There is an increasing body of literature from both clinical and basic science studies regarding opioid-induced hyperalgesia (OIH). Although there has been debate about its clinical relevance, it is becoming clear that OIH presents a clinical challenge in acute, chronic, and cancer pain settings. OIH is a paradoxical response to an opioid agonist, whereby instead of an analgesic, or antinociceptive effect occurring, there is an increase in pain perception. This may occur in the area of the pain being treated or may be a more generalized increase in pain, often with features associated with neuropathic pain, such as hyperalgesia or allodynia. It is different from tolerance, where an increased dose of opioid is required to get the same analgesic effect, but there is no increase in pain as a result of opioid administration. In order to address this problem, a greater understanding of the underlying mechanisms and more knowledge about its clinical manifestations of OIH are needed.

Basic science studies are beginning to clarify some of the contributory mechanisms, many of which are similar to those that underlie the development of tolerance.1 From laboratory models of OIH, it is clear that, as with many chronic pain states, there are both peripheral and central changes in nociceptive processing. Alterations in the spinal cord are important, with some form of central sensitization occurring. This is likely to involve the ionotropic glutamate receptor, the N-methyl-D-aspartate (NMDA) receptor, known to play a key role in central sensitization. In rodent models of OIH, using chronic opioid administration, C-fibre potentiation has been demonstrated, similar to that seen with central sensitization. This can be prevented with NMDA receptor block and a range of studies have demonstrated the efficacy of NMDA receptor antagonists in preventing OIH.2,3 Spinal neurones in culture show increased NMDA receptor activity after chronic morphine administration, also seen acutely with remifentanil or a dynorphin agonist.4 Further evidence for the involvement of glutamate comes from work using gabapentin, which has a presynaptic effect on glutamate release, and dose dependently decreases OIH from repeat fentanyl in rats.5 Minville and colleagues,6 in this issue of the British Journal of Anaesthesia, present findings that add further weight to the importance of the NMDA receptor in acute OIH. Their model has the benefits of more closely mimicking the clinical situation than some previous models, and as such their findings may be more directly translatable. Using a mouse fracture model combined with intramedullary pinning, and intermittent parenteral administration of sufentanil, they demonstrated the development of both mechanical and thermal hyperalgesia, after an initial antinociceptive effect. This OIH was prevented by ketamine, which also prevented the reduced efficacy of postoperative morphine if sufentanil was given alone.

Modulation of spinal input by descending pathways from the brainstem is also implicated in the development of OIH, with a shift in the balance between descending inhibitory control towards pronociceptive systems. These pronociceptive systems may be more active in certain chronic pain states and also seems to play a role in OIH, acting via 5-HT3 and possibly 5-HT2 receptors. Ondansetron, a widely used 5-HT3 antagonist, blocks signs of OIH. Several endogenous neuropeptides may also work via descending spinal pathways, with increased endogenous cholecystokinin (CCK) in the brainstem contributing to OIH, with this effect being reversed by CCK-2 antagonists.7 Substance P, acting via NK-1 receptors, may also be involved, as destruction of NK-1 containing neurones, with the toxin saporin, prevents OIH.8,9 Spinal administration of an NK-1 antagonist reverses OIH, with increased NK-1 receptor internalization in the dorsal horn detected in OIH.10 The NK-1 receptor may also interact with NMDA receptors to modify descending control.
The role of opioid receptors is complex, with mixed evidence from laboratory studies: manipulation of opioid receptor activity either by using naloxone or mu, delta, or kappa knockout mice did not alter development of OIH in mice. It has been shown that chronic opioid exposure may alter G-protein activity related to mu-receptor activation, with an increase in G_i activity, that can be reduced by low-dose naloxone. In addition, there may be a difference between particular opioids—for example, d-methadone does not appear to cause OIH and reduces morphine-induced OIH, with both l-methadone and racemic methadone demonstrating hyperalgesic effects. This has been postulated to be due to an action of d-methadone at the NMDA receptor, although the issue of cross-reactivity between different opioids is far from clear.

Peripheral receptors also play a role in OIH, with evidence that the transient receptor potential (TRP)-V1 is important in the development of hyperalgesia. A TRPV1 antagonist was found to reverse OIH, with an associated increase in TRPV1 receptors in the dorsal root ganglia, and an increased response to capsaicin. TRPV1 knockout mice did not develop either tactile or thermal hypersensitivity to chronic morphine administration. There is interest in the use of TRPV1 antagonists as an analgesic for some pain states and there may be an additional clinical role in the management of OIH. Alterations in cytokine levels has also been detected in the periphery in mice with OIH, where higher levels of IL-1beta, IL-6, G-CSF, KC, and TNF-alpha were found, along with increased mechanical sensitivity.

Intracellular mechanisms share some similarities with opioid tolerance, in that blocking L-type calcium channels or using PKC antagonists prevent or reduce OIH. Nitric oxide synthase (NOS) knockout mice show much reduced development of OIH, and NOS inhibitors preventing development of OIH.

In summary, the neurobiology of OIH is complex and likely to involve more than one system, with probable differences between acute and chronic settings at both pre- and post-synaptic levels, affecting NMDA receptor activity, G-proteins, and intracellular systems.

While the clinical definition of OIH is relatively clear—a paradoxical increase in pain as a result of opioid administration—in practice, the situation is much more complex. The overlap with opioid toxicity, where hyperalgesia may occur, and tolerance, which has many similar mechanisms to OIH needs to be studied further. As with neuropathic pain, as we define the clinical situation more specifically, it may emerge that OIH represents a spectrum of syndromes where the underlying neurobiology varies between individuals.

Why some individuals suffer from OIH while others on even larger doses of opioids do not is not understood. A small number of studies have looked at the clinical characteristics of OIH in patients with chronic pain on strong opioids. Both opioid dose and duration of treatment seem to be important factors, affecting descending inhibitory control and also pain and unpleasantness to a defined noxious stimulus, particularly in females. Thermal hyperalgesia has been found with heat hyperalgesia and evidence of temporal summation, thought to be indicative of central sensitization. Few studies have looked systematically at the effect of reducing opioid doses, although one retrospective study of patients undergoing detoxification for opioid addiction found a decrease in allodynia when patients were converted onto non-steroidal anti-inflammatory drugs for their pain.

In the acute setting, a large double-blind randomized controlled trial of patients undergoing major abdominal surgery found only transient OIH from remifentanil for up to 2 h after surgery. Patients all received epidural analgesia, which may have altered central responses. Clinical studies need to be designed to differentiate between acute tolerance and OIH.

Genetic factors are also likely to play a role in susceptibility to OIH, with evidence from study of different strains of mice that the degree of OIH depends on particular haplotypes of the Abcb1b p-glycoprotein drug transporter gene and also that variants of beta-2-adrenergic receptor gene may be important in the allodynia that can occur. A clinical study of 43 healthy volunteers using a painful thermal stimulus found that individuals homzygous for the met (158) polymorphism of the catechol O-methyl transferase gene had greater pain sensitivity after a potent parenteral opioid.

Reviewing studies of the clinical syndrome of OIH has highlighted the lack of good quality clinical research in this area, despite the fairly extensive basic science evidence. Further research is needed to define the clinical problem, in order to develop clinical strategies to reduce OIH. Likely targets would include agents that act on glutaminergic systems, such as NMDA receptor antagonists or gabapentin, and also using agents to target peripheral effects, such as non-steroidal anti-inflammatory drugs, or more novel agents, such as TRPV1 antagonists. Given the complex nature of the problem and the multiple factors likely to be involved, including genetic influences, dose, duration, type, and route of administration of opioid, along with the effect of the type of pain being treated, clinical research will need to be appropriately targeted to produce meaningful results.

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References
1. Dietis N, Guerrini R, Calo G, Salvadori S, Rowbotham DJ, Lambert DG. Simultaneous targeting of multiple opioid receptors:
4 Zhao M, Joo DT. Enhancement of spinal N-methyl-D-aspartate receptor function by remifentanil action at delta-opioid receptors as a mechanism for acute opioid-induced hyperalgesia or tolerance. Anesthesiology 2008; 109: 308–17
9 Vera-Portocarrero LP, Zhang ET, King T, et al. Spinal NK-1 receptor expressing neurons mediate opioid-induced hyperalgesia and antinociceptive tolerance via activation of descending pathways. Pain 2007; 129: 35–45
16 Liang D, Shi X, Qiao Y, Angst MS, Yeomans DC, Clark JD. Chronic morphine administration enhances nociceptive sensitivity and local cytokine production after incision. Mol Pain 2008; 4: 7
26 Jensen KB, Lonsdorf TB, Schalling M, Kosek E, Ingvar M. Increased sensitivity to thermal pain following a single opiate dose is influenced by the COMT val(158)met polymorphism. PLoS ONE 2009; 4: e6016
27 Angst MS, Clark JD. Opioid-induced hyperalgesia: a qualitative systematic review. Anesthesiology 2006; 104: 570–87