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Topical review

# Mechanisms of opioid-induced pain and antinociceptive tolerance: descending facilitation and spinal dynorphin

Todd W. Vanderah[a,b], Michael H. Ossipov[a,b], Josephine Lai[a,b], T. Philip Malan Jr.[a,b], Frank Porreca[a,b,*]

[a]*Department of Pharmacology, University of Arizona Health Sciences Center, Tucson, AZ 85724, USA*
[b]*Department of Anesthesiology, University of Arizona Health Sciences Center, Tucson, AZ 85724, USA*

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## 1. Introduction

Although opioid analgesic tolerance is recognized experimentally and clinically (Foley 1995), the mechanisms underlying this phenomenon remain largely unknown. At the physiological level, tolerance to opioid antinociception can be blocked or prevented by inhibition of many diverse endogenous transmitter and receptor systems. Among the many different substances that have been shown to prevent and/or reverse opioid antinociceptive tolerance, perhaps the most well studied are NMDA receptor antagonists (e.g. Trujillo and Akil, 1991; Mao et al., 1995; Manning et al. 1996; Kest et al., 1997; Celerier et al. 1999). Many of these studies have suggested possible mechanisms by which the modulation of opioid antinociceptive tolerance by NMDA antagonists might occur. Most proposed mechanisms have focused on the likely co-localization of NMDA and opioid receptors and common intracellular pathways, though a key concern was the failure to clearly identify the source of possible NMDA receptor activation during prolonged opioid exposure (e.g. Mao et al., 1995). An additional complicating factor in the interpretation of mechanisms by which modulation of opioid antinociceptive tolerance might occur is the great diversity of substances that have been reported to produce such effects. These include, among others, CGRP antagonists (Menard et al., 1996; Powell et al., 2000), NO synthase inhibitors (Powell et al., 1999), calcium channel blockers (Aley and Levine, 1997), CCK antagonists (Xu et al., 1992), cyclooxygenase inhibitors (Powell et al., 1999) and protein kinase C inhibitors (Mao et al., 1995). That so many systems can be identified to modulate opioid antinociceptive tolerance makes it difficult to implicate a common cellular mechanism for the actions of all these substances. For this reason, we have focused on possible commonalities in the endogenous mechanisms which promote, rather than block, opioid antinociceptive tolerance.

Increased expression of spinal dynorphin resulting from sustained opioid exposure was recently suggested to be pronociceptive. The resulting state of enhanced nociceptive sensitivity manifested behaviorally as opioid antinociceptive tolerance (Vanderah et al., 2000). Opioid antinociceptive tolerance was also shown to depend upon tonic descending facilitation to increase nociceptive sensitivity (Vanderah et al., 2001). Both mechanisms relate to opioid-induced enhancement of baseline pain states. Many of the manipulations which block opioid analgesic tolerance also block opioid-, and injury-induced hyperalgesia. The behavioral manifestation of opioid antinociceptive tolerance is suggested to result, in part, from increased pain. Pain can thus be thought of as a 'physiological antagonist' of opioid antinociception, something which is certainly true clinically, and manipulations which block opioid-induced pain will also be expected to block opioid antinociceptive tolerance. Whether this hypothesis can be substantiated for the many classes of substances which have been reported to block opioid tolerance awaits experimental validation.

## 2. Opioid-induced pain

Clinical reports suggest that opioids, intended to abolish pain, can unexpectedly produce abnormally heightened pain sensations (see Arner et al., 1988, for review) which are characterized by increased sensitivity to noxious stimuli (hyperesthesias) and pain elicited by normally innocuous stimulation (allodynia). Such abnormal pain has been

* Corresponding author. Department of Pharmacology, University of Arizona Health Sciences Center, Tucson, AZ 85724, USA. Tel.: +1-520-626-7421; fax: +1-520-626-4182.
*E-mail address:* frankp@u.arizona.edu (F. Porreca).


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described as being qualitatively different from normal pain sensation and differentially localized from the site of the original pain complaint. Opioid-induced abnormal pain, even after short term exposures, has also been repeatedly demonstrated in animal studies (e.g. Mao et al., 1995; Celerier et al., 1999). Such abnormal pain in humans has been suggested as an explanation for the poor results of preemptive analgesia in humans (Eisenach, 2000). Spinal morphine has been associated with paradoxical algesia and hyperesthesias, which were naloxone-insensitive (Yaksh and Harty, 1988).

It has been suggested that repeated opioids maintain their efficacy, but the concurrent expression of hyperalgesia counteracts antinociception, producing an impression of tolerance (Celerier et al., 1999). Opioid-induced hyperalgesia has been hypothesized to result from unmasking of compensatory neuronal hyperactivity which becomes evident after the opioid is removed or occurring intermittently between injections (Gutstein, 1996). Thus, opioid-induced hyperalgesia might result from repeated episodes of opioid withdrawal ('mini-withdrawals') (Gutstein, 1996). Demonstration of opioid-induced pain with paradigms of repeated injection are subject to this criticism.

Recent studies have shown that continuous opioid exposure produces exaggerated pain and, importantly, such pain occurs while the opioid is continuously present in the system (Vanderah et al., 2000, 2001). Continuous spinal infusion of either [D-Ala$^2$,*N*-Me-Phe$^4$,Gly-ol$^5$]enkephalin (DAMGO) or morphine produced both increased sensitivity to normally innocuous mechanical stimulation and thermal hyperalgesia while these agonists were still being delivered and antinociceptive tolerance was observed at the same time (Vanderah et al., 2000). Similar effects were seen when prolonged morphine exposure resulted from subcutaneous (s.c.) implantation of pellets or osmotic minipumps (Vanderah et al., 2001). Such opioid-induced abnormal pain was also demonstrated with repeated daily removal and concurrent replacement of subcutaneous morphine pellets (Vanderah and Porreca, unpublished observations). The demonstration of abnormal pain during continuous opioid delivery, by multiple routes and through minipumps and pellets, minimizes concerns that the sensory changes were due to the development of states of 'mini-withdrawals'.

## 3. Mechanisms of opioid-induced pain: descending facilitation

Recent studies have indicated that opioid-induced pain and antinociceptive tolerance may result from tonic activation of a descending pain facilitatory pathway (Vanderah et al., 2001). Noxious inputs to the spinal cord are known to be modulated from supraspinal sites. One region critical to integration of nociceptive processing and descending modulation is the rostroventromedial medulla (RVM) (Fields and Basbaum, 1999; Fields and Heinricher, 1985). Based on response characteristics, Fields and colleagues (Fields and Basbaum, 1999; Fields and Heinricher, 1985) have identified three classes of neurons in the RVM. These cells appear to have different roles in nociceptive processing with 'OFF'-cells mediating antinociception when activated by disinhibition, 'ON'-cells facilitating nociceptive processing through both local interactions within the RVM and descending projections to the spinal cord and 'neutral' cells having no, or unknown, roles in nociception (see Fields and Basbaum, 1999, for review).

Prolonged delivery of a noxious thermal stimulus produced increased 'ON' cell discharge along with a facilitation of nociceptive reflexes (Morgan and Fields, 1994). Inactivation of RVM activity with lidocaine blocked the facilitated withdrawal response (Morgan and Fields, 1994). The microinjection of $CCK_8$ into the RVM attenuated morphine-induced activation of 'OFF' cell activity (Heinricher et al., 2001) and elicited enhanced sensitivity to normally innocuous mechanical stimuli (Kovelowski et al., 2000). Electrical stimulation of the RVM facilitated dorsal horn neuronal activity and the spinal nociceptive tail flick reflex (Zhuo and Gebhart, 1997). Spontaneous 'ON'-cell activity increases along with facilitated nocireponsive behavior during naloxone-precipitated withdrawal (Kaplan and Fields, 1991). These actions were blocked by microinjection of lidocaine into the RVM (Kaplan and Fields, 1991). In spite of these investigations, the state of 'ON'-cell or 'OFF'-cell firing during sustained morphine administration, in the absence of withdrawal, has not been directly studied. As sustained opioid exposure elicits enhanced pain, and enhanced pain can result from increased 'ON' cell activity, then it is reasonable to suggest that a component of opioid-induced abnormal pain and antinociceptive tolerance may be the result of increased activity of pain facilitation cells arising in the RVM.

Continuous morphine exposure by s.c. pellet implantation or osmotic minipump produces enhanced sensitivity to normally innocuous mechanical stimuli and thermal hyperalgesia that is reversibly blocked by the microinjection of lidocaine into the RVM (Vanderah et al., 2001). Such abnormal pain developed over a period of days and did not reflect the acute (antinociceptive) activity of the opioid (Vanderah et al., 2001). The effectiveness of RVM lidocaine to block opioid-induced abnormal pain supports the concept of tonic discharge of pain facilitation cells in the RVM. Spinopetal projections from RVM neurons make up the majority of fibers of the dorsolateral funiculus (DLF) (Fields and Heinricher, 1985). Lesions of the DLF have blocked antinociception produced by manipulations in the RVM and other supraspinal nuclei, indicating that inhibition of spinothalamic neurons in the dorsal horns of the spinal cord may be meditated through this pathway (Cho and Basbaum, 1989). Electrical stimulation of the DLF produced excitation of neurons in the superficial dorsal horn, demonstrating a clear descending facilitation through this pathway (McMa-

hon and Wall, 1988). Consistent with these observations, disruption of the DLF blocked the enhanced sensitivity to normally innocuous mechanical stimuli and thermal hyperalgesia resulting from sustained opioid delivery by subcutaneous pellets or osmotic minipump (Vanderah et al., 2001). Such findings are also consistent with the reversal of nerve injury-induced abnormal pain by either RVM lidocaine (Kovelowski et al., 2000) or DLF lesion (Ossipov et al., 2000). These observations suggest that tonic activation of descending facilitation may represent a mechanism of chronic pain resulting from nerve injury or opioid exposure.

The manipulations employed to block opioid-induced pain were also demonstrated to block the behavioral manifestation of opioid antinociceptive tolerance (Vanderah et al., 2001). Rats with subcutaneous morphine pellets displayed a rightward displacement of the i.th. morphine antinociceptive dose-response curve which was blocked in a time-related fashion by RVM lidocaine (Vanderah et al., 2001). Bilateral DLF lesions prior to morphine pellet implantation prevented the development and expression of morphine antinociceptive tolerance as shown by a lack of rightward displacement of the i.th. dose-response curve. Normal nocifensive responses and the antinociceptive action of morphine in rats implanted with placebo pellets was not affected by DLF lesions, indicating that these changes were not due to a disruption of normal sensory processing (Vanderah et al., 2001). An additional feature of opioid antinociceptive tolerance is the well-known loss of supraspinal/spinal antinociceptive synergy (e.g. Roerig et al., 1984). RVM lidocaine blocked the rightward displacement seen in the s.c. morphine dose-response curve in s.c. morphine pellet-implanted rats, possibly due to the now present supraspinal/spinal synergy as a consequence of restored spinal morphine potency (Vanderah et al., 2001).

## 4. Mechanisms of opioid-induced pain: spinal dynorphin

The studies described above suggest that sustained morphine exposure elicits neuroplasticity, either in the RVM or in structures communicating with the RVM, resulting in tonic bulbospinal facilitation (Vanderah et al., 2001). Such descending facilitation might also play a significant role in spinal plasticity resulting from sustained exposure to opioids. A consistent observation is the increase in expression of dynorphin in the spinal dorsal horn following opioid administration. Evidence suggests that spinal dynorphin is an important mediator of sustained abnormal pain (Malan et al., 2000; Wang et al., 2001). Although dynorphin was originally identified as an endogenous kappa-opioid agonist (Goldstein et al., 1979) and may act as an endogenous antinociceptive agent under certain conditions (Ossipov et al., 1996) this peptide has significant non-opioid activity. Considerable evidence now supports the conclusion that enhanced expression of spinal dynorphin is pronociceptive (Cho and Basbaum, 1989; Caudle and Isaac, 1988; Kajander et al., 1990; Draisci et al., 1991; Dubner and Ruda, 1992; Nahin et al., 1992; Stanfa and Dickenson, 1995; Wang et al., 2001) and promotes opioid tolerance (Vanderah et al., 2000).

Elevations in spinal dynorphin content are seen in animals with s.c. morphine pellets or with intrathecal infusion of opioids (Vanderah et al., 2000; Gardell and Porreca, unpublished observations). Spinal infusion of DAMGO over 6–7 days produced increased sensitivity to normally innocuous mechanical stimuli and thermal hyperalgesia during the infusion period (Vanderah et al., 2000). This treatment elevated lumbar dynorphin content and the spinal injection of dynorphin antiserum blocked enhanced sensitivity to normally innocuous mechanical stimuli and thermal hyperalgesia in DAMGO-treated rats. Dynorphin antiserum (but not control serum) also unmasked the antinociceptive action of the still-present DAMGO and blocked the rightward displacement of the dose-effect curve for spinal morphine in DAMGO-infused rats, indicating a blockade of antinociceptive tolerance (Vanderah et al., 2000). Dynorphin antiserum did not alter baseline sensory thresholds or the antinociceptive activity and potency of spinal morphine in vehicle-infused rats (Vanderah et al., 2000). Thus, manipulations which block opioid-induced pain, in this case due to spinal infusion of opioid, also block the behavioral manifestation of antinociceptive tolerance. The data suggest that sustained opioid administration leads to elevated expression of spinal dynorphin which in turn promotes an abnormal pain state, increases the requirement for opioid dose in order produce a comparable antinociceptive effect as in animals without increased nociception, resulting in an apparent manifestation of antinociceptive tolerance. It should be emphasized that such pain occurs while the opioid is continually delivered to the spinal cord, arguing against opioid withdrawal as an explanation of altered sensory level.

Systemic opioid administration also increases spinal dynorphin expression (Vanderah et al., 2000). The precise mechanisms through which increased spinal dynorphin expression promotes pain, and consequently the manifestation of opioid tolerance, remain to be elucidated. However, there is evidence that non-opioid actions of dynorphin promote the release of excitatory transmitters from primary afferent neurons, suggesting a positive feedback which amplifies further sensory input. Microdialysis studies have demonstrated localized, dose-dependent release of excitatory amino acids by exogenous dynorphin in the hippocampus and spinal cord (Faden, 1992). Dynorphin facilitates capsaicin-evoked substance P release from trigeminal nuclear slices, an effect blocked by MK-801 but not by opioid antagonists (Arcaya et al., 1999). More recently, Hargreaves and colleagues demonstrated that capsaicin-stimulated release of CGRP in spinal cord slices was potentiated by dynorphin$_{(2–13)}$, a non-opioid fragment (Claude et al., 1999). These data were confirmed in our laboratory. These findings are consistent with extensive data supporting

non-opioid, excitatory activity of dynorphin in vivo (Bakshi et al., 1992; Stewart and Isaac, 1991; Vanderah et al., 1996).

## 5. Synthesis

Opioid analgesic tolerance is well documented and may limit the effectiveness of these substances in the treatment of chronic pain. Although cellular mechanisms of tolerance have been proposed, it has not yet been possible to clearly interpret these effects in terms of mechanisms which elicit antinociception. Many clinical and experimental reports indicate that prolonged opioid administration can produce paradoxical pain. We have suggested that opioid-mediated paradoxical pain may result from neuroplastic changes that lead to tonic activation of descending facilitation from the RVM. Such descending facilitation may influence increased expression of spinal dynorphin resulting in enhanced pain. Underlying opioid-induced abnormal pain may be an important reason why opioid requirements to produce a consistent level of analgesia increase after prolonged opioid exposure, thus producing the behavioral manifestation of antinociceptive tolerance. These suggestions also offer an approach for testing the possibility that the many substances reported to block opioid antinociceptive tolerance do so, ultimately, by blocking opioid-induced mechanisms which promote pain. Critically, once manipulations are made which block either the expression or maintenance of opioid-induced pain, no apparent change in opioid signal transduction is seen, suggesting that such manipulations may improve the effectiveness of opioids used for treatment of chronic pain.

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