CAPSTONE

Opioid-induced hyperalgesia and enhanced pain in opioid withdrawal: a comparison of cellular mechanisms

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Opioids are clinically invaluable analgesics during acute administration. Chronic use can unfortunately lead to abuse and dependence. Part of the reason why people sustain opioid use is to stave off the unpleasant withdrawal symptoms. A highly supported theory for the mechanism of withdrawal is homeostasis imbalance: chronic use of high-dose opioids causes a compensatory reaction in neurons, and subsequent cessation of drug induces withdrawal. Opioid-induced hyperalgesia (OIH) which increases pain or causes normal touch sensation to be perceived as painful, is a side-effect of chronic opioid use. In therapeutic settings, clinicians may respond to OIH by increasing opioid dosage if pain is the target symptom of treatment. As opioid dosage is a predictor for addiction potential, this increase in prescription could worsen outcomes. Experiments have revealed that OIH correlates with changes in both spinal (upregulation of NMDARs in the central glutamatergic pathway, increase in spinal dynorphin) and supraspinal domains (hyperactivation of neural populations of the rostro-ventral medulla(RVM)). These same changes have been implicated in opioid withdrawal, though withdrawal research has a larger focus on changes in the supraspinal RVM, periaqueductal gray, and locus coeruleus. This review will compare current research describing the mechanisms underlying both pain in opioid withdrawal and opioid-induced-hyperalgesia. If these are symptoms of the same process, it would implicate acute withdrawal as a moderator and target of intervention for the progression from chronic opioid use to abuse. Additionally, treatments uncovered in OIH research could be applied to ease opioid withdrawal symptoms.

Introduction

Opioids are an invaluable family of substances that for many, alleviate otherwise unmanageable pain. Due to their effectiveness, opioid prescription rates increased four-fold between 1999 and 2010. Unfortunately, the rate of deaths due to opioid overdose increased at the same rate.[1] This trend has continued to the present day, in 2018 there were 14,975 reported opioid overdose deaths in the United States.[2] This suggests that many people who end up suffering from opioid abuse started with a legitimate prescription for a surgery or pain problem which develops into an opioid use disorder (OUD). As many people with OUD continue to use in order to avoid withdrawal, the preferred treatment for OUD is to replace short-acting potent opioids such as oxycodone, heroin, and fentanyl with much slower acting opioids such as methadone or buprenorphine, followed by a slow tapering of the long-acting opioid.[1] This strategy is called medication-assisted treatment or MAT. MATs not only prevent withdrawal, but they also stabilize patients' extreme highs and lows which minimize the morbidity caused by opioid abuse. MATs are far from perfect, but they are a viable solution for many struggling with OUD.

MATs are effective at reducing opioid abuse for a large population, but findings are inconsistent regarding MATs effectiveness at treating pain.[3] Some patients are able to manage pain during MAT with use of additional non-opioid painkillers or therapies such as acceptance and commitment therapy, while others find that their continuing opioid use actually exacerbates their pain instead of treating it.[3] This phenomenon is known as opioid-induced

hyperalgesia (OIH). Since OIH was first described in 1975, a broad collection of research teams have investigated possible mechanisms underlying OIH; including dysregulation of the central glutamatergic system in the dorsal horn of the spinal cord, increased systemic concentration of dynorphin, alterations in descending facilitation from the rostro-ventral-medial medulla (RVM) and long-term potentiation of the C-fibers that carry pain information.[4] As this is a shortened list of the theorized mechanisms underlying OIH, it is difficult to ascertain what mechanism is the best to target for the development of novel opioids that do not cause this increase in pain. This is where a cross-sectional analysis of OIH and opioid withdrawal research may be useful.

Occam's razor has led to a robust model of what causes withdrawal: chronic use of a substance leads to cellular adaptations (i.e. downregulation of substance receptors) in order to maintain holistic homeostasis. These cellular changes constitute tolerance, which causes more substance to be taken in order to achieve the same effect. Continued escalation of the dose eventually leads to dependence. When substance use is halted, the shift in homeostasis due to chronic use is what causes the negative symptoms of withdrawal. If this model is true, it implies that the process underlying tolerance in the presence of the substance is the same as the process that causes withdrawal in the absence of substance. Where does OIH fall into this equation, a symptom of withdrawal or tolerance? One of the symptoms of opioid withdrawal is hyperalgesia, possibly caused by changes in the spinal dorsal horn or descending RVM facilitation.[5] However, a study investigating OIH during MAT found a positive correlation between methadone dosage and severity of pain.[3] Methadone is known as an ultra-long lasting opioid with a half-life lasting 36 hours, which means that these patients may have been experiencing OIH while opioid was still in their system.[6] If true, this would imply that hyperalgesia during withdrawal (absence of substance) may function through a different mechanism than OIH (presence of substance). It is very possible this hyperalgesia is due to an interaction of various processes. As such, the following review will seek to describe these processes and if possible, determine if any are exclusive to either OIH or withdrawal-induced hyperalgesia.

Methods and results

A systematic literature search was performed on pubmed, accessed between 2/25/20 and 3/26/20. The search terms utilized were "opioid+induced+hyperalgesia" with "mechanism," and "opioid+withdrawal" with "mechanism." Articles published before 2010 were discarded as well as review articles. 22 OIH and 15 withdrawal papers were coded for 6 domains: model organism, pain treatment for OIH induction, Type of measure (i.e. behavioral, immunohistochemistry, real-time PCR, etc.), specific opioid, the withdrawal time between last opioid and measure, and major findings. A description of the literature analyzed is available in Table 1 post-references. For brevity of report, only the spinal and supraspinal findings will be discussed.

Discussion

In some studies, OIH is defined as an upregulation of C-fiber activity in the spinal cord.[7,8] C-fibers are a class of primary afferents that carry pain information from nociceptors into the spinal cord. The axons of C-fibers are unmyelinated, their somas reside in the dorsal root ganglion, and they synapse onto neurons in lamina I and II of the dorsal horn, which in turn carry pain information to the brain.[9] The mechanisms underlying long term potentiation of this pathway have been investigated presynaptically (increased activity of C-fibers themselves) as well as post-synaptically (neurons downstream of C-fibers have heightened responses). These mechanisms that lead to C-fiber pathway LTP have been detected using immunohistochemistry and RT-PCR to measure densities of proteins associated with LTP, as well as electrophysiology to measure the properties of LTP itself. Within the dorsal root ganglia, morphine injections over 5 days caused an upregulation of both BDNF mRNA and protein, while heroin self-administration

over 12 days increased P2X2 and P2X3 receptor expression.[10,11] Important to note is that P2X2 and P2X3 expression was upregulated after 8 days of spontaneous withdrawal, though thermal hyperalgesia had recovered to baseline at this time-point.[11] Antagonizing BDNF targets in the DRG effectively blocked OIH in rodent studies which suggests BDNF within C-fiber somas is necessary for potentiation.[10] Important to note is this study's use of behavioral rather than electrophysiological measures for OIH: animals may have desensitized to the paw pressure test while still experiencing heightened pain which would go undetected.[10] This underlies the need for new, more sensitive behavioral measures of hyperalgesia.[12]

In contrast to dorsal root ganglia, there is a larger body of evidence investigating changes *within* the spinal cord contributing to OIH. Following 5 days of morphine injections, the density of α2δ-1–GluN1 protein complexes and pre-synaptic NMDAR expression were both increased in the dorsal horn, though post-synaptic NMDAR expression was decreased.[13] This change in expression occurred after only 20 minutes of morphine washout suggesting that this LTP may have been associated with tolerance rather than withdrawal. A single injection of remifentanil increased annexin receptor density in the dorsal horn as well as NMDAR activity: this receptor expression remained elevated for 48 hours of spontaneous withdrawal, though the increased NMDAR evoked current only lasted for 120 minutes post washout.[8,14] This is further evidence of opioid-induced modulation of protein expression persisting after detectable hyperalgesia. Hyperalgesia in two of these studies was reversed through separate administration of α2δ-1 and annexin antagonists. This supports the dorsal horn's involvement in hyperalgesia both with (annexin) and without (α2δ-1) long-term withdrawal. LTP of the C-fiber synapse in the dorsal horn may be also dependent on the rate of opioid cessation, one study found. Following one hour of remifentanil infusion, C-fiber field potentials were increased only with abrupt termination of remifentanil but not a tapered infusion.[7] This is strong evidence that OIH does not occur in the absence of withdrawal. Most of these OIH studies attribute L-fiber LTP to modulation of glutamatergic receptors, but changes in the activity of non-glutamatergic receptors within the spinal cord may also contribute to hyperalgesia. A study using dorsal horn cells *in vitro* found that B2-Adrenergic receptors may modulate hyperalgesia by heterodimerizing with morphine receptors to regulate their internalization.[15] This was followed by a study *in vivo* that found co-administration of morphine with a B2-AR agonist increased behavioral hyperalgesia while co-administration with a B2-AR antagonist reduced hyperalgesia.[15] Another receptor that may be involved spinally is the 5-HT3 receptor. A study found that the hyperalgesia induced with morphine injections over 4 days was reversed with an intrathecal but not intraplantar injection of the 5-HT3R antagonist ondansetron.[16] Although the 5-HT3 may be a useful target for treating hyperalgesia, it might not be involved in the natural process of opioid hyperalgesia.

Changes in protein expression not only occur in the spinal cord to upregulate the effects of C-fibers, they also occur in the brain during hyperalgesia. These changes in brain protein expression are comparatively sparse in opioid withdrawal research. In an intensive rodent study, phosphorylation of ERK2 (*p*-ERK2) was found to correlate with the mechanical hyperalgesia that followed 5 days of spontaneous withdrawal from high-dose fentanyl while *p*-ERK1 did not.[17] The study was thorough as the research team found a systemic signaling pathway of *p*-ERK2 that correlated with hyperalgesia. A MEK inhibitor which prevents ERK2 phosphorylation was injected into the central nucleus of the amygdala and the spinal cord. Astoundingly, both reversed not only behavioral hyperalgesia, but also normalized LTP induction following high-frequency stimulation.[17] In the analyzed opioid withdrawal literature, GluR1 expression in the amygdala, as well as adenyl cyclase and D2R expression in the striatum correlated to different aspects of withdrawal, but none of the analyzed withdrawal papers mentioned ERK2 supraspinally.[17,18,19] This would be a good target for future withdrawal studies. Protein expression in the amygdala may be especially important for OIH as it is not only associated with

hyperalgesia through *p*-ERK2 activity, but in a separate study, rats who maintained self-administration behavior of morphine were more likely to have increased GluA1 expression in the amygdala over rats who ceased self-administration.[18] Another study that implicates the amygdala's role in hyperalgesia consisted of fMRI brain imaging following a single 30-minute administration of remifentanil to humans. Note that any participants with a pre-existing pain condition were excluded from the study which is a clinical population of interest for treating OIH. Self-reports of thermal pain were not altered by this acute remifentanil withdrawal, though fMRI activity during thermal pain was significantly increased in the posterior-insula, the thalamus contralateral to stimulus and bilateral amygdalae. Activity in descending pathways from the rostral-ventral medulla was also increased.[20] The amygdala may be a site of importance for integrating affective and physical pain sensations.

This literature review has concretely shown that opioid-induced hyperalgesia is a symptom of opioid withdrawal, though it is still not certain if OIH may occur in the absence of withdrawal. Although LTP in the dorsal horn was detected after only 20 minutes of washout, another study found that 3 washouts after morphine administration (no time period listed) had a comparable effect to naloxone-induced withdrawal, which may imply this 20-minute washout could have induced acute withdrawal.[13,21] OIH being only a symptom of withdrawal is supported by the fact that only abrupt and not gradual cessation of opioid-caused hyperalgesia.[7] Thus far, opioid-induced hyperalgesia has not been reported with continuous perfusion of opioid, which would definitively classify OIH as a separate process from opioid withdrawal. The body of literature analyzed lacked mechanistic studies of opioid withdrawal in the brain that were correlated with behavioral assays. If research is intended to end with clinical translation, the assays used need to include a measure of the animals' behavior as restoring function is the goal for treating pain, opioid-induced or not. Furthermore, none of the withdrawal studies investigating mechanisms in the brain utilized a non-opioid pain source. This is an important factor in research as many people who suffer from OIH receive opioids for a pre-existing pain that is not associated with opioid use. Non-opioid pain was severely under-represented in the literature analyzed, with only 8 of 37 papers investigating OIH in surgery or inflammatory pain. These proposed directions in research would 1. Ensure that hyperalgesia was detected during opioid withdrawal and 2. Better define the various processes that contribute to opioid withdrawal, with or without a pre-existing pain condition.

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