, pain tolerance	n=102, post-remifentanil infusion pain threshold and tolerance were not different after 1 month of oral morphine
[87]	cancer patients on opioids vs. not on opioids undergoing interventional pain procedure tested with pain sensation to lidocaine injection	Observational	opioid (oxycodone, morphine, hydromorphone, codeine, fentanyl)	PO, TD	BPI, NRS, unpleasantness score, behavior pain score	n=82 (62 opioid, 20 non-opioid), lidocaine injection NRS, unpleasantness, and behavior pain score were increased in opioid group, negative correlation between functional status and post-injection NRS
[61]	patients with moderate to severe chronic lumbar radicular pain, compared before and after 4 weeks of opioid therapy; CPT, phasic heat pain	prospective, open-label preliminary study	hydromorphone	PO	VAS, pain threshold, pain tolerance	n=40 (30 on hydromorphone, 10 controls),patients on hydromorphone had increased VAS to heat pain,

Abbreviations: ADP: Acute opioid physical Dependence Protocol; BPI: Brief Pain Inventory; CES: Cutaneous Electrical Stimulus of earlobe; CPT: Cold Pressor Test; NPS: Numeric Pain Score; NRS: Numeric Rating Scale; TD: Transdermal; VAS: Visual Analog Scale

Hyperalgesia may be more relevant in the chronic pain setting. If prolonged opioid abuse or maintenance results in hypersensitivity to nociception, any offense such as injury or surgery can result in a relative increase in suffering compared to the non-opioid user. Moreover, rapidly increasing opioids, without concomitant addition of adjuvants that prevent hyperalgesia, may expose a patient to increased pain in the presence of a continuous nociceptive stimulus. Rapidly escalating the dose of opioid not only exposes a patient to greater risks but also hastens tolerance, and can lead to rapid onset of hyperalgesia. Opioid sparing techniques such as opioid rotation may allow for similar or improved pain control without inducing neuroexcitation as seen with rapid opioid escalation [106,107,108]

In humans, OIH is still a diagnosis of exclusion. There is no empiric test used clinically to diagnose a patient with OIH. Clinicians may diagnose patients with OIH based upon opioid use history, response to opioids, physiological signs of hyperalgesia, a patient's subjective complaints, and exclusion of other possible causes of decreased threshold to pain. Although OIH is thought of more often in patients on chronic opioids, it may also occur in the acute setting as well [78]. Patients may experience an increase in pain with increase in

opioid as well as a decreased threshold for detection of pain, two signs that differentiate tolerance from hyperalgesia. Objective physiological signs may be evident; a patient's heart rate, respiratory rate, and level of awareness may paradoxically increase despite escalating doses of opioid, and without disease progression. A prudent strategy to avoid OIH would be to employ multi modal analgesia in both the operating room and the clinic, avoid rapid dose escalation of opioids, and instead employ the principle of opioid rotation for patients who continue to suffer despite high and escalating dose of opioid.

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