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Topical review

Opioid-induced abnormal pain sensitivity: implications in clinical opioid therapy

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1. Introduction

Opioids produce analgesic effects through their modulatory role in nociceptive transmission. Under many circumstances opioids are the most efficacious analgesics commonly used in the clinical management of moderate to severe pain. Besides the known side effects, opioid treatment is associated with the development of tolerance to and dependence on opioid analgesics. A notable feature of opioid dependence is that hyperalgesic responses may occur both in animals and human subjects during a precipitated opioid withdrawal. This observation suggests that a pronociceptive process may have developed during opioid treatment, which may be unmasked following an opioid withdrawal.

Over the last several years, compelling evidence has accumulated indicating that abnormal pain sensitivity including hyperalgesia and allodynia occurs in animals receiving opioid administration even in the absence of overt, precipitated opioid withdrawal. This paradoxical opioid-induced pain sensitivity may be contributory to the behavioral manifestation of apparent opioid tolerance, a need for a dose increase to maintain the same analgesic efficacy. Similar changes in pain sensitivity have been observed in pain patients with opioid therapy and in former opioid addicts maintained on methadone treatment. Moreover, a growing body of evidence suggests that the development of opioid-induced pain sensitivity is mediated through neural mechanisms that involve cellular changes and neural circuits and that interact with the mechanisms underlying the development of pathological pain. The current evidence also suggests that opioid-induced pain sensitivity may be preventable by interrupting the cellular and molecular changes associated with the development of opioid tolerance. These issues will be discussed in the article with the emphasis on their clinical implications.

2. Preclinical evidence of opioid-induced pain sensitivity

A commonly employed experimental paradigm in studies of opioid tolerance is to assess changes of the antinociceptive efficacy (e.g. a comparison of dose response effects) before and after either repeated opioid boluses or continuous opioid administration. The tail-flick test is often used to evaluate the antinociceptive effects of opioids in preclinical studies. The presence of opioid-induced pain sensitivity would be indicated if baseline nociceptive thresholds are reduced following an opioid treatment regimen. For years, differences in baseline nociceptive thresholds before and after an opioid treatment have not been readily detectable using the tail-flick test, because this test often uses a steep stimulation curve with a fast-rising stimulation intensity that could mask changes in baseline nociceptive thresholds. In contrast with the tail-flick test, a test that utilizes a slow-rising stimulation curve such as the paw withdrawal test (Hargreaves et al., 1988) enables the detection of even subtle changes in baseline nociceptive thresholds.

When the paw withdrawal test is applied, there clearly is a progressive reduction of baseline nociceptive thresholds in rats receiving repeated intrathecal morphine administration over a 7 day period (Mao et al., 1994, 2002a,b). A reduction of baseline nociceptive thresholds also is observed in animals after subcutaneous fentanyl boluses using the Randall–Sellitto test in which a constantly increasing pressure is applied to a rat's hindpaw (Celerier et al., 2000; Laulin et al., 2002). In the latter studies, decreased baseline nociceptive thresholds lasted as long as 5 days after the cessation of four fentanyl bolus injections. A similar phenomenon of reduced baseline nociceptive thresholds has been observed in animals with repeated heroin administration (Celerier et al., 2001). These studies strongly indicate that repeated opioid administration could lead to a progressive and lasting reduction of baseline nociceptive thresholds, hence an increase in pain sensitivity.

As mentioned earlier, abnormal pain sensitivity such as hyperalgesia can be observed in association with an opioid

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withdrawal. Thus, it is logical to consider that decreased baseline nociceptive thresholds observed in animals treated with opioid boluses may reflect a subliminal withdrawal in which changes in baseline nociceptive thresholds could precede other withdrawal signs such as wet-dog shake and jumping. This is unlikely to be the case because in several studies progressive reduction of baseline nociceptive thresholds is unequivocally demonstrated in animals receiving a course of continuous intrathecal opioid infusion via osmotic pumps (Vanderah et al., 2000; Mao et al., 2002a,b). More importantly, opioid-induced pain sensitivity including thermal hyperalgesia and tactile allodynia is observed in these animals even when an opioid infusion continues (Vanderah et al., 2000; Mao et al., 2002a). Collectively, these data indicate an important concept that prolonged opioid treatment not only results in a loss of opioid antinociceptive efficacy, a negative sign of system adaptation (desensitization), but also leads to activation of a pronociceptive system manifested as reduction of nociceptive thresholds, a positive sign of system adaptation (sensitization).

3. Clinical evidence of opioid-induced pain sensitivity

Unlike laboratory studies in which changes in baseline nociceptive thresholds are measured in a controlled setting, it is often difficult to determine whether changes in pain sensitivity occur clinically following opioid administration. With this in mind, there is evidence suggesting a similar phenomenon of opioid-induced pain sensitivity in clinical settings. First, decreases in opioid analgesic efficacy following a course of opioid administration, such as that after an intraoperative remifentanil infusion, have been observed (Cooper et al., 1997; Vinik and Igor, 1998; Guignard et al., 2000), although a lack of change in opioid analgesic efficacy under a similar condition also has been reported (Cortinez et al., 2001). While reduced opioid analgesic efficacy may be interpreted as apparent opioid tolerance (Vinik and Igor, 1998), these observations alone do not adequately distinguish whether the presence of apparent opioid tolerance is due to a diminished opioid analgesic efficacy, an opioid-induced increase in pain sensitivity, or both. For either reason, there can be an increased opioid demand from the patients who had received opioids as compared to the matched patients without the intraoperative opioid infusion (Guignard et al., 2000). However, a strong indication for increased pain sensitivity in those opioid-treated patients is that they actually reported more pain than the matched non-opioid controls (Guignard et al., 2000). Conceivably, the level of postoperative pain would be comparable between these two groups, if there were just a loss of opioid analgesic efficacy but no increase in pain sensitivity in those opioid-treated patients.

Second, for a long time there have been empirical observations that pain sensitivity differs between subjects with opioid addiction and normal subjects (Martin and Inglis, 1965; Ho and Dole, 1979; Compton et al., 2001). More recently, it has been reported that pain sensitivity to experimental pain stimulation such as cold pressor is increased in opioid addicts (Compton et al., 2001). Moreover, those former opioid addicts maintained on a methadone maintenance program reported the further enhancement of pain sensitivity as compared to the matched former opioid addicts not enrolled in a methadone maintenance program (Compton et al., 2001). This observation indicates that a prolonged methadone maintenance program may enhance abnormal pain sensitivity in former opioid addicts. To date, little information is known concerning cancer or non-cancer pain patients with chronic opioid therapy with respect to changes in their pain sensitivity. Clinical studies are urgently needed to address this issue in this large population of pain patients.

4. Neural mechanisms contributory to opioid-induced pain sensitivity

As discussed above, the development of opioid-induced pain sensitivity is closely linked to the development of pharmacological opioid tolerance. Both are initiated by opioid administration and could contribute to the manifestation of apparent opioid tolerance. In fact, these two components of opioid-induced changes would be indistinguishable if the assessment endpoint was to determine a shift of opioid antinociceptive dose response curves in animal studies or a change in opioid dose demand in clinical settings. However, these two components of apparent opioid tolerance may involve opposing cellular mechanisms, i.e. a desensitization process (pharmacological tolerance) versus a sensitization process (opioid-induced pain sensitivity). Most importantly, clinical approaches to resolving apparent opioid tolerance may very well be different between these two processes. The following discussion focuses on the evidence indicating an active (sensitization) process following opioid administration that may be critical to the neural mechanisms of opioid-induced pain sensitivity.

4.1. Role of the central glutamatergic system

An important development over the last decade is that activation of excitatory amino acid receptors such as the *N*-methyl-D-aspartate receptor (NMDAR) has been implicated in the mechanisms of pharmacological opioid tolerance (Trujillo and Akil, 1991; Marek et al., 1991). Subsequently, the NMDAR has been shown to be critical to the cellular mechanisms of opioid-induced pain sensitivity as well (Mao et al., 1994; Laulin et al., 2002). Although many details remain to be elucidated, the current data suggest that opioid-induced desensitization (pharmacological tolerance) and sensitization (opioid-induced pain sensitivity) processes may share common cellular mechanisms in part mediated through activation of the central glutamatergic system.

First, inhibition of NMDARs prevents the development

of both pharmacological tolerance and opioid-induced pain sensitivity (Trujillo and Akil, 1991; Marek et al., 1991; Mao et al., 1994). Second, perturbation of spinal glutamate transporter activity, which regulates extracellular glutamate availability, modulates the development of both morphine tolerance and the associated pain sensitivity (Mao et al., 2002a). Third, the Ca^{2+}-regulated intracellular protein kinase C (PKC) is likely to be an intracellular link between cellular mechanisms of tolerance and opioid-induced pain sensitivity (Mao et al., 1994; Narita et al., 2001; Zeitz et al., 2002). Fourth, cross-talk between the neural mechanisms of opioid tolerance and pathological pain may exist and contribute to the exacerbated pain and reduced opioid analgesic efficacy under such circumstances (Mao et al., 1995a; Mao, 1999). Fifth, prolonged morphine administration induces NMDAR-mediated neurotoxicity in the form of apoptotic cell death, which is, at least in part, contributory to both morphine tolerance and abnormal pain sensitivity (Mao et al., 2002b). Taken together, these lines of evidence strongly indicate a critical role of the central glutamatergic system in the neural mechanisms of both opioid tolerance and opioid-induced pain sensitivity.

4.2. Role of spinal dynorphin

Convincing evidence has indicated that spinal dynorphin plays an important role in the expression of both opioid tolerance and abnormal pain sensitivity (see review by Vanderah et al., 2001). Of significance to note is that spinal dynorphin content increases following a period of continuous infusion with a μ-opioid receptor agonist (Vanderah et al., 2000). Moreover, there is an increase in the evoked release of spinal excitatory neuropeptides such as calcitonin gene-related peptide from primary afferents in morphine-treated animals that requires the spinal dynorphin activity (Gardell et al., 2002). These observations lend further support to the concept that opioid administration induces a pronociceptive process in part by means of increases in the synthesis of excitatory neuropeptides and their release upon peripheral stimulation.

4.3. Role of descending facilitation

Additional evidence for the involvement of a sensitization process following opioid administration derives from a group of studies that indicate the influence of descending facilitation on opioid-induced pain sensitivity. First, subsets of neurons (on- and off-cells) within the rostral ventromedial medulla (RVM) have characteristic response patterns to opioids (Barbaro et al., 1986; Heinricher et al., 1992). Their activities may contribute to the mechanisms of descending facilitation that influence spinal nociceptive processing (Morgan et al., 1992). Second, on-cell activity within the RVM increases in association with the behavioral manifestation of naloxone-precipitated hyperalgesia (Bederson et al., 1990). Third, bilateral lesioning of the dorsolateral funiculus, an anatomic pathway connecting the brainstem and spinal cord, blocks the increase in spinal excitatory neuropeptides in opioid-treated animals (Gardell et al., 2002), suggesting that the descending facilitation may function in part through the modulation of spinal neuropeptide contents.

These lines of evidence strongly support an active pronociceptive process that is initiated by opioid administration. An integrated view of interactions between individual elements of this opioid-induced pronociceptive process is beyond the scope of this article. However, it would be reasonable to suggest that the involvement of each of these elements may depend on the route (intrathecal versus systemic) and the duration of opioid administration as well as assessment endpoints. For instance, a distinct difference between the involvement of the central glutamatergic system and dynorphin is that, although inhibition of both systems reverses opioid-induced pain sensitivity, apparent opioid tolerance could only be reduced acutely by a dynorphin antiserum but not by an NMDAR antagonist (Trujillo and Akil, 1991; Mao et al., 1994; Vanderah et al., 2000). This suggests that spinal dynorphin may be involved in the expression of apparent opioid tolerance that is likely reflected in part by increased pain sensitivity. Another interesting issue is that since the descending facilitation is triggered by activation of opioid receptors, would the development of opioid tolerance (a desensitization process) at the cellular level diminish this facilitatory mechanism over time? Future studies may provide insightful data with respect to interactions between neural mechanisms mediated through the glutamatergic system, spinal dynorphin, and descending facilitation.

5. Clinical implications

The diminishing opioid analgesic efficacy during a course of opioid therapy is often considered as a sign of pharmacological opioid tolerance. As such, an opioid dose escalation has been a common approach to restoring opioid analgesic effects, assuming that there are no contraindications and no apparent disease progression. This conventional practice of opioid therapy may be revisited in light of both preclinical and clinical evidence of paradoxical opioid-induced pain sensitivity. That is, apparent opioid tolerance is not synonymous with pharmacological tolerance, which calls for opioid dose escalation, but may be the first sign of opioid-induced pain sensitivity suggesting a need for opioid dose reduction. This is a practical issue encountered by nearly every healthcare provider who manages pain patients. The challenge is how to distinguish the elements of apparent opioid tolerance (pharmacological tolerance versus opioid-induced pain sensitivity) in clinical settings, since approaches to resolving these two elements of apparent opioid tolerance could be very different. The following discussion offers some perspectives on this issue.

5.1. Opioid-induced pain versus preexisting pain

Several features of opioid-induced pain observed in

preclinical and clinical studies may be helpful in making distinctions between opioid-induced pain and preexisting pain. First, since opioid-induced pain would conceivably exacerbate a preexisting pain condition, pain intensity would be increased above the level of preexisting pain following opioid treatment in the absence of apparent disease progression. Second, opioid-induced pain is expected to be diffuse, less defined in quality, and beyond the distribution of a preexisting pain state, given that the underlying mechanisms of opioid-induced pain involve neural circuits and extensive cellular and molecular changes. Third, examination of responses to experimental pain stimulation using quantitative sensory testing may reveal changes in the pain threshold, tolerability, and distribution pattern associated with the development of opioid-induced pain sensitivity. These parameters may also help make distinctions between the exacerbation of preexisting pain and opioid-induced pain. Fourth, undertreatment of a preexisting pain or the development of pharmacological tolerance may be overcome by a trial of opioid dose escalation. To the contrary, opioid-induced pain could be worsened following an increase in opioid doses.

5.2. Opioid regimens and opioid-induced pain sensitivity

Several factors regarding an opioid therapy may influence the development of opioid-induced pain sensitivity. First, it remains to be investigated as to what opioid dose ranges lead to opioid-induced pain sensitivity. In preclinical studies, opioid doses given through neuraxial or systemic routes are comparable to moderate opioid doses in clinical settings. Second, are there differences between different categories of opioid medications (e.g. morphine versus methadone) in terms of their ability to induce pain sensitivity? Some evidence suggests that the development of opioid-induced pain sensitivity may differ between individual opioid medications (Compton et al., 2001). Furthermore, is there cross-pain sensitivity to other opioids following the treatment with one opioid? Third, the temporal correlation between an opioid therapy and the development of opioid-induced pain sensitivity remains unknown, although opioid-induced pain sensitivity has been demonstrated in patients receiving a short course of intraoperative opioids (Vinik and Igor, 1998). With a given dose of opioid treatment, how long would it take to develop opioid-induced pain sensitivity in a clinical setting? Conceivably, opioid-induced pain sensitivity would be more likely to develop in patients receiving high opioid doses with a sustained treatment course.

5.3. Opioids and preemptive analgesia

While the clinical relevance and effectiveness of preemptive analgesia remains an issue in debate, several reasons may argue against the use of opioids as the main agent for preemptive analgesia. First, a large dose of intraoperative opioids may activate a pronociceptive system leading to the development of abnormal pain sensitivity postoperatively. This may confound the assessment of postoperative pain and counteract the opioid analgesic effects. Second, the idea of preemptive analgesia calls for preemptive inhibition of neural plastic changes largely mediated through the activation of the central glutamatergic system. Opioids are thought to inhibit the nociceptive input that could activate the central glutamatergic system. Paradoxically, opioid administration may initiate rather than inhibit the activation of the central glutamatergic system as discussed above. Third, neural mechanisms of opioid tolerance and opioid-induced pain sensitivity may interact with those of pathological pain and pathological pain could be exacerbated with opioid administration (Mao et al., 1995b).

In summary, the issue of opioid-induced pain sensitivity should be considered when an adjustment of opioid doses is contemplated because an opioid treatment fails to provide expected analgesic effects and/or there is an unexplainable pain exacerbation following a period of an effective opioid treatment. Thus, increasing the opioid dose is not always the answer to an ineffective opioid therapy. Less (opioid) can be more (in pain reduction) in some cases. This approach may also be accompanied by an opioid rotation and/or by adding additional non-opioid adjunctive medications. In addition, studies from basic science have suggested new strategies for preventing or reducing the development of both pharmacological tolerance and opioid-induced pain sensitivity such as a combined use of an opioid and a clinically available NMDAR antagonist (Mao et al., 1995b). More studies are warranted to further address this important issue that has enormous implications in clinical pain management.

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