Editorial
Opioids: From analgesia to anti-hyperalgesia?

Nowadays, opioids are well recognized as unsurpassed analgesics for relieving severe acute and chronic pain. However, as previously suggested (Scholz and Woolf, 2002), clinical pain is not a monolithic entity limited to integration of nociceptive inputs but is associated with neuronal plasticity that by increasing pain elicits pain hypersensitivity might lead to pain pathogenesis. In other words, this means that treating pain may not be limited to the use of anti-nociceptive agents even if they are very potent like opioids, but an anti-hypersensitivity strategy per se should be also considered.

On this issue, Koppert and colleagues report that buprenorphine, a partial μ-receptor agonist and κ- and δ-receptor antagonist, exerts not only analgesic effects as classically described for opioids but also induces anti-hyperalgesic effects in a human model of electrically evoked pain and hyperalgesia (Koppert et al., 2005). Interestingly, buprenorphine’s anti-hyperalgesic effects are more pronounced and have significant longer half-times as compared to antalgic effects. This long-lasting anti-hyperalgesia observed with intravenous and sublingual buprenorphine contrasts with the delayed and long-lasting hyperalgesia observed with several pure μ-opioid receptor agonists in both animal models and clinical studies (Angst et al., 2003; Célérier et al., 2001; Guignard et al., 2000; Laulin et al., 1998; Mao et al., 1994; Vanderah et al., 2001). Indeed, it has been previously reported that the larger the intraoperative opioid fentanyl or remifentanil doses, the greater is the postoperative pain level and morphine requirement (Guignard et al., 2000). It has been proposed that such a paradoxical phenomenon might account for exaggerated post-operative pain and acute tolerance after using them in surgery (Ossipov et al., 2003; Richebe et al., 2005; Simonnet and Rivat, 2003).

Two classes of opioids may be distinguished independently of their analgesic potencies according to the current study of Koppert et al. A first class of pure μ-opioid receptor agonists would induce undesirable long-lasting hyperalgesia and a second one would have anti-hyperalgesic properties. Interestingly, authors defined an anti-hyperalgesia/analgesia ratio with which analgesic drugs may be graded. Among opioids tested in this study, buprenorphine has the highest ratio. This new insight is probably predictive of future advances in opioid management of pain states dominated by central sensitization, e.g. exaggerated post-operative pain and some forms of chronic pain. Why so?

Depending on whether pain sensation enhancement induced by nociceptive inputs is facilitated or not by some opioids, especially they are administered at large doses, we need to re-examine opioid profiles, not only for their own anti-nociceptive capacities but also for their ability to facilitate or prevent central pain sensitization. Based on recent experimental and clinical studies, the pure μ-opioid receptor agonists, although very potent analgesics, would not have the best pharmacological profile since they facilitate development of long-lasting pain hypersensitivity in which pronociceptive glutamate/NMDA receptor systems play a critical role (Simonnet and Rivat, 2003). This explains why NMDA receptor antagonists, like ketamine or related compounds, may improve management of exaggerated postoperative pain in patients treated with high doses of pure μ-opioid receptor agonists as fentanyl or remifentanil for surgery (Guignard et al., 2000; Richebe et al., 2005). By contrast, results from Koppert’s study suggest that some opioids like buprenorphine, although a weaker anti-nociceptive agent, might have an attractive pharmacological profile because of its anti-hyperalgesic properties. Koppert et al. suggest that the anti-hyperalgesic property of buprenorphine is related to its k-opioid receptor antagonistic property. This is supported by the well recognized notion that dynorphin, the main endogenous k-opioid receptor agonist that was originally believed to be anti-nociceptive, exerts pronociceptive actions through a NMDA receptor-dependent mechanism (Vanderah et al., 1996). Obviously, the current study reported the highest ratio of anti-hyperalgesic/analgesic effects for the NMDA receptor antagonist ketamine. Interestingly, Koppert et al. (2004) reported in a recent issue of Pain that COX inhibitors reduced central hyperalgesia in the same human volunteer model. Since hyperalgesia produced by intrathecal NMDA is blocked by COX inhibitors (Malmberg and Yaksh, 1992), this confirms that drugs which act at various levels in the complex cascade involving dynorphin/k-receptor-glutamate NMDA receptors and COX systems may have potent clinical interest for opposing pain sensitization regardless of their own analgesic potency. Indeed, most opioids were also...
reported to be weak non-competitive NMDA receptor antagonists (Ebert et al., 1991). Therefore, clinical trials might need to be conducted with ‘poly receptor targeting’ drugs such as buprenorphine or with mixtures of pure μ-opioid receptor agonists and antagonists of sensitization-pronociceptive systems. These last systems may facilitate exaggerated pain and perhaps the transition from acute to chronic pain. As a matter of interest, both the COX inhibitor study (Koppert et al., 2004) and the present study indicate that anti-hyperalgesia is obtained at doses, which are significantly lower than those for obtaining a significant analgesic effect.

Although the present Koppert’s study is limited to human volunteers and that clinical studies on painful patients are required, it shows that our pharmacological concepts for determining the best profile for opioids probably need to be re-evaluated. Today, opioids cannot only be considered for their potency to reduce nociceptive symptoms but also for their ability to oppose active processes leading to pain hypersensitivity. This might be a new and beneficial approach for preemptive analgesia and improving the treatment of some forms of chronic pain dominated by central sensitization. Buprenorphine, like ketamine and related compounds, were reported to be effective in patients with long-term neuropathic pain unresponsive to morphine (Sittl, 2005). Since it has been suggested that pain hypersensitivity induced by opioids might play a critical role in inducing tolerance to analgesic effects of opioids (Ossipov et al., 2003; Simonnet and Rivat, 2003), some analgesic opioids like buprenorphine, methadone and related compounds with anti-k-opioid receptor or anti-NMDA receptor properties, might be worthwhile pharmacological agents for avoiding such a phenomenon even though they have weak antalgic effects per se. Although relationships between tolerance and dependence to opioids are probably complex and still poorly understood, it could not be unexpected that these two opioid drugs are the most used for pharmacological management of heroin addicts since hyperalgesia is a more consistent sign of withdrawal.


References


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