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Opioids: keeping the good, eliminating the bad

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Abstract

Two new studies show that mechanisms mediating the opioid side effects of tolerance, hyperalgesia and physical dependence are mediated spinally and can be dissociated from analgesia. These side effects can be selectively targeted by clinically available drugs without affecting their pain-relieving effects.

For thousands of years, opioids have been the gold standard for the treatment of severe pain. However, side effects such as tolerance, dependence and addiction have contributed to the current epidemic of opioid abuse and overdose-related deaths in the US¹. Recently, it has been shown that opioid side effects can be dissociated from analgesic effects, which presents the possibility that side effects could be selectively targeted to minimize the risk of opioids². It has been known for some time that tolerance to and physical dependence on opioids can be mediated by spinal mechanisms³. Two recent papers^{4,5} detail spinal and peripheral mechanisms underlying opioid tolerance, opioid-induced hyperalgesia (OIH) and physical dependence. Furthermore, these studies identify potential mechanisms for treating these devastating side effects by using drugs that are in common clinical use for other medical conditions.

Analgesic tolerance, or the need for higher doses to maintain pain relief with chronic drug use, increases the risks of opioid use because tolerance to other side effects, such as life-threatening respiratory depression, develops much more slowly. Physical dependence, a series of drug-induced physiological changes that leads to a withdrawal syndrome if drug use is stopped, is extremely unpleasant, although not life-threatening for opioids, and is hypothesized to be an important component underlying addiction⁶. Another side effect of chronic opioid use is OIH, or pain sensitization induced by opioids. This phenomenon was described initially in the context of opioid withdrawal⁷. However, some studies have demonstrated this phenomenon clinically in people with opioid addiction who were not overtly withdrawing from narcotics⁷.

A current challenge with regard to opioid use is how to selectively prevent opioid-induced side effects without altering their pain-relieving properties. Opioid side effects were previously assumed to be a direct consequence of opioid receptor signaling. Tolerance and

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physical dependence were also thought to be mediated by the brain because of the complex behavioral responses elicited. Studies examining the neuroanatomical substrates underlying tolerance and OIH have also suggested that the activation of spinal microglia by opioids could have an important role in tolerance development^{8,9}. It has also been shown that chronic opioid administration can induce long-term synaptic potentiation (LTP), a persistent increase in synaptic strength that occurs with repeated stimulation of the synapse, at the spinal level.

Corder *et al.*⁵ use genetic approaches to demonstrate that the μ -opioid receptors (MORs) expressed on primary afferent nociceptors, which convey information about pain from the periphery to the spinal cord, drive the initiation of opioid tolerance (Fig. 1). Mice lacking the MOR on nociceptors did not develop tolerance, whereas pain relief was unaffected. This implies that the analgesic effects of morphine are mediated centrally, either in the spinal cord or brain, and reinforces the concept that the signaling mechanisms underlying tolerance and analgesia can be dissociated². Corder *et al.*⁵ also demonstrated that the MOR was not expressed in spinal microglia. Interestingly, morphine was shown to activate microglia in MOR-knockout mice. However, neither tolerance nor OIH was observed in these mice. Taken together, these results argue strongly that the presynaptic MOR in afferent nociceptors is necessary for the development of both tolerance and OIH. Additionally, they imply that the proposed role of microglia in opioid tolerance⁹ is also mediated through presynaptic MORs on the nociceptors. Importantly, they showed that opioid antagonists that are unable to penetrate into the brain or spinal cord blocked the initiation of opioid tolerance without affecting pain relief in mice. These drugs, which are currently approved for clinical use for opioid-induced constipation, also blocked the onset of opioid tolerance in inflammatory and nerve-injury pain models.

Burma and colleagues⁴ focus on opioid withdrawal in their study. Like Corder *et al.*⁵, they demonstrate that microglia were activated by morphine. The depletion of microglia using a targeted cellular toxin decreased withdrawal behaviors markedly, consistent with previous descriptions of microglial involvement in opioid withdrawal⁹. They further show that chronic morphine administration upregulated the PANX1 ATP channel in spinal cord microglia. Importantly, they show that PANX1 is activated during withdrawal, and that activation is restricted to spinal cord microglia. Interestingly, they also demonstrated that chronic morphine stimulation upregulated the P2X7 receptor, which is activated by ATP and also known to open PANX1 channels. P2X7 inhibition reduced withdrawal symptoms. Taken together, we propose these findings suggest that the P2X7-PANX1 signaling cascade could function as a feed forward loop, amplifying the cellular response to withdrawal. Mice lacking PANX1 on microglia showed decreased withdrawal behaviors as compared to controls, yet morphine analgesia was not affected. Finally, when the PANX1 inhibitors probenecid—currently used for the treatment of gout—and mefloquine, an antimalarial drug, were administered before the opioid antagonist naloxone in mice, withdrawal behaviors were markedly reduced.

Both articles show that repeated morphine injections lead to microglial activation in the spinal cord. However, Corder *et al.*⁵ provide strong evidence that the MOR is not expressed on microglia. Burma *et al.*⁴ did see effects of opioids in microglial culture, which suggests

that the MOR is expressed in microglia. It is possible that culturing microglia could induce MOR expression, or that these data could simply reflect two different mechanisms causing microglial activation. Corder *et al.*⁵ also showed that OIH was prevented in global MOR-knockout mice but microglia were still activated. This seems to conflict with prior work demonstrating that microglial inhibition blocks OIH and tolerance⁹. However, it could be that both microglial activation and presynaptic MORs are necessary for opioid tolerance and/or OIH to occur. Perhaps microglia release cytokines that sensitize primary afferent-nerve terminals, which then permits the development and maintenance of tolerance and/or OIH.

In addition, Corder *et al.*⁵ show that synaptic potentiation induced by opioids was presynaptic, whereas Burma *et al.*⁴ observed postsynaptic facilitation (Fig. 1), reflecting both sides of a hotly contested controversy in the field^{10,11}. One possible explanation for these observations is differences in experimental paradigms. However, it could be that presynaptic LTP could underlie OIH, whereas postsynaptic facilitation could underlie opioid withdrawal. As mentioned above, OIH has been described as a symptom of opioid withdrawal¹². Thus, pre- and postsynaptic facilitation could represent two manifestations of the same physiological process, but underlie different behavioral responses.

Both of these studies reinforce the concepts that opioid tolerance, physical dependence and OIH are mediated at the level of the spinal cord and peripheral nociceptors, and that the undesirable side effects of opioids can be dissociated from pain relief and selectively targeted. Both papers also raise the exciting possibility that effective treatments might be available soon, given that drugs currently used for other indications markedly reduced opioid side effects in animals without reducing pain relief. Future translational studies could enable us to eventually eliminate suffering for untold millions of patients with chronic pain, allowing opioids to do good without causing patients negative side effects.

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Figure 1.

Spinal and peripheral mediation of opioid side effects. Corder *et al.*⁵ show in mice that the binding of morphine (shown in yellow) to μ -opioid receptors (MOR) expressed on primary afferent nociceptors mediate tolerance and opioid-induced hyperalgesia, possibly through presynaptic long-term potentiation (LTP). These side effects can be reduced by an opioid antagonist that does not penetrate into the spinal cord (shown in red). Burma and colleagues⁴ show that microglia mediate opioid withdrawal by activating P2X7 receptors, which leads to the release of ATP through the PANX1 channel and postsynaptic facilitation (field post synaptic potential (fPSP)) in the dorsal horn of the spinal cord. Withdrawal signs can be reduced by the Panx1 inhibitors probenecid or mefloquine (shown in blue).