# Postoperative Hyperalgesia

# Its Clinical Importance and Relevance

Oliver H. G. Wilder-Smith, M.B.Ch.B., M.D., Ph.D.,\* Lars Arendt-Nielsen, Ph.D., D.MSc.†

PAIN after surgery continues to be a major management challenge in clinical practice. In a recent meta-analysis covering some 20,000 patients and 800 publications, Dolin et al.<sup>1</sup> concluded that 41% of all surgical patients still experience moderate to severe acute postoperative pain and that 24% experience inadequate pain relief. Unfortunately, acute postoperative pain control seems not to have substantially improved over the last decade or so.<sup>2</sup> The picture is equally unsatisfactory regarding long-term outcomes, where chronic pain is increasingly identified as a direct consequence of surgical intervention. Recent surveys of chronic pain after surgery demonstrate that this problem is much more common than previously thought, with some types of surgery (e.g., thoracotomy, mastectomy, limb amputation) being associated with chronic pain incidences of more than 50% at 1 yr postoperatively.<sup>3,4</sup>

The past two decades have seen significant improvements in our understanding of the mechanisms underlying nociception and pain. A key insight has been that nervous system processing of nociception and pain is not hardwired, and that the gain of the nervous system can change as a result of noxious sensory inputs or the drugs used to modulate these. Nociception is now well accepted to result in sensitization of the nervous system, *i.e.*, increased sensitivity regarding nociception and pain.<sup>5</sup> Increased pain sensitivity is increasingly recognized as a potential-paradoxical and undesirable-effect of analgesic use to combat surgical pain and nociception, particularly for opioids.<sup>6</sup> In a patient, such hyperexcitability of pain processing is expressed as increased pain for a given stimulus, a phenomenon termed hyperalgesia in the absence of modality shifts.

The presence of hyperalgesia has a major impact on primary and secondary pain processing by the brain, with these changes having the potential to be both adaptive and maladaptive.<sup>7</sup> These alterations may be detrimental in the early postoperative period for a number of reasons. First, hyperalgesia tends to increase the amount of pain the patient experiences—an unwanted outcome of itself—because of greater amplification of given noxious inputs. Second, more pain typically means more patient stress in the postoperative period, with the possibility of negative consequences for a variety of complications and outcomes. Finally, abnormal persistence of nervous system sensitization subsequent to nociception, *i.e.*, excitatory neuroplasticity expressed as hyperalgesia and increased pain, is now considered a major candidate mechanism for the development of chronic pain.<sup>3,5</sup>

The reliable diagnosis of hyperalgesia is difficult based on clinical symptoms alone. The very definition of hyperalgesia—more pain accompanying a given stimulus makes it clear that its detection is based on construction and comparison of stimulus-response curves before and after nociception or drug application. Therefore, the systematic diagnosis and quantification of hyperalgesia requires the formal, serial determination of stimulus dose-response curves under standardized conditions, a process termed quantitative sensory testing (QST). If postoperative hyperalgesia is not diagnosed, it will not be subject to targeted treatment, which fact may—as will be discussed below—be a contributing factor to the lack of substantive progress in postoperative analgesia mentioned above.<sup>2</sup>

The purpose of this review is, first, to explain how nociceptive and opioid-induced hyperalgesia may develop in the early postoperative period; second, to provide data indicating that such hyperalgesia can actually occur in clinical practice; third, to weigh the evidence to date supporting the usefulness of hyperalgesia management in the postoperative context; and fourth, to evaluate current knowledge regarding effective treatments of early postoperative hyperalgesia.

#### **Causes of Postoperative Hyperalgesia**

Hyperalgesia after surgery can occur either due to nervous system sensitization by surgical nociception (nociception-induced hyperalgesia) or as an effect of anesthetic drugs (drug-induced hyperalgesia). Both are potentially undesirable, and both can share similar underlying mechanisms such as the involvement of excitatory amino acids *via* the *N*-methyl-p-aspartate (NMDA) receptor.<sup>5,8</sup> Pa-

<sup>\*</sup> Associate Professor for Pain and Nociception, Pain Centre, Department of Anaesthesiology, University Medical Centre St. Radboud. † Professor, Laboratory for Experimental Pain Research, Centre for Sensory-Motor Interaction, University of Aalborg, Aalborg, Denmark.

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Figures 1 and 2 in this article have been prepared by Dimitri Karetnikov, 7 Tennyson Drive, Plainsboro, New Jersey 08536.

Address correspondence to Dr. Wilder-Smith: Pain Centre, Department of Anaesthesiology, University Medical Centre St. Radboud, P.O.B. 9101/520, NL-6500 HB Nijmegen, The Netherlands. o.wildersmith@anes.umcn.nl. Individual article reprints may be accessed at no charge through the Journal Web site, www.anesthesiology.org.

tient-related factors such as age, sex, and genetic makeup (with its effects on receptor and enzyme systems) are likely to influence the development of postoperative hyperalgesia, but these factors are only just beginning to be investigated.<sup>9</sup>

#### Nociceptive Hyperalgesia

Nociception-induced hyperalgesia manifest in the postoperative period is a consequence of surgical tissue and nerve trauma.<sup>10</sup> Nociceptive inputs, neuronal as well as humoral, alter subsequent sensory (and motor) nervous system processing—both peripheral and central.<sup>5,11</sup> Such nociceptive neuroplasticity is usually initially excitatory (i.e., "sensitization"), moving from activation (acute, transient, activity-dependent) via modulation (subacute, slower, but still reversible functional changes) through to modification (chronic structural and architectural alterations).<sup>5</sup> Activation is a rapidly reversible physiologic process involving use-dependent augmentation of transduction (peripheral nociceptors, autosensitization) and transmission (central processing, windup).<sup>5</sup> Modulation, a more slowly reversible process with early connotations of functional pathology, results in peripheral and central sensitization, due at least in part to phosphorylation of neuronal receptors and ion channels.<sup>5</sup> For the peripheral nervous system, examples are activation of the TPVR1 receptor or SNS/PN3 sodium channel; for the central nervous system, activation of excitatory amino acid (e.g., NMDA or also AMPA) receptors or associated substance-gated slow calcium ion channels.<sup>5</sup> *Modification*, generally considered the basis of chronic, pathologic pain, involves altered regulation and cell connectivity together with cell death.<sup>5</sup> In peripheral nociceptors, typical mechanisms comprise target-derived growth factors, induction of novel genes resulting in phenotype change and C-fiber death with spinal rewiring involving A-β fibers.<sup>5</sup> Central changes include modified gene transcription combined with loss of inhibition, both functionally and via death of inhibitory interneurons.<sup>5</sup>

The brain is now recognized to be an important modulator of nervous system pain sensitivity.<sup>12</sup> Originating in medulla and midbrain, acting on the spinal dorsal horn, and operating via multiple tonic and phasic systems, descending modulation is an integral part of the complex processing nociceptive signals normally undergo during transmission from peripheral to central in the nervous system.<sup>12-14</sup> Persistent nociception may trigger both descending facilitation and inhibition, with ultimate net pain sensitivity being the result of the balance between local (spinal) and descending gain effects.<sup>15</sup> These net local effects can differ according to the neuronal pools involved (e.g., primary vs. secondary hyperalgesia) and the type of nociceptive input.<sup>15</sup> In addition, spinal nociceptive input can also sensitize subcortical structures, leading to generalized-as opposed to local—hyperalgesia.<sup>16</sup> Therefore, hyperalgesia, generalized and localized, can be the result more directly of central or descending facilitation, or more indirectly of deficient inhibitory mechanisms.<sup>12-14</sup> Inhibition, the intact organism's usual defense against excitatory neuroplasticity, can be spinal, (*i.e.*, segmental or propriospinal) or supraspinal. The latter, *i.e.*, descending inhibition, is closely related to parallel descending facilitatory systems.<sup>12,13</sup> The absence of the ability to produce an inhibitory response (*e.g.*, descending noxious inhibitory controls) may contribute to hyperalgesia, and variations in the ability to generate these are now considered to be important prognostic factors for chronic pain development in humans.<sup>17,18</sup>

Nociceptive excitatory neuroplasticity expresses itself clinically as increased sensitivity to pain, *i.e.*, hyperalgesia. Peripheral nervous system excitation (primary hyperalgesia) increases sensitivity in the area of damaged tissue. For spinal sensitization (secondary hyperalgesia), hypersensitivity segmentally surrounds and extends beyond the area of primary hyperalgesia. Supraspinal excitation, even more widely distributed, frequently affects the entire body (e.g., descending facilitation<sup>12</sup>). The neuroplasticity accompanying pain chronification is clinically manifest in three ways: first, increasing predominance of excitation; second, decreasing dependency on original nociceptive input; and third, increasing deviation from normal, physiologic patterns of pain processing.<sup>5</sup> Figure 1 summarizes some of the mechanisms implicated in nociceptive hyperalgesia.

# Opioid-induced Hyperalgesia

Opioids represent the most frequently used class of drugs for acute and chronic control of moderate to severe pain. However, the existence of the paradoxical phenomenon of opioid-induced hyperalgesia and the related occurrence of tolerance are increasingly recognized in anesthesia and chronic pain therapy.<sup>8,19</sup> Therefore, the use of opioids can be associated not only with loss of analgesic efficacy (tolerance) but also with activation of pronociceptive mechanisms leading to increased pain sensitivity (hyperalgesia). The circumstances under which opioid-induced hyperalgesia may occur are not yet entirely understood but may include high doses, long-term treatment, or abrupt changes in concentrations.<sup>8</sup>

Three major mechanisms are implicated in opioid-induced hyperalgesia and tolerance. The first involves activation of the central glutaminergic system, mainly *via* the NMDA receptor, homeostatically coupled to opioidergic and enkephalinergic systems, and also central to nociception-induced hyperalgesia.<sup>8</sup> A second mechanism operates *via* the release of spinal dynorphin, a hyperalgesic substance.<sup>20</sup> Descending spinal *facilitation* mediated *via* opioid-sensitive on-cells situated in the rostral ventromedial medulla comprises the third main



Fig. 1. Schematic summary of mechanisms of nociception-induced hyperalgesia. NMDA = N-methyl-D-aspartate.

mechanism.<sup>12</sup> The latter two mechanisms have recently been recognized as at least partially linked to increased rostral ventromedial medulla cholecystokinin levels.<sup>21</sup> Spinal dorsal horn expression of calcitonin gene-related peptide and substance P may also be increased.<sup>21</sup> Further mechanisms include increased expression of the opioid receptor in the excitatory Gs-coupled *versus* the inhibitory Gi/Go-coupled state and antiglycinergic effects of the excitatory morphine metabolite morphine-3-glucuronide.<sup>8</sup> Some of the mechanisms implicated in opioid-induced hyperalgesia are shown in figure 2.

The precise circumstances controlling the appearance of opioid-induced hyperalgesia are not well understood. As for nociception-induced hyperalgesia, opioid-induced hyperalgesia manifests itself by increased sensitivity to pain,<sup>22,23</sup> typically diffuse and present over the entire body.<sup>8</sup> Its induction reduces the analgesic efficacy of subsequent applications of opioid,<sup>8,24</sup> and, once gener-

ated, it may remain latent for long periods of time, permitting rekindling of hyperalgesia by later opioid application.<sup>24</sup> It has been suggested that this effect on nociceptive memory may be linked to an increased—as opposed to decreased—incidence of development of chronic pain with preemptive use of opioid analgesia in the surgical context.<sup>25</sup> Finally, other anesthetic drugs, including volatile (*e.g.*, isoflurane<sup>26</sup>) and intravenous agents (*e.g.*, propofol,<sup>27</sup> clonidine<sup>28</sup>), have also been linked to hyperalgesia, especially at concentrations likely to be encountered in the early postoperative period.

# **Does Postoperative Hyperalgesia Occur?**

It should be emphasized that both nociception- and opioid-induced hyperalgesia can only be formally and reliably diagnosed using some form of perioperative



Fig. 2. Schematic summary of mechanisms of opioid-induced hyperalgesia. NMDA = N-methyl-D-aspartate; RVM = rostral ventromedial medulla.

QST. For the clinical perioperative detection of hyperalgesia, QST (*e.g.*, measurement of pain thresholds) must be performed both preoperatively/preopioid (baseline) and postoperatively/postopioid (change *vs.* baseline). QST evidence of this type is now available supporting the occurrence of both nociception- and opioid-induced hyperalgesia in human volunteers.<sup>6,29,30</sup> Nociception-induced hyperalgesia has similarly been demonstrated in several QST studies in the clinical postoperative context, but there is currently only one QST study available formally clinically demonstrating postoperative opioid-induced hyperalgesia<sup>31</sup>—although other indirect clinical evidence is accumulating.<sup>32,33</sup>

It is important to note that the relation between QSTdemonstrated hyperalgesia and clinical pain measures such as visual analog scale or morphine consumption is consistently weak.<sup>10,34</sup> The weakness of this relation is not surprising in view of the multistep serial processing that nociceptive input undergoes from spinal cord to cortex before ending as subjective pain experience.<sup>14</sup> As a result, subjective pain experience is subject to multifactorial modulation, making this measure subject to more variability than, e.g., QST measures of hyperalgesia. Hence, demonstrating the impact of analgesic therapeutic interventions is often easier (in statistical terms, e.g., sample size) using QST-measured hyperalgesia as compared with clinical pain measures.<sup>10,31,33-35</sup> The pertinent question of the clinical usefulness of diagnosing hyperalgesia in the context of postoperative pain management will be addressed in the next section.

#### Nociception-induced Hyperalgesia

The development of mechanical hyperalgesia, both primary and secondary, after experimental skin incision has recently been documented in detail in human volunteers.<sup>29</sup> A number of patient studies have demonstrated various forms of nociception-induced hyperalgesia postoperatively using QST<sup>10,34,36</sup> (for review of studies up to 1999, see Wilder-Smith<sup>34</sup>). Taken together, these studies document marked primary hyperalgesia (i.e., on the wound) to mechanical and thermal stimulation from hours up to 4 days postoperatively (hysterectomy, hernia). Secondary mechanical hyperalgesia (i.e., tissue near the wound) has been seen from hours up to 7 days after surgery (hysterectomy, nephrectomy). Using electrical skin stimulation, segmental hyperalgesia is visible from hours up to 5 days postoperatively, with generalized hyperalgesia also becoming apparent at 5 days (back surgery). An example of one of these studies is illustrated in figure 3. It should be emphasized that clinical experimental evidence directly linking reduced postoperative hyperalgesia to better acute and chronic pain outcomes after surgery is scarce, although first clinical studies supporting such a link are now becoming available.<sup>37</sup>

#### **Opioid-induced Hyperalgesia**

Opioid-induced hyperalgesia is well documented during clinical long-term use of opioids.<sup>22</sup> The reality of the phenomenon after acute opioid use has recently been formally demonstrated using QST in a number of human volunteer studies and one clinical perioperative study.<sup>6,30,31</sup> All of



Fig. 3. Change in arm electric pain tolerance thresholds (*vs.* baseline, in mA) after back surgery under volatile anesthesia (isoflurane in oxygen-nitrous oxide) supplemented by placebo or fentanyl. Values are means and 95% confidence intervals, the difference between the placebo and fentanyl-supplemented groups is significant in the overall time course (analysis of variance, P < 0.05). \* Significant change *versus* baseline value (P < 0.05 on *post boc* testing). Modified from figure 3 in Wilder-Smith *et al.*<sup>10</sup> with permission.

these studies used remifentanil infusions at clinically typical rates, and all of them showed clear hyperalgesia (i.e., decreased pain thresholds, increased size of hyperalgesic area, or more evoked pain) either shortly after discontinuing infusion (volunteer studies) or 1 and 2 days postoperatively. In the clinical study cited, greater 48-h cumulative postoperative morphine consumption accompanied increased postoperative hyperalgesia without any differences in clinical pain scores.<sup>31</sup> The studies did not investigate how long such hyperalgesia lasted, nor did they study effects on subsequent opioid application. An example of such a study is provided in figure 4. Supporting indirect evidence for the clinical reality of this phenomenon is provided by anesthesia studies demonstrating that higher/ additional intraoperative remifentanil infusion is associated with greater postoperative pain and morphine requirements.32,33 We therefore have early evidence that opioids may cause hyperalgesia and that this can negatively impact early pain outcomes. However, further studies are clearly needed in this area, particularly with regard to chronic pain outcomes.

### Could Postoperative Hyperalgesia Management Be Useful?

From the above, both nociceptive and drug-induced hyperalgesia have the potential of combining in the early postoperative period to create a period of high vulnerability to nociception and pain. Interestingly, recent animal studies have suggested synergism between opioid- and nociception-induced hyperalgesia.<sup>23</sup> In the following section, we will weigh the evidence that post-



Fig. 4. Change in pressure pain tolerance thresholds (vs. baseline, in kPa) during remifentanil or placebo infusion. Values are means and 95% confidence intervals. M2 = measure during 1 ng/ml target concentration of remifentanil (or placebo equivalent); M3 = measure during 2 ng/ml target concentration of remifentanil (or placebo equivalent); M4 = measure during 1 ng/ml target concentration of remifentanil (or placebo equivalent); M5 = measure 10 min after discontinuing infusion. \* Significant change versus baseline value (P < 0.05). Modified with permission from Lippincott Williams & Wilkins, from figure 2B in Luginbuhl *et al.*<sup>30</sup>

operative hyperalgesia, as a factor separate from the subjective pain experience, could have significant effects on acute and chronic pain outcomes after surgery.

Pain processing in the context of hyperalgesia differs quantitatively and qualitatively from pain processing in its absence.<sup>7</sup> The presence of hyperalgesia in the acute postoperative period is likely to increase the amount of pain experienced. This, in turn, potentially increases the overall impact of subsequent and ongoing nociception (e.g., from the wound) on the patient regarding stress, immunity, and tissue trophism. Such effects carry the risk of more complications, impaired mobilization, prolonged hospital stay, and many other undesirable outcomes after surgery. More pain frequently results in more analgesia use, leading to an increase in analgesiaassociated side effects, well documented for opioids and respiratory, gastrointestinal, and urologic function. Hyperalgesia itself may make opioid analgesic titration more difficult, as suggested by the quantal dose-response relation for acute postoperative pain<sup>38</sup> versus the linear dose-response curve for experimental pain without hyperalgesic component.

Taken together, these acute potential effects of hyperalgesia suggest that hyperalgesia diagnosis followed by specific antihyperalgesic therapy might improve pain and nociception management in the early postoperative period. How strong is the evidence for such benefits? That perioperative hyperalgesia can be diagnosed clinically using QST is relatively well established.<sup>10,30,31,39</sup> Currently, we have only early formal evidence that less postoperative hyperalgesia results in better acute postoperative pain control.<sup>31,37</sup> Indirect support is provided by studies demonstrating that interventions associated with alterations of postoperative hyperalgesia are also associated with changes in acute postoperative pain outcomes<sup>32,33</sup> (for review, see Richebe *et al.*<sup>40</sup>).

Postoperative hyperalgesia may also influence chronic outcomes after surgery. It has recently been highlighted that chronic pain as a direct result of surgery (not due to preexisting or underlying conditions) is more common than previously recognized.<sup>3</sup> Reviews particularly identify two somatic factors as increasing risk for postoperative chronic pain: nerve injury and increased and/or persistent pain in the early postoperative period (e.g., in the first week postoperatively).<sup>3,4</sup> Both of these factors are closely associated with hyperalgesia: nerve injury as a cause, and persistent and/or increased pain as a symptom thereof. Moreover, pain and other consequences of nerve injury are liable to be increased in the presence of hyperalgesia. Furthermore, the abnormal persistence of excitatory neuroplasticity (expressed as hyperalgesia) is now considered to be a major mechanism for the development of chronic pain.<sup>5</sup> These two major lines of evidence in combination suggest that the presence of hyperalgesia in the postoperative period-particularly if abnormal in extent or duration-may also be a significant risk factor for the subsequent development of chronic pain. However, it should be noted that, currently, clinical research evidence supporting this scenario is limited to one study linking decreased postoperative hyperalgesia to less residual pain up to 1 yr after surgery.37

# Modulation of Postoperative Hyperalgesia

#### Nociception-induced Hyperalgesia

The specific effects of a variety of drugs on nociception-induced hyperalgesia have been confirmed and elucidated in animal studies.41 The most well-characterized effective substances include opioids (particularly if used preemptively), nonsteroidal antiinflammatory drugs, NMDA-antagonists such as ketamine, and substances binding to the voltage-gated calcium channel  $\alpha_2 \delta$  proteins such as gabapentin and pregabalin.<sup>23,42-44</sup> The effect of drugs specifically on nociception-induced postoperative hyperalgesia in humans is much less well studied. A limited number of studies support the effectiveness of opioids<sup>10</sup> (particularly if started preoperatively) and NMDA antagonists<sup>37,39</sup> (mainly ketamine) given for anesthesia supplementation in inhibiting postoperative hyperalgesia.34 One study of nonsteroidal antiinflammatory drug supplementation<sup>10</sup> (ketorolac) failed to demonstrate antihyperalgesic effects postoperatively. Figure 3 illustrates the effect of preemptive fentanyl on postoperative hyperalgesia. The evidence regarding the relation between hyperalgesia modulation and improved acute and chronic pain outcomes is much sparser. Only one clinical study is currently available, demonstrating that multimodal perioperative analgesic management can reduce postoperative hyperalgesia and that this is associated with better early and late pain outcomes.<sup>37</sup> We have found no studies studying the treatment (*vs.* prophylaxis) of established hyperalgesia in the postoperative context.

#### Opioid-induced Hyperalgesia

With regard to opioid-induced hyperalgesia, the majority of the animal studies published to date involve NMDA receptor antagonists, particularly ketamine.<sup>8</sup> Here, the use of ketamine has proven effective in inhibiting both short- and long-term consequences of opioid-induced hyperalgesia. The few available human volunteer studies on modulation of opioid-induced hyperalgesia concentrate mainly on the short-term effects of concurrently applied ketamine, where two studies have shown ketamine to be effective in suppressing hyperalgesia shortly after cessation of remifentanil infusion, with one further study reporting equivocal results.<sup>6,30</sup> The first clinical study showing that 48-h perioperative administration of small-dose ketamine successfully suppresses postoperative hyperalgesia after intraoperative large-dose remifentanil has recently been published.<sup>31</sup> This study also demonstrated that suppression of hyperalgesia improved acute pain outcome in the sense of reduced postoperative opioid consumption.<sup>31</sup> Further indirect support for the effectiveness of ketamine supplementation for modulating opioid-induced hyperalgesia and tolerance is provided by studies showing decreased intraoperative remifentanil doses and reduced postoperative morphine consumption with better pain scores after anesthetic ketamine supplementation.35 No clinical studies are currently available addressing the impact of postoperative hyperalgesia modulation on chronic pain outcomes.

#### **Summary and Conclusions**

A key insight deriving from pain research of the past decade or so is that hyperalgesia can occur in the early postoperative period as a result of surgical nociception as well as drug (particularly opioid) use. That such hyperalgesia can and does occur postoperatively in the clinical context is now increasingly established. Such hyperalgesia is undesirable because it can increase pain and resulting stress, negatively impacting the early postoperative course of surgery. Moreover, evidence is increasingly available that hyperalgesia in the days after surgery may be linked to subsequent development of chronic pain, an ever more recognized but unwanted surgical outcome.

In clinical practice, it is difficult to reliably diagnose hyperalgesia based on clinical symptoms alone. However, with the introduction and adaptation of QST to

clinical practice, we now have a valid method for reliably diagnosing hyperalgesia after surgical intervention. Clinical studies are now becoming available that provide early evidence for effective prophylactic and therapeutic approaches to postoperative hyperalgesia-and for the impact of such approaches on acute and chronic postoperative pain outcomes. Clearly, however, further studies are needed to clarify and establish the role of postoperative hyperalgesia diagnosis and management in achieving better short- and long-term pain outcomes after the nociception of surgery. It is hoped that increased recognition and diagnosis of postoperative hyperalgesia will accompany the development and implementation of effective preventive and therapeutic management strategies and that this will, in turn, make possible significant improvements in postoperative pain outcomes, both acute and chronic, in the near future.

#### References

1. Dolin SJ, Cashman JN, Bland JM: Effectiveness of acute postoperative painmanagement: I. Evidence from published data. Br J Anaesth 2002; 89:409-23

2. Apfelbaum JL, Chen C, Mehta SS, Gan TJ: Postoperative pain experience: Results from a national survey suggest postoperative pain continues to be undermanaged. Anesth Analg 2003; 97:534-40

3. Perkins FM, Kehlet H: Chronic pain as an outcome of surgery: A review of predictive factors. ANESTHESIOLOGY 2000; 93:1123-33

4. Macrae WA: Chronic pain after surgery. Br J Anaesth 2001; 87:88-98

5. Woolf CJ, Salter MW: Neuronal plasticity: Increasing the gain in pain. Science 2000; 288:1765-9

6. Koppert W, Sittl R, Scheuber K, Alsheimer M, Schmelz M, Schuttler J: Differential modulation of remifentanil-induced analgesia and postinfusion hyperalgesia by S-ketamine and clonidine in humans. ANESTHESIOLOGY 2003; 99:152-9

7. Casey KL, Lorenz J, Minoshima S: Insights into the pathophysiology of neuropathic pain through functional brain imaging. Exp Neurol 2003;184 (suppl 1):880-8

8. Simonnet G, Rivat C: Opioid-induced hyperalgesia: Abnormal or normal pain? Neuroreport 2003; 14:1-7

9. Mogil JS, Wilson SG, Chesler EJ, Rankin AL, Nemmani KV, Lariviere WR, Groce MK, Wallace MR, Kaplan L, Staud R, Ness TJ, Glover TL, Stankova M, Mayorov A, Hruby VJ, Grisel JE, Fillingim RB: The melanocortin-1 receptor gene mediates female-specific mechanisms of analgesia in mice and humans. Proc Natl Acad Sci U S A 2003; 100:4867–72

10. Wilder-Smith OH, Tassonyi E, Crul BJ, Arendt-Nielsen L: Quantitative sensory testing and human surgery: effects of analgesic management on postoperative neuroplasticity. ANESTHESIOLOGY 2003; 98:1214-22

11. Wieseler-Frank J, Maier SF, Watkins LR: Glial activation and pathological pain. Neurochem Int 2004; 45:389-95

12. Gebhart GF: Descending modulation of pain. Neurosci Biobehav Rev 2004; 27:729-37

13. Bouhassira D, Chitour D, Villaneuva L, Le Bars D: The spinal transmission of nociceptive information: Modulation by the caudal medulla. Neuroscience 1995; 69:931-8

14. Price DD: Psychological and neural mechanisms of the affective dimension of pain. Science 2000; 288:1769-72

15. Vanegas H, Schaible HG: Descending control of persistent pain: inhibitory or facilitatory? Brain Res Brain Res Rev 2004; 46:295-309

16. Suzuki R, Dickenson A: Spinal and supraspinal contributions to central sensitization in peripheral neuropathy. Neurosignals 2005; 14:175-81

17. Kosek E, Ordeberg G: Lack of pressure pain modulation by heterotopic noxious conditioning stimulation in patients with painful osteoarthritis before, but not following, surgical pain relief. Pain 2000; 88:69-78

18. Edwards RR, Ness TJ, Weigent DA, Fillingim RB: Individual differences in diffuse noxious inhibitory controls (DNIC): Association with clinical variables. Pain 2003; 106:427-37

19. Mao J: Opioid-induced abnormal pain sensitivity: Implications in clinical opioid therapy. Pain 2002; 100:213-7

20. Vanderah TW, Ossipov MH, Lai J, Malan TP Jr, Porreca F: Mechanisms of opioid-induced pain and antinociceptive tolerance: Descending facilitation and spinal dynorphin. Pain 2001; 92:5-9

21. Ossipov MH, Lai J, King T, Vanderah TW, Porreca F: Underlying mechanisms of pronociceptive consequences of prolonged morphine exposure. Biopolymers 2005; 80:319-24

22. Compton P, Geschwind DH, Alarcon M: Association between human mu-opioid receptor gene polymorphism, pain tolerance, and opioid addiction. Am J Med Genet 2003;121B:76-82

23. Richebe P, Rivat C, Laulin JP, Maurette P, Simonnet G: Ketamine improves the management of exaggerated postoperative pain observed in perioperative fentanyl-treated rats. ANESTHESIOLOGY 2005; 102:421-8

24. Celerier E, Laulin JP, Corcuff JB, Le Moal M, Simonnet G: Progressive enhancement of delayed hyperalgesia induced by repeated heroin administration: A sensitization process. J Neurosci 2001; 21:4074-80

Eisenach JC: Preemptive hyperalgesia, not analgesia? ANESTHESIOLOGY 2000;
92:308-9

26. Kingery WS, Agashe GS, Guo TZ, Sawamura S, Davies MF, Clark JD, Kobilka BK, Maze M: Isoflurane and nociception: Spinal alpha2A adrenoceptors mediate antinociception while supraspinal  $\alpha$ 1 adrenoceptors mediate pronociception. ANESTHESIOLOGY 2002; 96:367-74

27. Petersen-Felix S, Arendt-Nielsen L, Bak P, Fischer M, Zbinden AM: Psychophysical and electrophysiological responses to experimental pain may be influenced by sedation: Comparison of the effects of a hypnotic (propofol) and an analgesic (alfentanil). Br J Anaesth 1996; 77:165-71

28. Quartilho A, Mata HP, Ibrahim MM, Vanderah TW, Ossipov MH, Lai J, Porreca F, Malan TP Jr: Production of paradoxical sensory hypersensitivity by  $\alpha_2$ -adrenoreceptor agonists. Anesthesiology 2004;100:1538-44

29. Kawamata M, Watanabe H, Nishikawa K, Takahashi T, Kozuka Y, Kawamata T, Omote K, Namiki A: Different mechanisms of development and maintenance of experimental incision-induced hyperalgesia in human skin. AN-ESTHESIOLOGY 2002; 97:550-9

30. Luginbuhl M, Gerber A, Schnider TW, Petersen-Felix S, Arendt-Nielsen L, Curatolo M: Modulation of remifentanil-induced analgesia, hyperalgesia, and tolerance by small-dose ketamine in humans. Anesth Analg 2003; 96:726-32

31. Joly V, Richebe P, Guignard B, Fletcher D, Maurette P, Sessler DI, Chauvin M: Remifentanil-induced postoperative hyperalgesia and its prevention with small-dose ketamine. ANESTHESIOLOGY 2005; 103:147-55

32. Guignard B, Bossard AE, Coste C, Sessler DI, Lebrault C, Alfonsi P, Fletcher D, Chauvin M: Acute opioid tolerance: Intraoperative remifentanil increases postoperative pain and morphine requirement. ANESTHESIOLOGY 2000; 93:409-17

33. Rauf K, Vohra A, Fernandez-Jimenez P, O'Keeffe N Forrest M: Remifentanil infusion in association with fentanyl-propofol anaesthesia in patients undergoing cardiac surgery: Effects on morphine requirement and postoperative analgesia. Br J Anaesth 2005; 95:611-5

34. Wilder-Smith OH: Pre-emptive analgesia and surgical pain. Prog Brain Res 2000; 129:505-24

35. Guignard B, Coste C, Costes H, Sessler DI, Lebrault C, Morris W, Simonnet G, Chauvin M: Supplementing desflurane-remifentanil anesthesia with small-dose ketamine reduces perioperative opioid analgesic requirements. Anesth Analg 2002; 95:103-8

36. Ilkjaer S, Bach LF, Nielsen PA, Wernberg M, Dahl JB: Effect of preoperative oral dextromethorphan on immediate and late postoperative pain and hyperalgesia after total abdominal hysterectomy. Pain 2000; 86:19-24

37. Lavand'homme P, De Kock M, Waterloos H: Intraoperative epidural analgesia combined with ketamine provides effective preventive analgesia in patients undergoing major digestive surgery. ANESTHESIOLOGY 2005; 103:813-20

38. Tverskoy M, Oren M, Dashkovsky I, Kissin I: Alfentanil dose-response relationships for relief of postoperative pain. Anesth Analg 1996; 83:387-93

39. Stubhaug A: A new method to evaluate central sensitization to pain following surgery: Effect of ketamine. Acta Anaesthesiol Scand Suppl 1997; 110:154-5

40. Richebe P, Rivat C, Rivalan B, Maurette P, Simonnet G: Low dose ketamine: Antihyperalgesic drug, non-analgesic [in French]. Ann Fr Anesth Reanim 2005; 24:1349-59

41. Whiteside GT, Harrison J, Boulet J, Mark L, Pearson M, Gottshall S, Walker K: Pharmacological characterisation of a rat model of incisional pain. Br J Pharmacol 2004; 141:85-91

42. Leung A, Wallace MS, Ridgeway B, Yaksh T: Concentration-effect relationship of intravenous alfentanil and ketamine on peripheral neurosensory thresholds, allodynia and hyperalgesia of neuropathic pain. Pain 2001; 91:177-87

43. Svensson CI, Yaksh TL: The spinal phospholipase-cyclooxygenase-prostanoid cascade in nociceptive processing. Annu Rev Pharmacol Toxicol 2002; 42:553-83

44. Hurley RW, Chatterjea D, Rose Feng M, Taylor CP, Hammond DL: Gabapentin and pregabalin can interact synergistically with naproxen to produce antihyperalgesia. ANESTHESIOLOGY 2002; 97:1263–73