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Opioid-Induced Hyperalgesia

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Abstract

Opioid-induced hyperalgesia (OIH) is a state of sensitization of pain receptors caused by opioid use. In OIH, there is a paradoxical response to opioids, in which opioids that are used to produce analgesia will instead induce sensitization to certain painful stimuli. The resulting pain might be similar or different from the original pain for which the opioids were taken. OIH is a characteristic phenomenon that could explain the loss of opioid effectiveness in many patients. The exact molecular mechanism for OIH is not yet fully understood. However, four proposed mechanisms are being considered in the present review to explain OIH including; N-methyl-D-aspartate (NMDA) receptor activation; spinal dynorphin; descending facilitation; and finally decreased reuptake and enhanced nociceptive response. It is important for clinicians to consider OIH in opioid-treated patients, particularly for any new appearance of unexplained pain, or when increasing the opiate dose results in worsening of the pain. OIH is managed by reducing opioid dosage, tapering opiods off, and adding NMDA receptor antagonists.

Keywords: Opioid-induced hyperalgesia; Dynorphin; Nociceptive response; Opioids; Facilitation; Treatment

Introduction

The use of opioids in the treatment of chronic non-cancer pain has escalated significantly in recent years. Long-term opioid use is problematic for many reasons, first: there is no evidence to support the long-term effectiveness of their use, second, opioids are well-known to be misused and abused among patients of all ages, and finally, opioids are associated with adverse events including opioid-induced hyperalgesia (OIH), which is the focus of the present review.

Hyperalgesia by definition is the enhanced response to pain from a stimulus that usually causes pain [1]. OIH is a state of sensitization of the nociceptive receptors caused by opioids use. In OIH, patients who originally take opioids for treating pain end up becoming more sensitive to certain painful stimuli. In other words, in addition to their analgesic effects, opioids can also result in paradoxical sensitization to painful stimuli. This type of pain experienced in patients with OIH might be the same type of pain they take the opioids for or a different type of pain. In contrast to tolerance, which is a progressive decrease in response to a drug that requires increasing the dose to achieve the desired effect, OIH cannot be managed by increasing the dose of the drug. OIH is a form of an exaggerated response to pain induced by the drug itself. Lowering the dose or completely eliminating the drug can alleviate the OIH; whereas increasing the dose can worsen it. As such, it is essential to know that OIH is reversible, but can require a long period of abstinence from opioids [2]. Administration of large doses of opioids for a long period of time (days to weeks) is associated with higher incidence of OIH, but in some cases giving the drug for shorter periods can lead to the same result [3,4]. For example, after acute administration of opioids, analgesic effects are seen within 1 to 5 hours, followed by a reduction in pain threshold that remains for several hours or days [3]. Therefore, chronic or acute use of opioids can cause OIH.

OIH caused by high doses of morphine (a commonly used opioid) is mediated by two non-opioid receptors; glycine and the NMDA receptors in the spinal cord and not by the opioid receptor system. This is evidenced by the fact that opioid antagonists have no effect on the OIH caused by high versus low opioid doses [4].

Mechanisms of development of OIH

The precise mechanism of OIH is yet to be determined. However, for the purpose of this review four proposed mechanisms for the development of OIH will be described. These mechanisms include NMDA receptor activation, spinal dynorphins, descending facilitation and finally decreased reuptake and enhanced nociceptive response.

NMDA-receptor activation: NMDA receptors play a crucial role in pain signaling. Some opioids and their metabolites possess agonistic effect on the NMDA receptors in the spinal cord. Such opioids activate NMDA receptors resulting in calcium influx, which in turn enhances the excitability of neurons. Enhanced neuronal excitability will facilitate the transmission of painful impulses initiated by any painful stimulus. Further, calcium influx activates protein kinase C (PKC), which results in phosphorylation and inactivation of opioid receptors. Additionally, increased calcium influx activates nitric oxide (NO) synthesis in the neurons [particularly NO isoform (nNOS)] which reduces the effect of opioids such as morphine [5-9].

Spinal dynorphin: Spinal dynorphin is an endogenous opioid that activates primarily the kappa opioid receptor and to a lesser extent the NMDA receptors [10]. Levels of spinal dynorphin were shown to increase with continuous infusion of opioids like morphine [10]. Increased levels of spinal dynorphin results in a release of spinal excitatory neuropeptides, such as calcitonin gene related peptide (CGRP) from primary afferents in the spinal cord [11]. An enhanced release of the excitatory neuropeptides after a painful stimulus takes place induces OIH [12]. As such, the analgesic effects of morphine can be restored by blocking the effects of spinal dynorphin by using dynorphin antiserum [10].

Descending facilitation: Rostral ventromedial medulla (RVM) is a part of the descending pathway, which modulates the transmission, and processing of painful stimuli at the level of the dorsal horn of the spinal cord. RVM has three different types of neurons; On-cells, Off-cells, and Neutral-cells, which respectively promote, inhibit, or have no effect on nociception processing in the dorsal horn of spinal cord [13]. Morphine given in doses sufficient to produce analgesia causes activation of the

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Off-cells, and inhibition of the On-cells [14]. It was observed in a study on rat animal models that chronic morphine exposure increases the number of the On-cells and promotes pain sensation via enhanced sensitization of the On-cells to painful stimuli. This finding could explain the development of OIH [15]. Anecdotally, a lesion to the dorsolateral funiculus (a region that carries the descending facilitative fibres from the RVM to the dorsal horn of spinal cord) can prevent or reverse OIH [16].

Decreased reuptake and enhanced nociceptive response: Decreased reuptake of nociceptive neurotransmitters such as substance P and glutamate from the afferent fibres in the spinal cord and the increased responsiveness of the spinal neurons to such transmitters after chronic opioid intake have been implicated in the development of OIH [17]

Other mechanisms: The inhibition of an important transport system known as P-glycoprotein, which is involved in the secretion of toxins including morphine and its metabolites out of the cerebrospinal fluid (CSF) can contribute to the induction, maintenance, and the severity of OIH [18]. Inhibition of this transport system (using medications such as verapamil, cyclosporin, ketoconazole, and quinine) can result in higher CSF levels of morphine and its metabolites [18].

In clinical studies, OIH has been observed in patients taking high doses of opioids, but not in patients taking low or moderate doses. Many reports have explained that in cases where opioid levels are rapidly rising (as in intrathecal administration); opioid metabolites (example morphine-3-glucuronide) cause neuroexcitation and could induce hyperalgesia, as many patients reported increased pain at the sites of ongoing pain [19-21].

Diagnosis of OIH

OIH typically produces diffuse, ill-defined pain distribution pattern. This new pain extends to other areas beyond the pre-existing pain areas. In contrast to tolerance, OIH becomes worse with higher opioid doses. Pain augmentation as a result of decreased opioid effectiveness in cases of tolerance can develop relatively slowly, however, pain augmentation in cases of OIH builds up quickly and with a stronger intensity than that of the initial pain [22].

Modulation of OIH

Preclinical studies point to the pathological activation of NMDA receptors in the development of OIH. Reduction or prevention of OIH can be achieved by means of antagonising the NMDA receptors with drugs such as ketamine, and methadone.

Ketamine: It is a non-competitive antagonist to the NMDA receptor. There is some evidence based on clinical studies that administration of low-dose Ketamine peri-operatively (either pre, intra, or post-operatively) can decrease the development of hyperalgesia in wounds in the post-operative period after acute intraoperative opioid administration [18].

Methadone: it is a weak NMDA receptor antagonist [23]. It is effective in reducing the OIH resulting from intake of high opioid doses [24]. Methadone is used in the process of opioid rotation to decrease the adverse effects of the offending opioid used. It has incomplete cross-tolerance with opioid receptors in addition to its NMDA receptor antagonistic effect [25-27]. It is worth mentioning that increased pain in former opioid addicts maintained on methadone has been reported. This implies that, in some cases, methadone can enhance pro-nociceptive pathways despite its NMDA receptor antagonistic properties [28].

Treatment strategies

Management of patients with OIH involves weaning from opioids, which can take a long time and requires patience and understanding from the patient's side, rotation to a different opioid, adding non-opioid pain medication, and alleviating withdrawal symptoms. Pain augmentation and development of withdrawal symptoms can happen anytime during opioid dose reduction and should be alleviated. Interventional pain management can be achieved via nerve block and behavioural pain management can also help [29-31]. Medications such as methadone and buprenorphine can be used for the treatment of OIH. Buprenorphine (currently available on the Canadian market under the trade name Butrans transdermal patches) is a partial opioid agonist and antagonist (i.e. it is a partial mu-opioid receptor agonist with kappa-opioid receptor antagonistic effect), in clinical trials buprenorphine showed an enhanced ability to treat hyperalgesia [32].

Conclusion

OIH is a less recognized adverse effect of chronic opioid use. It is now increasing as the number of people using opioids for chronic pain conditions has increased. In cases of failure of opioid therapy, OIH must be considered in the differential diagnosis. Before starting opioid treatment with any patient, the issue of OIH must be fully addressed in the informed consent.

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