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Pain And Opioid Systems, Implications In The Opioid Epidemic.

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Abstract

Pain has a useful protective role; through avoidance learning, it helps to decrease the probability of engaging in tissue-damaging, or otherwise dangerous experiences. In our modern society, the experience of acute post-surgical pain and the development of chronic pain states represent an unnecessary negative outcome. This has become an important health issue as more than 30% of the US population reports experiencing “unnecessary” pain at any given time. Opioid therapies are often efficacious treatments for severe and acute pain; however, in addition to their powerful analgesic properties, opioids produce potent reinforcing properties and their inappropriate use has led to the current opioid overdose epidemic in North America. Dissecting the allostatic changes occurring in nociceptors and neuronal pathways in response to pain are the first and most important steps in understanding the physiologic changes underlying the opioid epidemic. Full characterization of these adaptations will provide novel targets for the development of safer pharmacotherapies. In this review, we highlight the current efforts toward safer opioid treatments and describe our current knowledge of the interaction between pain and opioid systems.

INTRODUCTION

Acute and chronic pain are experienced by 30 to 40% of the US population at any given time (1– 4). The high occurrence of these pain conditions highlights the need for efficacious therapeutic management, including opioid analgesics. In the late 1990s, the false belief that pain-experiencing patients were less likely to develop opioid addiction led to an increase in prescription opioid therapies (5, 6). Decades later, opioid analgesics represent the most prescribed class of therapeutics in the US (7). This high prescription prevalence, together with the limited number of therapeutic alternatives, is correlated with the apparition of opioid diversion, misuse, addiction and ultimately overdoses (CDC, 2018). Recent reports describe a 5-fold increase in opioid overdose in the United States in the last 15 years (8). In

DECLARATION OF INTERESTS

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2015, opioids contributed to more than 17,500 deaths were accounted to opioid pain relievers in addition to alarming nonfatal opioid overdoses that required medical care in a hospital or emergency department (8). Altogether, opioid use has reached a dire levels, with a daily 115 opioid-induced lethal overdoses reported (4). The occurrence of these dramatic events can be explained by several factors.

The development of tolerance after exposure to a few, or even a single dose of opioid analgesics (9, 10), represents a possible explanation for the increase in involuntary overdoses. Indeed, the analgesic and rewarding properties of opioid therapeutics are strongly decreased after a short term use (11–14). In self-medicating patients, dose escalation in opioid medication to overcome the presence of analgesic tolerance could explain, at least in part, the observed increase in opioid-induced respiratory depression and subsequent accidental harm (8). *Furthermore, exposure to early life stress episodes or undertreated pain are believed to increase both the risk or development of chronic pain and opioid misuse through allostatic changes* (15–18). Yet, dissecting the allostatic changes leading to opioid analgesic tolerance and analgesia (see (19)) may help to curtail substance abuse and avoid involuntary overdoses and the undertreatment of pain (20).

As the opioid epidemic continues to worsen and has reached unprecedented proportions, many state and federal level policies and strategies have been rolled out to address this national health issue (prescription drug monitoring programs, CDC prescription guidelines, novel compounds development). However these attempts are likely to remain ineffective at reducing overdose rates until our scientific and medical community better understand the neurobiology of the intersection between pain and opioid systems. This strategy may uncover new pharmacological targets to safely treat pain and OUD afflicted patients. This review will focus on our current knowledge on pain and opioid systems overlap in the reward circuitry leading to possible drug misuse liability.

The opioid system, a hub for pain and reward interaction

The endogenous opioid system has been studied for decades for its involvement in pain processes and currently represents the main target for analgesic treatment. However, the opioid system is also involved in numerous behavioral functions such as learning and memory, stress, mood, reward and addiction. On a cellular level, the opioid system is composed of four main subcategories: the Noceptin/orphanin-FQ (NOP), the delta-opioid receptor (DOR), the mu-opioid receptor (MOR) and the kappa-opioid receptor (KOR) systems. Those four systems can interact with one another and are all deeply involved in the modulation of pain and reward. The NOP system, expressed mainly in the brainstem, forebrain and spinal cord (21–23), has a dual role in which its central stimulation blocks opioid- and stress-induced analgesia while intrathecal administration leads the analgesic properties (23–25). Because the NOP system activation decreases the reinforcing properties and abuse liability of many drugs of abuse, it is currently considered as a possible molecular target for substance abuse treatment (26–28). The DOR system is highly expressed in forebrain regions (29, 30) and modulates analgesia predominantly under in chronic pain conditions (31, 32). As a comparison the MOR and KOR systems, distributed throughout the brainstem, midbrain, and forebrain structures, are thoroughly involved in the integration of

reinforcing and aversive stimuli, including severe and acute pain (20, 33–44). Pain, composed of both a nociceptive and an emotional component, is detected by peripheral sensory neurons and processed though an interaction in between descending pain modulatory system and cortical networks. The MOR is expressed throughout this pain axis, and stimulation of MORs in both peripheral nociceptors and supraspinal structures alleviates the nociceptive component of pain. *After injury met-enkephalins, endogenous MOR agonists, can be locally released at injury site and provide rapid anti-nociception* (45). This pain relief represents a reinforcing experience, as alleviating painful stimuli improves general hedonic state, a phenomenon known as negative reinforcement (29, 30, 35–37, 39). On the other hand, in non-painful conditions the activation of MOR in the mesolimbic reward pathway, from the ventral tegmental area (VTA) to the nucleus accumbens (NAc), leads to reinforcing effects through the release of dopamine, known as positive reinforcement (29, 48, 49). While acute activation of the MOR system, the main target of current opioid pharmacotherapies such as morphine and fentanyl, is correlated with analgesic properties and reward (44, 49–51), activation of KOR system leads to dysphoric, anhedonic, and aversive behaviors (33, 34, 39–41, 43). Due to their reinforcing and aversive properties the MOR and KOR, respectively, are often referred as opponent systems. Interestingly, some studies have demonstrated that KOR stimulation, in pain conditions, disrupts the reinforcing properties of MOR agonists through a dopamine release inhibition in the NAc (52, 53) *while peripherally restricted KOR stimulation induces analgesia* (54). A thorough dissection of the impact of pain to trigger allostatic changes in all the four opioid systems represents a necessary step to understand the interaction in between pain and opioid misuse liability (Figure 1).

In animal models, the occurrence of pain has been shown to strongly affect the reinforcing properties of rewards (55–59). Numerous laboratories have shown a decrease in the reinforcing properties of morphine using a conditioned place paradigm in rodent models of neuropathic or chronic pain (52, 60–62). Interestingly, Wu and collaborators found that animals exposed to chronic pain developed morphine-induced place preference when the dose of morphine was increased (63). This suggests a rightward shift in the dose-response for reinforcing properties of opioid in animals experiencing pain. Similarly, using opioid self-administration, the gold-standard methodology in the study of addiction, animals in pain demonstrate a decrease in low-dose (62, 64–67) but an increase in high-dose opioid consumption when compared to control littermates (55). These alterations in opioid reward processing have been strongly correlated to impaired reinforcer-induced dopaminergic transmission and NAc function (68–71). This dopaminergic release impairment in the NAc contributes, at least in part, to the negative affective states that accompany drug withdrawal (72), suggesting a possible common mechanism for pain to drive negative affective states. In that sense, recent preclinical studies have characterized significant allostatic changes in rodents NAc medium spiny neurons when animals are exposed to an inflammatory or neuropathic pain condition (57, 58). The presence of negative affective states, a consequence of the emotional component of pain, have been highly correlated with these neuronal adaptations (57, 58). However, to fully decipher how pain promotes the appearance of negative affective states it is important to acknowledge the role of other brain regions (besides the VTA and the NAc) that are critical in the regulation of pain, stress, and reward

responses. The amygdala is very much involved in the processing of both positive and negative valence (see review (73)). Specifically, the BLA and the central nucleus of the amygdala, play major roles in the relationship in between pain and negative affective states (74, 75). The lateral hypothalamus (LH), a region critical to positive reinforcement through its direct connection to the mesolimbic pathway, is involved in pain responses, affect, and the rewarding properties of reinforcers (76, 77). This dual role in both pain and reward makes the lateral hypothalamus an ideal candidate to study interactions in between pain and the presence of negative affective states. Further studies dissecting the role of pain and opioid systems in these brain hubs, among others, will undoubtedly uncover the neuronal mechanisms responsible for the emotional component of pain.

Despite the promising outcomes of opioid analgesics with a low tolerance liability discussed earlier in the introduction, the rewarding properties of current opioid prescriptions remain a key factor in the North American opioid epidemic. Evidence from clinical studies depict a positive correlation between the increase in opioid prescription for pain treatment and the development of Opioid Use Disorders (OUD). According to recent reports, only 8% of pain patients go on to develop addiction (4, 78, 79). However, most interestingly, the rate of misuse and abuse behaviors occurs much more commonly, in 15 to 26% of patients (4, 78, 79). Thus, numerous groups of scientists have focused their efforts on developing novel opioid therapeutics which maintain the ability to relieve pain in the absence of abuse liability. For example, Spahn and collaborators recently developed a fentanyl derivate which acts strictly in painful, inflamed areas (80). Because pH is diminished at the site of painful inflammation, these authors were able to develop a fentanyl derivate with low pKA properties (NFEPP). This strategy allowed a specific action of the NFEPP in low pH milieu to provide analgesia in the absence of the central side effects (motor coordination, sedation, rewarding properties, constipation and respiratory depression) associated with fentanyl use (80). *Earlier this year, Ding and collaborators developed a bifunctional NOP/MOR agonist that acts as a potent analgesic while lacking the generally observed side-effects of MOR agonists treatment, such as respiratory depression, development of tolerance and abuse liability* (81). Another promising strategy can be found in the design of biased agonists. MOR agonist binding to their receptor can trigger the activation of several downstream pathways. Many laboratories have described selective role on these pathways activation to drive rewarding, tolerance, or analgesic properties of MOR agonists compounds. Embracing these numerous studies, Manglik and collaborators have recently uncovered, through a rigorous pharmacological compound screening, a novel biased MOR opioid agonist, PZM21, displaying analgesic properties while lacking rewarding properties in non-pain conditions (82). The same year, Brust and colleagues described a thorough assessment of a newly developed KOR biased agonist, triazole 1.1, which presents high analgesic properties without inducing any apparent sedation or dysphoric effects (83). While these elegant studies have only explored preclinical models of pain, biased agonists through which action on opioid receptors lead to selective activation of a certain pathway represent promising therapeutic candidates (10, 51, 84). Despite these encouraging results, the latency for novel therapeutics to emerge on the market will be substantial, given that these compounds have not yet made their way out of preclinical studies.

As for today, alternative therapies represent a possible way of decreasing opioid use and related morbidity and mortality. The rate of opioid related overdoses has been significantly decreased in the states where therapeutic cannabis has been legalized (85, 86). The analgesic and anxiolytic properties of cannabis may improve the treatment of both the nociceptive and emotional components of pain. However, further studies on the long-term effects of cannabis use would be prudent to ensure that this is a safe and sustainable means of ameliorating the opioid epidemic. In addition, acupuncture, meditation and other non-pharmacological approaches represents complementary and efficient ways to treat pain and its associated co-morbidities such as increased anxiety- and depression-like states (87–91).

In conclusion we firmly believe that a combination of safer pharmacotherapies, better understanding of pain-induced allostatic changes in opioid systems and neurocircuitry and non-pharmacological approaches will undoubtedly help the medical community to improve patient suffering health care and quality of life.

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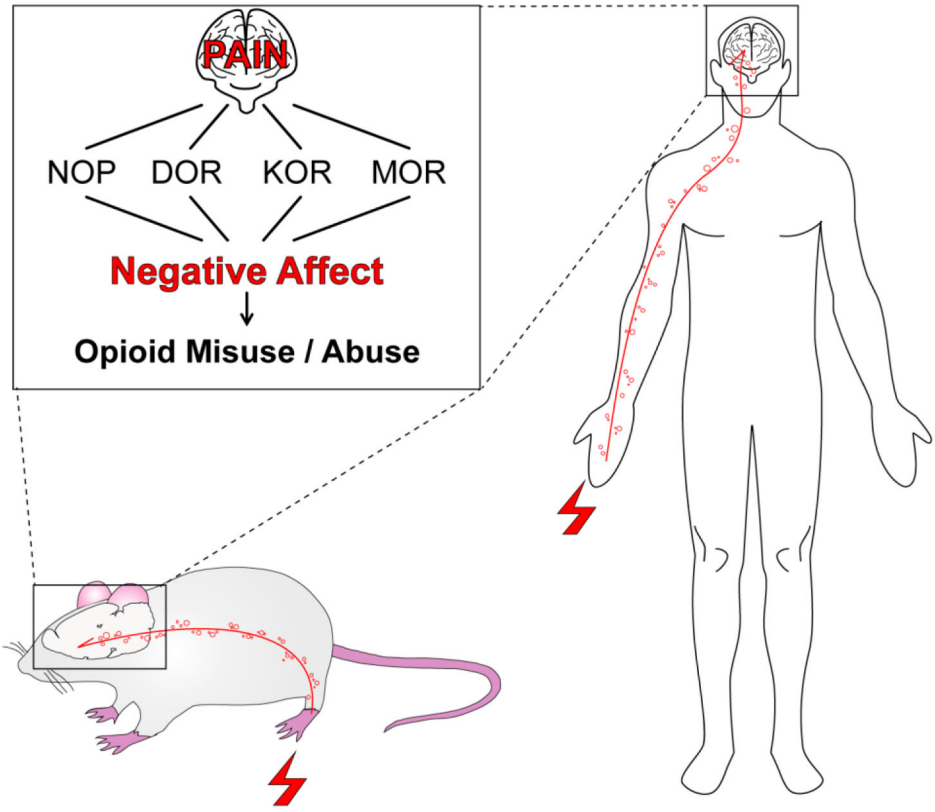

Figure 1:

Schematic representation of pain-induced allostatic changes in all four opioid systems driving the development of negative affective states. Ultimately, the presence of these negative affect together with the persistent/chronic nociceptive component of pain and the development of opioid treatment tolerance can lead to opioid prescription misuse and increased abuse liability.