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Opioids and central sensitisation: II. Induction and reversal of hyperalgesia

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Abstract

Opioids are powerful analgesics when used to treat acute pain and some forms of chronic pain. In addition, opioids can pre-empt some forms of central sensitization [Sandkühler and Ruscheweyh, Eur. J. Pain, in press, doi:10.1016/j.ejpain.2004.05.012]. Here we review evidence that opioids may also induce and perhaps reverse some forms of central sensitization.

1. Opioid-induced hyperalgesia

During the last years, it has become increasingly clear that opioids can induce central sensitization, aggravating preexisting pain or causing pain by themselves. Case studies reported that opioids can actually increase pain in some patients, often associated with a modification of the pain character and an extension of the affected region (Devulder, 1997; Wilson and Reisfield, 2003). This phenomenon has been reproduced in experimental settings in both humans and rodents, where thermal hyperalgesia, mechanical allodynia and increased pain behaviour in the formalin test are manifest not only during opioid withdrawal, but also during ongoing opioid administration and can last for several days (Li et al., 2001; Vanderah et al., 2001b; Angst et al., 2003). Opioid-induced hyperalgesia also occurs after intrathecal administration, demonstrating that activation of spinal opioid receptors is sufficient (Mao et al., 1994).

The mechanisms and signal transduction pathways that mediate opioid-induced hyperalgesia include activation of NMDA receptors and protein kinase C (PKC), activation of facilitatory supraspinal loops, upregulation of spinal dynorphin and apoptosis of spinal dorsal horn neurons (Vanderah et al., 2001a; Mao, 2002; Mao et al., 2002b). These mechanisms are very similar to those of both opioid tolerance and neuropathic pain, which has important implications for the understanding and treatment options of these states. First, it has been proposed that apparent behavioural tolerance to the antinociceptive effects of opioids may in fact be the result of opioid-induced hyperalgesia (Mao, 2002). While a true pharmacodynamic tolerance can be treated by increasing opioid doses, this will worsen the opioid-induced hyperalgesia that, in turn, requires dose reduction. Second, if opioids are able to activate the same signal transduction pathways as neuropathic pain, administration of opioids during or after nerve injury may facilitate, instead of pre-empt, the development of neuropathic pain (Mao, 2002). However, understanding of the mechanisms of opioid-induced hyperalgesia may disclose various targets to decrease opioid-induced central sensitization, thereby potentiating opioid analgesia and

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preventing tolerance and cross-talk to neuropathic pain mechanisms.

Opioid-induced hyperalgesia, tolerance and neuropathic pain are all prevented by application of NMDA receptor antagonists (Mao et al., 1994; Whiteside and Munglani, 2001; Laulin et al., 2002). Opioids are able to potentiate the actions of glutamate at NMDA receptors by a PKC-dependent pathway, probably involving increased open probability, reduction of the Mg^{2+} block and recruitment of NMDA receptors to the membrane (Chen and Huang, 1991; Chen and Huang, 1992; Martin et al., 1997; Lan et al., 2001). It has been hypothesized that this occurs also at the primary afferent terminal, leading to increased transmitter release (Ossipov et al., 2003). In addition, chronic opioid treatment leads to a downregulation of spinal glutamate transporters, presumably enhancing glutamate availability at spinal NMDA receptors (Mao et al., 2002a). On the other hand, opioids stimulate the expression of PKC in dorsal horn and its translocation to the membrane by an NMDA receptor-dependent pathway (Mayer et al., 1995; Mao et al., 1995), suggesting that a feedforward interaction between NMDA receptors and PKC is initiated by opioids. Consistently, PKCγ knockout mice do not develop opioid-induced hyperalgesia (Zeitz et al., 2001). Furthermore, chronic morphine exposure leads to NMDA receptor mediated neurotoxicity, causing apoptosis of inhibitory dorsal horn neurons that is at least in part responsible for opioid-induced hyperalgesia (Mao et al., 2002b).

These results provide a rationale for combining opioids with NMDA receptor antagonists in the treatment and prevention of pain. Ketamine was able to prevent opioid-induced hyperalgesia in a human experimental paradigm (Angst et al., 2003). In patients, intraoperative combination of opioids with subanalgetic doses of ketamine resulted in reduced postoperative pain scores (Suzuki et al., 1999; De Kock et al., 2001). It remains to be determined if the beneficial effect of this combination extends to neuropathic pain states.

In addition, it has been shown that a facilitatory supraspinal loop involving the rostroventral medulla takes part in opioid-induced hyperalgesia and tolerance and in neuropathic pain (Ossipov et al., 2000; Vanderah et al., 2001a). This descending facilitation induces an increase in spinal dynorphin content (Wang et al., 2001; Gardell et al., 2002). Dynorphin, an endogenous κ-opioid receptor agonist that was originally thought to be antinociceptive, was shown to exert non-opioid pronociceptive actions by potentiating NMDA receptors, facilitating release of excitatory transmitters and increasing intracellular Ca^{2+} levels (Lai et al., 2001). Consistently, tactile allodynia evoked by spinal dynorphin administration is blocked by NMDA receptor antagonists but not by naloxone (Vanderah et al., 1996). Dynorphin antiserum prevents opioid-induced hyperalgesia, tolerance and neuropathic pain in the rodent but has not been tested in humans (Vanderah et al., 2000; Wang et al., 2001).

How do opioids exert inhibitory effects, and how do they excite and sensitize spinal neurons? It has been shown that opioid receptors are coupled to both pertussis toxin (PTX) sensitive inhibitory G-proteins (G_i/G_o) and cholera toxin (CTX) sensitive stimulatory G proteins (G_s), so that the relative coupling proportions, together with binding affinity and receptor efficacy, determine the net action of the opioid (Fan et al., 1993; Fan and Crain, 1995). It has been suggested that under resting conditions, the majority of opioid-receptors are G_i/G_o-coupled but that G_s-coupled receptors are effective at lower agonist concentrations, explaining the observation that exceedingly low doses of opioids acutely induce hyperalgesia while ''normal'' doses induce analgesia (Kayser et al., 1987; Shen and Crain, 2001). The coupling of opioid receptors to G_s can be enhanced by interaction of the receptor with the membrane-associated glycolipid GM1 ganglioside (Wu et al., 1997). Interestingly, chronic opioid exposure increases GM1 ganglioside levels (Wu et al., 1995) and thus presumably promotes excitatory opioid actions. Substances that reduce the interaction between GM1 ganglioside and the opioid receptor, like the non-toxic B-subunit of CTX and the neuraminidase inhibitor oseltamivir, block low-dose morphine hyperalgesia and morphine tolerance and withdrawal hyperalgesia and potentiate and prolong morphine analgesia (Shen and Crain, 2001; Crain and Shen, 2004). Similar results have been obtained with ultra-low-dose naltrexone that presumably has a higher binding affinity for G_s- than for G_i/G_o-coupled receptors (Crain and Shen, 2001). Excitatory opioid receptors seem to be less prone to desensitization than inhibitory opioid receptors (Crain and Shen, 2001). Thus, selective desensitization of inhibitory opioid receptors during continuous opioid application or a shift in the proportions of G_s versus G_i/G_o-coupled receptors may lead to prevalence of stimulatory opioid effects and promote opioid-induced central sensitization. Identification of substances suitable for clinical use that selectively block excitatory opioid actions while retaining inhibitory opioid effects promises to greatly enhance the efficacy of the treatment of pain by opioids.

2. Reversal of central sensitization by opioids

Activity-dependent, long-lasting increase in efficacy at synapses between primary afferent C-fibres and nociceptive spinal neurons, e.g., NK1 receptor expressing neurons in lamina I of the spinal dorsal horn, is a cellular model of central sensitization (Sandkühler, 2000; Ikeda et al., 2003; Sandkühler and Ruscheweyh, in press). Depotentiation of an established long-term

potentiation (LTP) at nociceptive synapses is therefore a potential cellular mechanism of reversal of central sensitisation. Synaptic depotentiation or long-term depression (LTD) is often accomplished by stimuli very similar to those that induce LTP, and the outcome seems to essentially depend on concomitant circumstances, especially on the rise of intracellular calcium achieved during the stimulation (Lisman, 1989; Artola and Singer, 1993). Opioids interfere with the intracellular calcium level in a complex way, activating and/or inhibiting voltage-gated calcium channels, NMDA receptors, intracellular calcium stores and capacitive calcium entry (Jin et al., 1992; Jordan and Devi, 1998; Quillan et al., 2002). It can therefore be hypothesized that opioids, that are able to induce central sensitization as discussed above, may also reverse central sensitization under certain conditions. Preliminary data from our laboratory indicate that the clinically used μ-opioid receptor agonist remifentanil is indeed capable of depotentiating LTP at nociceptive synapses (Brechtel et al., 2001). In contrast, in a behavioural paradigm, remifentanil did not reverse the secondary allodynia induced by a heat injury that is generally thought to be a sign of central sensitization (Nozaki-Taguchi and Yaksh, 2002). As opioids are widely used and safe in the clinical application, their potential for reversal of central sensitization merits further investigation.

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