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Review

Drug-specific differences in the ability of opioids to manage burn pain

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ABSTRACT

Burn injury pain is a significant public health problem. Burn injury treatment has improved tremendously in recent decades. However, an unintended consequence is that a larger number of patients now survive more severe injuries, and face intense pain that is very hard to treat. Although many efforts have been made to find alternative treatments, opioids remain the most effective medication available. Burn patients are frequently prescribed opioids in doses and durations that are significantly higher and longer than standard analgesic dosing guidelines. Despite this, many continue to experience unrelieved pain. They are also placed at a higher risk for developing dependence and opioid use disorder. Burn injury profoundly alters the functional state of the immune system. It also alters the expression levels of receptor, effector, and signaling molecules within the spinal cord's dorsal horn. These alterations could explain the reduced potency of opioids. However, recent studies demonstrate that different opioids signal preferentially via differential signaling pathways. This ligand-specific signaling by different opioids implies that burn injury may reduce the antinociceptive potency of opioids to different degrees, in a drug-specific manner. Indeed, recent findings hint at drug-specific differences in the ability of opioids to manage burn pain early after injury, as well as differences in their ability to prevent or treat the development of chronic and neuropathic pain. Here we review the current state of opioid treatment, as well as new findings that could potentially lead to opioid-based pain management strategies that may be significantly more effective than the current solutions.

Contents

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1. Introduction

Burn injury is common, accounting for approximately 486,000 emergency room visits and 40,000 hospitalizations in the US in 2016 [1]. Fortunately, burn injury treatment has improved tremendously, resulting in ~97% of patients surviving major burns [1] (traditionally defined as burns covering >20% total body surface area). However, burn trauma often results in intense pain, and this pain remains undertreated [2]. This results in pain being the most frequent complaint of burn injury patients [3–6]. Moreover, an unintended consequence of improved treatment is that a large number of these patients are now faced with the development of long-term chronic pain which is very hard to treat [2,4–6]. Opioids are commonly utilized to treat burn pain [2]. However, emerging preclinical evidence indicates that some opioid drugs may be more effective to treat burn pain than others. The purpose of this review is to explore these findings, the mechanisms which potentially mediate such functional differences, and to highlight avenues for future research to explore with regard to this topic.

1.1. *Categories of burn pain*

Burn injury patients suffer from procedural, background, and breakthrough pain during the healing process. Background pain is defined as pain at rest that is almost always present and not caused by specific medical procedures. Procedural pain is defined as pain associated with medical procedures and treatment. Patients who suffer from persistent background pain may experience a transient increase in pain for brief durations, which is defined as breakthrough. Patient movement or activity often causes this.

Background pain is directly linked to the biological mechanisms underlying the development of the injury. Background pain is developed both at the injury site (primary pain) and in other areas (secondary pain), including areas surrounding the injury site and in other body parts. Primary pain is characterized by increased sensitivity to thermal and mechanical stimuli. Secondary pain is characterized by increased sensitivity predominantly to mechanical stimuli (but not thermal). In addition to this acute, inflammatory pain experienced right after an injury, one of the most common and severe long-term consequences of burn injury is the development of chronic and/or neuropathic pain [5]. It is thought that this type of pain arises from the development of central sensitization and other chronic, maladaptive alterations in intracellular signaling pathways [7,8].

1.2. *Burn pain management*

Burns require intense pain management. Burn injuries are known to be very painful. This is due to high levels of background pain and the necessity of painful treatment procedures, including wound debriding and bandage changes. Pain management is the specialized medical practice of reducing pain, and thus easing the suffering and improving the quality of life of individuals suffering from painful conditions. Opioids are commonly utilized to treat burn pain [2]. Alternative approaches to treat all phenotypes of pain, including burn pain and chronic pain, are actively researched. However, pain management using pharmacotherapies must target endogenous systems involved in the perception of pain. Given the central role that the opioidergic system plays in pain perception, opioid-based pharmacotherapies currently are the most successful analgesic agents, despite their inherent risks. For the same reason, opioids are likely to remain relevant for the foreseeable future of pain medicine. Thus opioids are the focus of this review.

Background pain, procedural pain, and breakthrough pain are commonly managed using different strategies. These strategies exploit known pharmacokinetic differences of opioids. Background pain is often managed with moderate-potency opioids with relatively long half-lives, administered orally where possible. Oral administration is preferred due to the increased duration of action, and the decreased risk of accidental overdose, as compared to intravenous administration. The opioids commonly utilized to control background burn pain include morphine (most common), oxycodone, and methadone [9]. For transient procedural pain, high-potency but short acting opioids (such as fentanyl, alfentanil, or remifentanil) are used. They are administered continuously via the intravenous route throughout the duration of the procedure [2,10]. Breakthrough pain is often managed via patient-controlled analgesia (PCA), commonly using either IV morphine infusion or intranasal fentanyl as needed. Recently, buccal fentanyl has become increasingly popular for controlling breakthrough pain. It is also seeing expanded use for procedural pain, particularly in the pediatric population (in the form of sucker or lozenge 'candies') [9].

Beyond tailoring duration of action to pain category, drug-specific differences in the actions of these compounds are taken into consideration when determining their use. For example, there is no clinical evidence that oxycodone is superior to morphine to control burn pain. However, it may be better tolerated in some patients, and is therefore utilized as an alternative to morphine. Methadone has numerous advantages including long duration of action, low abuse potential, and antagonist activity at the *N*-methyl-D-aspartate (NMDA) receptor, a mechanism which has been demonstrated to block the development of opioid analgesic tolerance [11,12] as well as producing direct analgesia [13]. For these reasons, NMDA receptor antagonism has been utilized for pain relief both on its own [14] as well as in combination with opioids [15]. However, use of methadone is limited by the fact that there is greater individual variability in the metabolism of methadone as compared to many other opioids. This increases the risk of overdose in unpredictable ways that varies from patient to patient [16].

Unfortunately, the practical clinical use of opioids for the treatment of burn pain is at odds with contemporary opioid dosing recommendations by the CDC. These recommendations emphasize minimizing both the dose and duration of opioid exposure [17]. In contrast, burn injuries often require higher-than-recommended doses to provide adequate pain relief [18]. Additionally, they are slow to heal, requiring long-term pain treatment [2,10]. Furthermore, under-treatment of burn pain early in the treatment program significantly increases risks of long-term negative outcomes, including future pain outcomes, depression, and anxiety [19,20]. Thus, physicians are often torn between two necessities: the need to provide adequate analgesia in this population throughout the healing process, and recommendations to withhold opioids as much as possible in order to minimize risk of addiction [21].

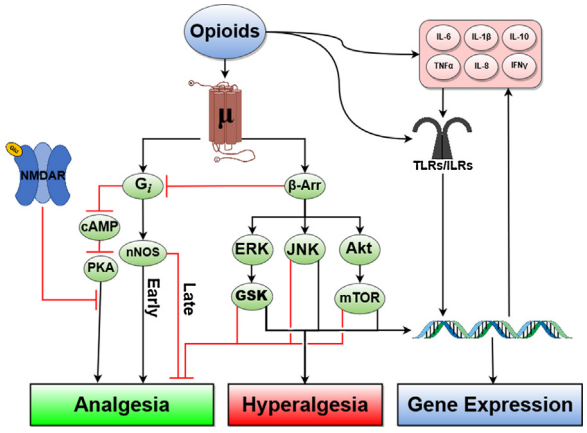

Fig. 1 – A simplified schematic of the cell signaling effects of opioids that mediate analgesic function. Opioid drugs are capable of engaging canonical, G-protein-mediated and non-canonical, β-arrestin-mediated signaling via the Mu opioid receptor (μ), the receptor considered responsible for the majority of opioid analgesia. G-protein-mediated signaling at the μ-opioid receptor is thought to be largely responsible for opioid analgesia, while β-arrestin-mediated signaling is thought to drive negative outcomes of opioids, including inhibition of analgesia and potentiation of hyperalgesia. Opioids also interact with the immune system directly (via TLRs) and indirectly (by increasing levels of pro-inflammatory cytokines which signal via the TLRs & ILRs). This interaction with the immune system drives gene expression of pro-inflammatory factors, resulting in a feed-forward loop of inflammation which leads to decreased analgesic function. Lastly, activity of the NMDA receptor (NMDAR) acts to inhibit opioid-mediated analgesia. β-Arr: β-arrestins; TLRs: toll-like receptors; IL: interleukin; ILRs: interleukin receptors; TNF: tumor necrosis factor; INF: interferon; ERK: extracellular-signal-regulated kinase; JNK: c-Jun N-terminal kinase; mTOR: mammalian target of rapamycin; GSK: glycogen synthase kinase-3β; NMDAR: *N*-methyl-D-aspartate receptor; nNOS: neuronal nitric oxide synthase.

2. The opioid system

Opioids (a term that refers to opiates, the natural products obtained from the opium poppy, as well as semi-synthetic and synthetic opioids) are a ubiquitous class of drugs that are routinely prescribed to alleviate moderate-to-severe pain [22]. They are unique among analgesics for their ability to act at both central and peripheral sites to silence pain signals. Opioids produce their various effects through activation of three classical receptors, the μ-opioid receptor, the δ-opioid receptor, and κ-opioid receptor. Most traditional opioid analgesics used in medicine are μ-selective (Fig. 1). That is to say, they have primary affinity for the μ-opioid receptor, as opposed to δ or κ-opioid receptors. The μ-opioid receptor is widely held to be primarily responsible for analgesia, which of course explains the fact that most analgesics are μ-selective. However, activation of μ-opioid receptors is also associated with many of the negative outcomes (see details below). Thus, recently the ability to exploit the unique properties of the other opioid receptors for clinical benefit has become a topic of interest. This includes research into δ-specific analgesics, especially at peripheral δ-receptors. Peripheral δ-receptor activation appears to be unconnected to many of the negative effects of opioid agonism which depend on central action, such as respiratory depression and addiction [23]. In addition, the use of κ-opioid receptor analgesics has been explored. A gender bias was noted using this approach, whereby females exhibit significantly more κ-mediated analgesia than males [24,25].

All three classical opioid receptors are G-protein coupled receptors (GPCRs), which are coupled to the $G_{i/o}$ (inhibitory/other) subunits, inhibit adenylate cyclase activity, and decrease production of cAMP (Fig. 1) [26,27]. This results in downstream decreases in PKA activity within the cell. This subsequently alters numerous downstream signaling cascades dependent upon PKA activity, such Akt and the MAPK family. Additionally, some evidence exists that spinal δ and supraspinal κ receptors also couple to $G_{\beta\gamma}$ subunits, which drive PLC pathway activity and inhibit voltage-gated calcium channel [27–29]. These G-protein-mediated signaling pathways are often referred to as the 'canonical' mechanism of GPCR action. Moreover, recent research has revealed that

opioid receptors can signal via 'non-canonical', that is to say G-protein-independent mechanisms as well [30,31]. Specifically, the opioid receptors have been shown to be capable of signaling via β-arrestins, multiple GRK isoforms, and the MAPK family including ERK, JNK, and P38 MAPK independent of their activation via G-protein-mediated pathways [32–38]. Lastly, opioids have been demonstrated to exhibit ligand-directed effects on intracellular signaling pathways [39]. This phenomenon is referred to by various names, including but not limited to biased agonism, ligand-directed signaling, and functional selectivity [40]. More recently, the more inclusive term 'ligand bias' has begun to be utilized [41]. This indicates that different opioid analgesics (opioid agonists) may engage different downstream signaling effects within the cell, despite binding to and activating the same receptor [39,42–47]. For example, it has been shown that G-protein coupled receptors can signal via a classical pathway activated via G-proteins and a noncanonical pathway activated via β-arrestin (βArr) [30–32,36]). Bias toward G-protein coupled signaling was demonstrated to increase analgesia. In contrast, bias toward βArr-dependent pathways is thought to mediate negative opioid-related outcomes, such as respiratory depression and the development of analgesic tolerance (Fig. 1; [48–50]). However, the balance of contribution of βArr-mediated signaling versus βArr-dependent desensitization and internalization of receptors is complex and, at the time of writing, poorly understood. Therefore, caution should be exercised in interpreting the role of βArr bias on analgesic tolerance [51].

Unfortunately, chronic opioid use is complicated by the development of antinociceptive tolerance and opioid-induced hyperalgesia [52–55]. Antinociceptive tolerance refers to a decrease in antinociceptive potency, which in turn usually requires dose escalation to restore original levels of antinociception [55]. Opioid-induced hyperalgesia refers to abnormal pain sensitivity due to sensitization of pronociceptive mechanisms by opioids [52,53,55]. This abnormal pain sensitivity refers both to increased sensitivity to noxious stimuli (termed hyperalgesia), and to increased painful responses to previously non-noxious stimuli (termed allodynia). The International Association for the Study of Pain (IASP) has recently released revised definitions of these terms, which help to characterize them physiologically rather than by patient perceptual experience [56]. Under the definitions of the IASP, hyperalgesia is characterized as a pain state above normal levels. This results from either lowered thresholds to evoke responses in pain fibers, or from increased pain fiber reactivity once thresholds are exceeded, or both. Importantly, hyperalgesia by definition must involve high-threshold pain sensory fibers. In contrast, allodynia is defined as pain or nociceptive behavioral responses resulting from the activation of low-threshold sensory fibers in the absence of activation of nociceptive fibers. Under this definition, any ambiguous aberrant pain mechanism is to be considered hyperalgesia (i.e. aberrant pain can only be defined as allodynia if it can be conclusively demonstrated that nociceptive fibers are *not* involved in the effect). Importantly, the development of opioid-induced hyperalgesia (OIH) requires reduced opioid doses to reverse or mitigate these abnormal alterations in nociceptive and/or low-threshold sensory fibers yielding increased pain sensitivity. Nonetheless, both antinociceptive tolerance and OIH could have similar clinical manifestations, and thus are hard to distinguish in patients suffering from other painful medical conditions, such as burns. Specifically, patients experiencing either tolerance or OIH are likely to report increased pain and reduced opioid potency. Nonetheless, these medical conditions require opposite treatment approaches, i.e. increased opioid doses to account for the development of antinociceptive tolerance or decreased opioid doses to mitigate the development of OIH. Importantly, the emergence of analgesic tolerance and OIH are common in burn patients administered opioids, which complicates treatment [9].

Other common side effects of opioids include sedation, dizziness, nausea, vomiting, constipation, and respiratory depression. Moreover, opioids also interact indirectly with the dopaminergic reward system in the brain, making them capable of causing euphoria, reward and reinforcement, rendering them liable for dependence, abuse, and addiction. Because of their propensity to be abused, physicians and researchers have long been searching for effective and less risky replacements for opioids. Despite these factors, opioids remain the gold standard for analgesia, and are the metric by which all other analgesic options are measured.

3. Burn trauma effects on inflammatory state, spinal cord, and the opioid system

Burn injury has a profound effect on different receptors, channels, and signaling pathways (such as NMDA receptor and TRPV1 channels discussed below). Improved understanding of the effects of burn injury on the different cellular effector systems can be leveraged to both improve the selection and design of opioids as well as non-opioid approaches for treating burn pain. Burn injury, like any large-scale traumatic injury, results in a significant amount of inflammation and profoundly alters the functional state of the organism's immune system [57]. In severe cases, a systemic inflammatory response syndrome (SIRS) can develop [58,59]. The complex inflammatory state induced by burn injury is known to be relatively unique from other forms of inflammatory pain [58–60], and is known to alter levels of immunomodulatory cytokines and prostaglandins [61–64]. Importantly, inflammatory signals have been demonstrated to modulate opioid pharmacology (Fig. 2; [65–73]). Several of the pathways and injury-related responses involved in burn injury are known to interact with the antinociceptive effects of opioids [60]. Further, it is known that a generally pro-inflammatory state is associated with reduced opioid analgesic efficacy [65,71,73–75]. Moreover, recent studies highlight the involvement of non-neuronal mechanisms in the antinociceptive effect of opioids (reviewed in Refs. [74,75]). For example, opioids have been demonstrated to activate Toll-like receptor (TLR), particularly TLR-4, signaling on immune cells, which in turn mediates development of analgesic tolerance and OIH [76,77]. Based on this knowledge, it is not far-fetched to posit that the experience of a burn injury, followed by the molecular alterations which such an injury precipitates, could cause a reduction in opioid antinociceptive potency. Further, many of the signaling pathways implicated in this effect also play a role in central sensitization to pain, which could account for the reports by burn patients of newly-developed pain in parts of the body far from the injury site [7].

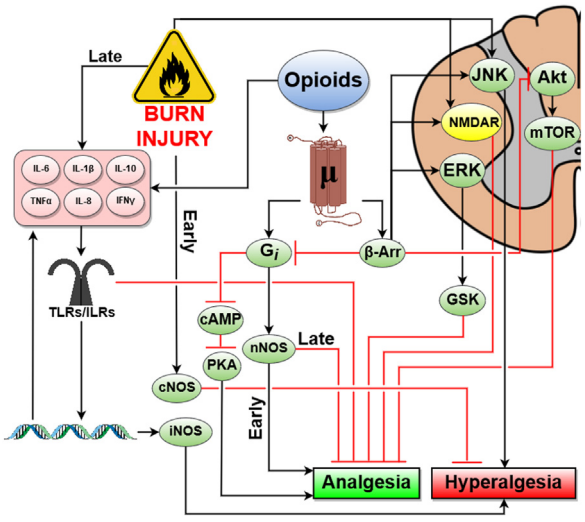

Fig. 2 – Effects of burn injury on opioids' cellular signaling. Burn injury results in the activation of a complex and relatively unique signaling state which interacts with the signaling effects of opioids to reduce their efficacy to relieve pain. Burn injury results in the activation of spinal JNK and NMDAR which act to enhance hyperalgesia and block analgesia, respectively. Early on following burn injury, the cNOS pathway is active, which inhibits hyperalgesia development, helping to mask burn-induced hyperalgesia resulting from spinal signaling activation. However, there is a shift away from cNOS activation and towards pro-inflammatory signaling and activation of the iNOS pathway as burn injury progresses, resulting in a shift toward increasing hyperalgesia. Opioids result in activation of canonical G-protein-mediated signaling, which results in analgesia through the PKA pathway. Additionally, G-protein-mediated signaling activates the nNOS pathway, which shifts from facilitating to inhibiting analgesia as opioid exposure progresses. Non-canonical opioid signaling via the β-arrestin pathway, and burn injury, have a synergistic effect on spinal cell signaling activation, enhancing the hyperalgesia and inhibiting the analgesia which results following burn injury. Thus, opioid-specific differences in signaling biases can result in different degrees of interaction with burn injuries, resulting in different ultimate pain outcomes. β-Arr: β-arrestins; TLRs: toll-like receptors; IL: interleukin; ILRs: interleukin receptors; TNF: tumor necrosis factor; INF: interferon; ERK: extracellular-signal-regulated kinase; JNK: c-Jun N-terminal kinase; mTOR: mammalian target of rapamycin; GSK: glycogen synthase kinase-3β; NMDAR: N-methyl-D-aspartate receptor; nNOS: neuronal nitric oxide synthase; cNOS: constitutive NOS; iNOS: inducible NOS.

Thus, the molecular alterations following burn injury may also account for the reduction in opioid antinociception observed in distal tissue.

Many of these molecular alterations may be occurring specifically within the spinal cord. Burn injury has been demonstrated to alter the expression levels of receptor, effector, and signaling molecules within the ipsilateral side of the spinal cord's dorsal horn [78,79]. This includes downregulation of μ-opioid receptors [80,81]. Alterations were also observed in the expression levels of NR1 subunit of the NMDA receptor as well as of multiple effector and signaling molecules such as Akt, protein kinase C, nitric oxide synthase, and glycogen synthase kinase-3β. Because of the widespread expression of opioid receptors, the pain relieving effects of opioids may be mediated at the spinal level, in addition to supraspinal and peripheral actions [82,83]. Thus, such observed alterations within the spinal cord following burn injury are 'prime suspects' to mediate altered opioid function. The role of NMDA receptors in particular in this effect, especially within the spinal cord, should not be overlooked. NMDA receptors are known to have an impact on opioid analgesic tolerance [11,12,84] as well as the development of chronic pain [79,85,86]. Indeed, the NMDA receptor antagonist ketamine has been explored as a non-opioid analgesic, to some degree of success. Work in this area has been well reviewed by others [87]. It should be noted, however, that the burn-induced alterations of the NMDA receptor system which are thought to reduce analgesic efficacy of opioids also reduce the effectiveness of ketamine [18,88], potentially limiting its implementation as an opioid replacement.

Another potential explanation includes alterations in Akt/mTOR, p38-MAPK, and JNK signaling which alter both antinociceptive response to opioids and pain hypersensitivity [89–96] and may themselves be differentially altered by opioids [97]. Opioid receptors activate P38-MAPK and JNK in what appears to be a β-Arr2-dependent manner [98]. β-Arr2 is also thought to scaffold and inactivate Akt [99], and β-Arr2 is known to be a crucial player in the reduction of opioid analgesia, as β-Arr2 knock out mice demonstrate significantly enhanced morphine analgesia [50]. Interestingly, burn injury has been demonstrated to reduce Akt phosphorylation [100]. Decreased pAkt in turn results in increased activation of P38 MAPK [101]. Therefore, β-Arr2-mediated reductions in the analgesic effects of opioids may be due to inactivation of Akt, activation of P38 MAPK/JNK or both.

As mentioned above, opioids have been demonstrated to act via differential activation of intracellular signaling pathways. In multiple cases, the effector molecules which are differentially affected by different opioids have also been demonstrated to be involved in nociception, including β-arrestin, activation of which appears to antagonize opioid antinociception [48–50]; JNK, which has been shown to be crucial in burn pain, morphine antinociceptive tolerance development, and central sensitization in the spinal cord [93,102–105]; Transient receptor potential cation channel subfamily V member 1 (TRPV1) channels, crucial for the experience of pain [106–108]; and P38-MAPK, implicated in antinociceptive tolerance [93,106,109,110]. The known ligand-specific alterations by opioids of effector molecules which influence nociception implies that burn injury may reduce the antinociceptive potency of opioids to different degrees, in a drug-specific manner.

4. Limitations of opioid treatment and potential future promise

Despite the common use of opioids to treat pain in burn patients, burn pain remains notoriously resistant to

treatment. As previously mentioned, burn pain patients often require opioid doses much greater than standard dosing recommendations to provide adequate analgesia [6,111]. Additionally, even when provided with higher dosages, they often report that their pain is not entirely managed [6,112]. A patient's reported reduction in opioid potency may be the result of burn pathology, tolerance, or hyperalgesia. It may also represent an attempt by a dependent patient to obtain a higher dose or larger supply of opioids which they go on to abuse. It is difficult to parse analgesic tolerance and OIH in the clinical setting, as they manifest with the same symptoms [113,114]. Indeed, for this reason clinicians were initially skeptical of the existence of OIH as a distinct phenomenon [4]. It is also the reason that the true prevalence of OIH remains unknown [5].

Recent studies using an animal burn model suggest that burn pathology might play a bigger role than tolerance and hyperalgesia in the reported reduction in opioid potency by patients. These studies demonstrated that antinociceptive tolerance is less likely to develop in burn-injured animals as compared to pain-free animals [115,116]. Moreover, these studies demonstrated that OIH might not develop to a significant degree in response to all opioids. Specifically, it might be more likely to develop in response to treatment with morphine than in response to treatment with oxycodone or hydrocodone.

4.1. *Burn injury reduces the antinociceptive potencies of opioids*

As mentioned above, the cellular and molecular alterations in response to burn trauma could account for the reduced potency of opioids experienced by burn patients [2,18]. This includes alterations in receptor expression within the spinal cord dorsal horn, such as downregulation of spinal μ-opioid receptors [80,81], alteration in signaling molecules as well as altered inflammatory state. Different animal models have been used to evaluate the potency of treatment on burn pain (reviewed in Ref. [60]). These studies demonstrated that the burn trauma itself had a pronounced effect on reducing the potency of opioids. In a rat model, burn injury has been demonstrated to reduce antinociceptive potency of morphine [81]; however, interestingly, this effect appears to be specific to adults, and is not present in adolescent rats [79]. In a mouse model, burn injury resulted in reduced antinociceptive potency of morphine, oxycodone, and hydrocodone [115,117]. Additionally, these studies demonstrated that the burn trauma itself had a pronounced effect on reducing the potency of opioids in both the burned limb and in the contralateral limb [115]. Surprisingly, these studies demonstrated that the reduction in opioid potency was more pronounced in the contralateral limb than in the burned limb.

In these aforementioned animal studies, it was also observed that burn injury reduced the antinociceptive potencies of opioids by equivalent degrees; no drug-specific differences were observed in burn-induced antinociceptive reductions [115]. This implies that, most likely, whatever mechanisms underlie the reduced potency of opioids following burn injury, these mechanisms are general, as opposed to drug-specific, and are shared by at least all the opioids examined in that study. Indeed, this conclusion, coupled with knowledge of drug-specific differences in the signaling cascades engaged by these drugs, helps narrow and refine the list of potential mechanisms. Namely, those mechanisms which differ between these drugs, such as receptor internalization (sometimes exhibited by oxycodone but not by morphine) or desensitization without internalization (displayed by morphine and the oxycodone metabolite oxymorphone, but not oxycodone) [38,118–121] are not likely to mediate the reduced antinociceptive potency of opioids following burn injury. It should be noted that the ability of oxycodone to induce receptor desensitization and/or internalization is highly dependent upon the model [122]. The same concept applies when considering the role of specific intracellular pathways engaged by these compounds, as whatever signaling cascade may be responsible, must be shared by all three compounds. It may be that the molecular mechanisms underlying the observed reduction in opioid potency following a burn injury are partially antagonized by signals released by the inflammation and tissue damage associated with the burn wound. These counteractive signals may be reduced or absent in distal tissue due to the absence of inflammation in that tissue, resulting in overall greater reductions in opioid potency in distal, non-injured tissue. Although these studies do not preclude the involvement of other mechanisms to explain the observation that burn patients require greater-than-standard opioid doses to provide adequate analgesia, they do indicate that the burn trauma itself might be an important contributing factor for why burn patients often report that their pain is not entirely managed.

4.2. *Differential effects of various opioids on burn pain*

Burn injury results in the development of hyperalgesia including chronic, neuropathic pain [5,123]. Historically it has been the opinion of the medical community at large that opioids are mostly ineffective for treating neuropathic pain [124]. Therefore they should not be considered a first-line treatment option, due to the increased risk of addiction outweighing the minimal analgesic benefits [125]. However, recent findings indicate that this perceived ineffectiveness of opioids may be due to the prior research bias towards using morphine as a model opioid. Indeed, in contrast to the sound literature documenting the differential effects of various opioids in vitro (well reviewed by Ref. [39]), additional studies are still required to fully appreciate how the spectrum of signaling biases of various opioid agonists relate to their clinical effectiveness. Drug-specific differences in the ability of opioids to manage burn pain during the early phase following treatment, as well as differences in their ability to prevent or treat the development of chronic, neuropathic pain in burn sufferers, has not previously been well explored. The literature comparing effectiveness of various opioids to treat burn pain in humans is limited [126]. Such studies are difficult for a number of reasons, not least of which is the routine strategy of proactive opioid rotation to minimize tolerance, which makes interpretation of long-term outcomes difficult. However, opioids have been demonstrated to have drug-specific differences in their effectiveness to treat other pain phenotypes in both animal models [124,127–130] and humans [124,131,132]. In line with the literature on other pain phenotypes,

differences in the ability of opioids to manage burn pain could influence the treatment of burn pain as well as the development of novel pharmaceutical compounds which capitalize on features of existing drugs which are found to be more efficacious.

Recent studies employing an animal burn model demonstrated significant differences between opioids in their ability to prevent the development of burn pain [116,133]. These studies demonstrated that although oxycodone and morphine significantly attenuated mechanical allodynia following administration, the effect was only partial, and mechanical reactivity thresholds did not return to baseline levels. Moreover, they did not prevent the development of burn-induced hyperalgesia (as was measured before drug administration). The finding that morphine and oxycodone are ineffective at treating chronic pain is not surprising, and is well supported by the literature. As mentioned above, morphine is notoriously ineffective at relieving neuropathic pain in both humans and animals [124,134,135]. Indeed, a recent study demonstrated that morphine treatment may in fact exacerbate and prolong neuropathic pain in rats for months following cessation of treatment [136]. Surprisingly, recent studies found that hydrocodone was most effective in mitigating the development of burn-induced hyperalgesia. Importantly, in contrast to morphine and oxycodone, hydrocodone fully reversed mechanical allodynia, returning mechanical reactivity thresholds to baseline (pre-injury) values following administration of hydrocodone. This is likely because hydrocodone significantly decreases the development of burn-induced hyperalgesia (as measured before drug administration).

The finding that hydrocodone is significantly more effective at preventing the development of chronic hyperalgesia following a burn injury is especially surprising. This is in light of the common belief that hydrocodone is a weaker opioid than both morphine and oxycodone, and is usually considered insufficient to treat more severe pain [137,138]. These findings imply that hydrocodone is functionally or mechanistically different from oxycodone and morphine in ways that differentially interact with the mechanisms underlying development of pain following burn injury. Alternatively, or in addition to differing pharmacodynamics, it is possible that burn injury differentially alters the pharmacokinetics of different opioids, resulting in differing profiles. In pain free animals, and using the same gavage administration, the duration of analgesic action of hydrocodone was demonstrated to be equivalent to that of both morphine and oxycodone [139]. However, as discussed earlier, the presence of burn injury might alter this relationship. This could represent a potential mechanism by which hydrocodone is functionally or mechanistically different from oxycodone and morphine.

This research demonstrates that opioid compounds with functionally equivalent abilities to relieve pain can differ in key ways including, paradoxically, their ability to control pain. This is to say, despite the both acute and chronic equianalgesic effects observed between oxycodone, hydrocodone and morphine, a fundamental difference was revealed in the differential ability of these compounds to prevent/control the development of long-term injury-induced pain. This result provides compelling, albeit indirect, evidence that the pain mechanisms mediating acute pain response, and the mechanisms responsible for chronic pain development, are dissociable processes. It is important to note that in real life situations, if the burn covers a larger body area than used in the rodent burn model, hydrocodone might not suffice in the early phase of burn treatment to provide adequate pain relief. However, understanding the molecular mechanisms that makes certain opioids, like hydrocodone, superior in treating burn pain will allow for the design of novel stronger opioids with particular signaling biases that will boost the ability of opioids to suppress burn pain.

5. Conclusions

Several important conclusions can be drawn from recent findings. The first is that they provide compelling evidence against the *status quo* of opioid research. This *status quo* has for years entailed exhaustive research and analysis on a particular archetypal opioid, most often morphine, followed by extrapolation of those findings to other classical opioids with adjustments for known differences between the compounds. While this research model has been particularly effective for deducing the basic workings of opioid pharmacology, receptor structure and function, mechanisms of action, etc., it remains incapable of allowing prediction of drug-specific differences in downstream signaling and long-term behavioral outcomes.

Recent results presented here indicate that the specific identity of the opioid used for pain management may have enormous ramifications on the results of treatment. This implies that research should be performed upon individual opioid compounds with regards to not only their analgesic profile, but also for wide-ranging and diverse functional characteristics which may differ from one another in ways that are unpredictable based solely on chemical features and/or pharmacological characteristics. This is due to recent indications that some opioid compounds should be preferentially used over others for pain treatment despite apparently similar analgesic potencies. This conclusion somewhat contradicts the current research and clinical *status quo* which assumes that analgesic potency and long-term outcomes are intrinsically linked. Future research in this area should examine and characterize additional opioids, with a particular focus on opioids which have traditionally not been favored due to perceptions that they are pharmacologically 'weak' compounds. The current results indicate that not only can pharmacologically 'weak' compounds such as hydrocodone provide equivalent analgesic potency to 'strong' opioids, they may do so with greater benefits and fewer adverse effects. Additionally, future research should address discovering the mechanisms by which these compounds differ from one another. Elucidation of these differences would greatly enhance our ability to predict which opioids would result in preferable outcomes, as well as greatly aid in the development of novel opioid compounds which are biased towards beneficial mechanisms and pathways, and away from harmful ones.

At the time of writing, opioid use, misuse, and overdose deaths were rising exponentially in the United States, reaching levels characterized by public health officials as epidemic proportions [140]. This rise in opioid-related adverse outcomes

has been driven, in part, by the increasingly common use of opioids to treat pain disorders in the clinical population. However, the choice of which specific opioids to be prescribed has generally not been guided by empirical, scientific, evidence-based research, because of the assumed inseparability of analgesic function from adverse outcomes. Considering the prevalence of chronic pain and its resistance to treatment with many opioid drugs, these findings hint at potential opioid-based pain management strategies for chronic pain which may be significantly more effective than current solutions. Far more research is still needed to parse out the pros and cons of specific common opioids across a variety of pain modalities, and the current literature reviewed here indicates that this research investment of time, energy and money is one worth making, as it is likely to bear fruit.

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Conflict of interest

The authors have no conflicts of interest

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