

## Pain

## Acute pain

Daniel B Carr, Leonidas C Goudas

**Postanaesthesia care units used to echo with cries of patients in pain after general anaesthesia. Each as-needed dose of analgesia was given only after permission of the surgeon or anaesthesiologist. Once conscious, patients were required to request each subsequent analgesic dose until hospital discharge. Not surprisingly, nearly half the patients who have an operation experience moderate to severe pain after surgery. Acute pain control has advanced dramatically and is now a field with dedicated texts, journals, and research. Despite improved surgical techniques that have transformed many operations into same-day procedures, inadequately controlled pain may still extend the length of hospital stay and predispose to expensive, time-consuming complications such as pneumonia. Recognition of economic and humanitarian benefits of pain control has prompted worldwide attention from professional groups, insurers, and governments. This paper describes the process of acute pain and measures to control it with drugs or non-pharmacological interventions. Even brief intervals of acute pain can induce long-term neuronal remodelling and sensitisation ("plasticity"), chronic pain, and lasting psychological distress. Hence, acute pain and other types of pain (cancer-related or chronic) that are classified as distinct actually have many similarities.**

### What is acute pain?

A common definition of acute pain is "the normal, predicted physiological response to an adverse chemical, thermal or mechanical stimulus . . . associated with surgery, trauma and acute illness".<sup>1</sup> Yet patients' attitudes, beliefs, and personalities also strongly affect their immediate experience of acute pain. Over 50 years ago, Beecher found soldiers requested less analgesic medication than civilians with comparable injuries. He observed that the injured soldier expected evacuation and safe recuperation, but the civilian expected loss of wages and social hardship. Beecher set up placebo trials,<sup>2</sup> trials of clinical analgesics,<sup>3</sup> and investigated how personality and culture shape the experience of acute pain.<sup>4</sup> Accordingly, experimental clinical pain research may produce results that are not duplicated in clinical settings, where anxiety, sleep disruption, and illness burden are present.<sup>5</sup>

The traditional dichotomy between acute pain with its recent onset and short duration and chronic pain that persists after an injury has healed is increasingly untenable. An international task force has acknowledged that acute pain associated with new tissue injury may last for less than 1 month, but at times for longer than 6 months.<sup>6</sup> Preclinical studies show that neuronal expression of new genes—the basis for neuronal sensitisation and remodelling—occurs within 20 min of injury. Basic research models of chronic pain can initiate long-term behavioural and histological changes within a day or so after interventions such as transient nerve ligation. An emerging clinical literature also suggests that acute pain may rapidly evolve into chronic pain. Neonatal heel lancing provokes weeks of local sensitivity to touch<sup>7</sup> and infant circumcision is associated with exaggerated behavioural responses to immunisation

months later.<sup>8</sup> In adults, meticulous perioperative analgesia for radical prostatectomy lowers analgesic requirement and improves functional status for months afterwards.<sup>9</sup> Pain intensity during acute herpes zoster predicts the likelihood of developing postherpetic neuralgia. These pilot observations indicate that the biological and psychological foundation for long-term persistent pain is in place within hours of injury.<sup>10</sup>

Acute pain should therefore be viewed as the initiation phase of an extensive, persistent nociceptive and behavioural cascade triggered by tissue injury.<sup>11</sup> This cascade<sup>12</sup> has the potential to span orders of magnitude of space and time (figure 1), but generally subsides within weeks. If suppression of pain responses was not mobilised along with processes of pain amplification, any minor injury could progress to chronic pain (unfortunately some do). An individual's responses for months after transient injury may be determined by processes that occur within the first day. As with other complex dynamic systems,<sup>13</sup> small differences in the initial state of the host and in the intensity, quality, and meaning of the nociceptive stimulus can produce major differences in the detailed manner in which this process unfolds.

### Control of acute pain

Methods to control acute pain have progressed as a result of the discovery that early control of pain can shape its subsequent evolution, the recognition that nociception elicits important physiological responses even in unconscious anaesthetised individuals (figure 2), and an appreciation that for many patients minimisation of pain can improve clinical outcomes.<sup>14</sup> New ways to control pain include novel (or rediscovered) molecules,<sup>15</sup> delivery schedules superior to as-needed administration, and drug delivery targeted to peripheral sites of injury or central nociceptive pathways, chiefly the spinal cord.<sup>11</sup> Combinations of drugs are increasingly used to control pain.

These new methods allow clinicians to uncouple tissue injury from the nociceptive and behavioural cascade that normally ensues (figure 3). In 1910, the visionary

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Department of Anesthesia and Medicine, Tufts University School of Medicine, New England Medical Center, Box 298, Boston, MA 02111, USA (Prof D B Carr MD, L C Goudas MD)

Correspondence to: Prof Daniel B Carr  
(e-mail: dcarr02@emerald.tufts.edu)

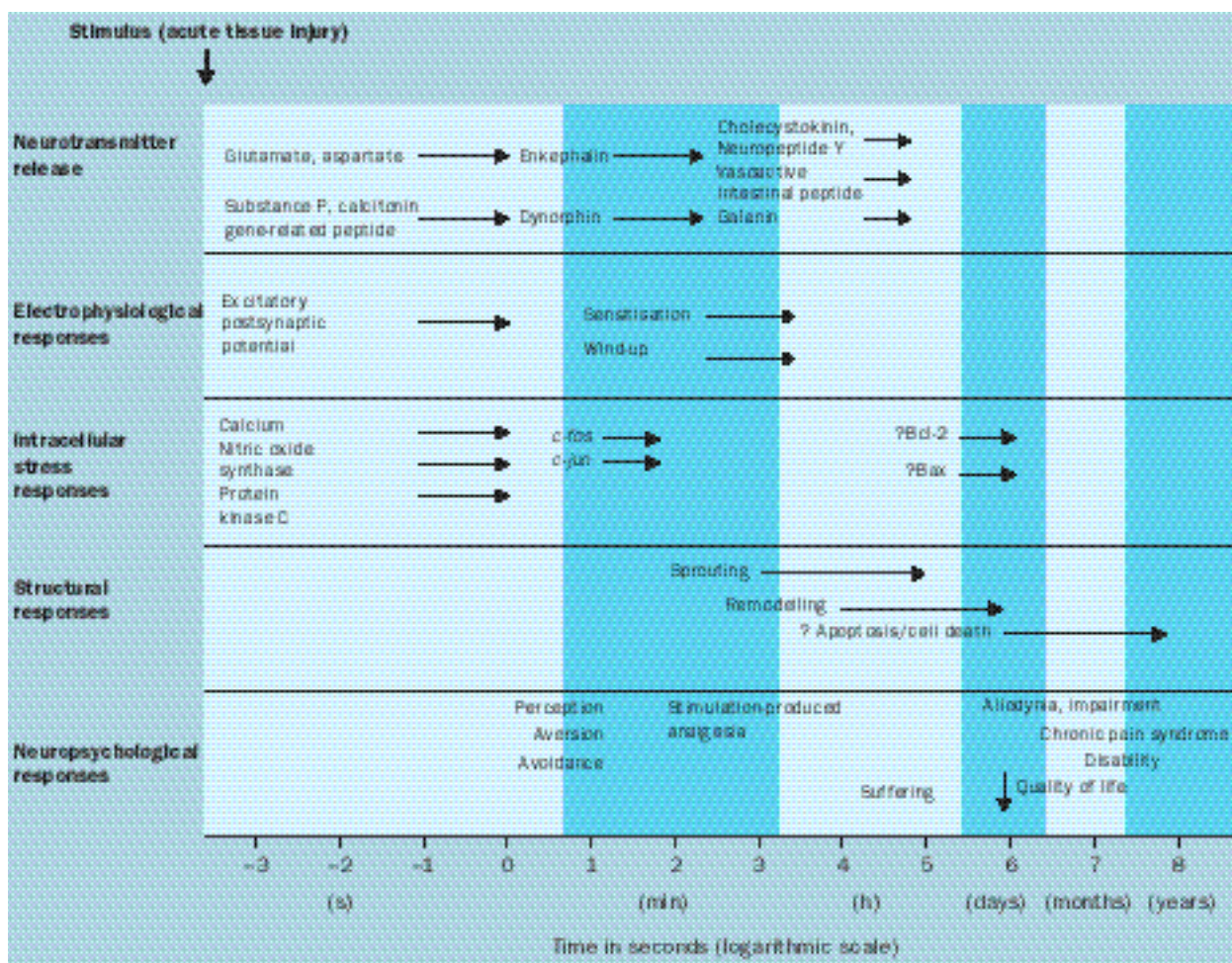


Figure 1: Acute tissue injury elicits cascades of responses of different orders of magnitude over time and space

These responses may lead directly to chronic pain. Adapted with permission from Jones.<sup>12</sup>

surgeon George Crile<sup>17</sup> proposed this uncoupling (“anoci-association”) as the core of an integrated approach to operation, anaesthesia, and speedy recovery. In the late 1990s, Kehlet<sup>18</sup> dramatically shortened length of hospital stay after surgery through the use of a multimodal framework of perioperative rehabilitation together with preoperative instruction, minimisation of intraoperative stress, aggressive mobilisation, and early feeding. Assessment of new measures to increase the efficiency of perioperative care must not overlook that for the patient and family, pain reduction per se is valuable, apart from any additional physiological, functional, or economic benefit.

**How acute pain works**

J-M Besson,<sup>19</sup> and Clifford Woolf and Richard Mannion<sup>20</sup> described the neurobiology of pain earlier in this series. A brief synopsis of acute pain is helpful here to delineate steps targeted by analgesic interventions. Mechanical, chemical, or thermal threats to tissue integrity cause nociceptive neurons to increase their discharge rate. Nociceptors with a wide dynamic range discharge in proportion to the logarithm of stimulus intensity. High-threshold nociceptors respond only when the stimulus intensity exceeds a threshold.<sup>21</sup> Tissue destruction activates nociceptors and initiates a local inflammatory response sustained by multiple mediators and immune cells. These mediators sensitise functional

nociceptors or activate dormant ones. Continuous or recurrent release of mediators during cancer or chronic illnesses, such as arthritis or infection, is another interface between chronic and acute pain. Sensitised nociceptors have an increased rate of basal (non-stimulated) discharge, a lowering of the stimulus threshold above which firing rate increases, a supranormal increase in discharge rate with each increase in stimulus strength, or a combination of these changes. At the site of injury, inflammatory mediators (monoamines, cytokines, prostanoids, peptides), neurotransmitters, and growth factors bathe sensitised nociceptors (figure 4).<sup>22</sup> Multiple interacting mediators

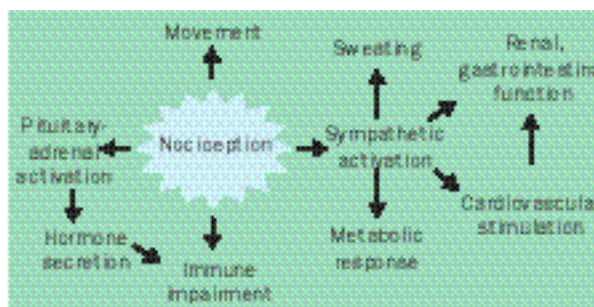


Figure 2: Nociception elicits important physiological responses even in unconscious anaesthetised patients

These intraoperative responses may have persistent effects postoperatively.

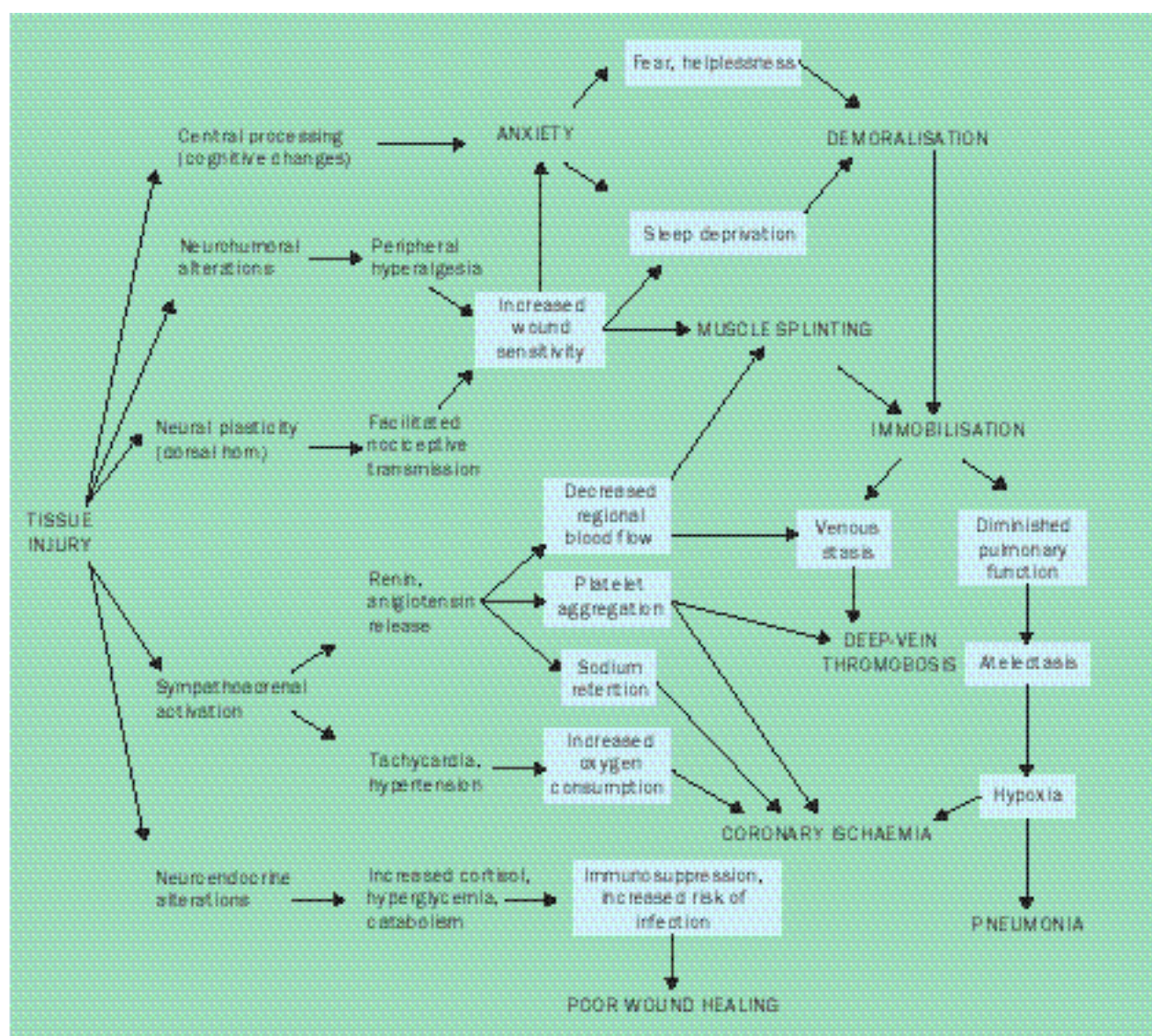


Figure 3: Behavioural and physiological sequelae of tissue injury relevant to acute pain in patients after surgery or trauma

Adapted with permission from Sinatra.<sup>16</sup>

and receptors allow for sensory integration and modulation (mainly amplification) of nociceptive input in the periphery.<sup>23</sup> Analgesic molecules engineered to act peripherally and not centrally are now in wide clinical use, as are topical analgesic creams.

C and A  $\Delta$  fibres convey nociceptive information from visceral and somatic sites to the dorsal horn of the spinal cord. Ascending pathways then relay nociceptive information rostrally to thalamic, limbic, and cortical structures responsible for affective and sensory-discriminative responses. Later in this series, Richard Chapman and Jonathan Gavrin<sup>24</sup> emphasise the importance of these cephalad structures for the experience and memory of pain and suffering. As Besson<sup>19</sup> and Woolf have already described, the dorsal horn integrates incoming signals,<sup>20</sup> through multiple mechanisms and quickly adapts to them. Many molecules that take part in peripheral nociceptive processing also function in spinal nociceptive integration.<sup>11,23</sup> Agents that impair the synthesis, release, or effects of such substances within the dorsal horn include morphine, blockers of the N-methyl D-aspartate (NMDA) receptor or of sodium or calcium channels,

$\alpha 2$  adrenergic agonists,  $\alpha$ -aminobutyric acid (GABA), and antagonists of substance P. Current analgesic research encompasses analogues of inhibitory transmitters, such as GABA or enkephalins, antagonists for excitatory transmitters (figure 5) or proalgesic trophic factors, and the effects of specific gene deletions in animals<sup>25</sup> and their roles in nociception.

Nociception at the start of peripheral inflammation evokes expression of *c-fos* and other genes in the dorsal horn along with behavioural changes in animals within 1 h.<sup>19</sup> Endogenous analgesia also commences promptly at the onset of painful processes, such as inflammation or burn injury, and persists for hours.<sup>26</sup> Stress-induced analgesia reflects bilateral descending inhibition of neural activity from the brainstem to multiple spinal levels ("diffuse noxious inhibitory controls") and the analgesic and anti-inflammatory effects of humoral agents (eg,  $\beta$ -endorphin). Woolf<sup>20</sup> has emphasised that continuous nociceptive activity shifts the dorsal horn from basal to suppressed and then to sensitised modes. The abrupt change of the dorsal horn from a system that suppresses to one that exaggerates its response to input resembles other transitions in biological or physical systems.<sup>27</sup> Nociceptive-induced switching between modes is a

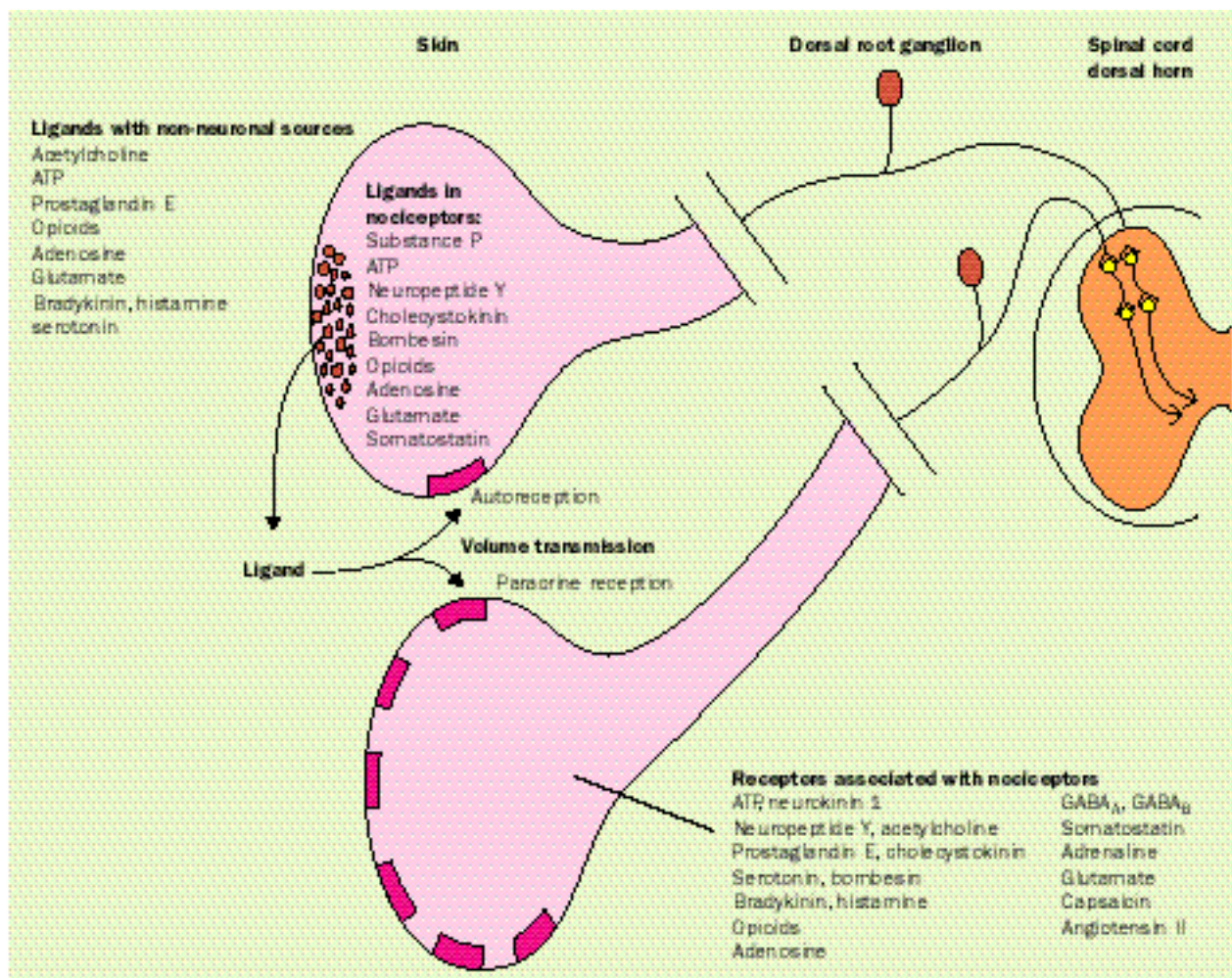


Figure 4: **Nociceptive input is modified and integrated in the periphery.**

Receptors on nociceptive primary afferent fibres are activated by mediators released from nearby damaged tissue, from the circulation, or from the same or adjoining neurons. Adapted with permission from Carlton and Uggeshall.<sup>23</sup>

highly conserved example of programmed instability. Invertebrates manifest no memory, apart from persistent sensory and motor hyper-responsiveness after brief noxious stimulation.<sup>28</sup> The essential property of any agent that can control acute pain is its ability to induce dorsal horn amnesia—ie, to regress the dorsal horn from any injury-induced state to its predecessor, and if possible back to the basal state. General Patton, Beecher's contemporary and another astute observer of pain on the battlefield, once stated that "Pain is just like any enemy. You keep moving around and the enemy cannot hit you. Same way with pain. The quicker you break away from the pain, the quicker you will drive the pain out of your system. You sit too long and you will not be able to move."<sup>29</sup>

### The analgesic menu

**NSAIDs and acetaminophen**—NSAIDs inhibit cyclo-oxygenase in the spinal cord and periphery, and thereby decrease prostanoid synthesis and diminish postinjury hyperalgesia at these sites.<sup>30</sup> Available evidence justifies the clinical treatment of mild to moderate pain with an oral NSAID or acetaminophen.<sup>31,32</sup> Nausea and vomiting after surgery or inaccessibility of the oral route in postoperative patients may require rectal or topical administration of NSAIDs. Intravenous dosage options are limited apart from ketorolac and propacetamol, an

injectable precursor to acetaminophen that is not available in every country. The introduction of ketorolac was followed by an unacceptably high number of cases of renal failure and gastrointestinal insufficiency in Europe; in the USA, a decrease in the recommended ketorolac dose resulted in fewer of these effects. The recent insight<sup>30</sup> that cyclo-oxygenase has two forms, COX-1 and COX-2, is encouraging. Inhibition of COX-1 interferes with renal function, gastric mucosal integrity, and platelet adhesiveness. COX-2 is expressed after tissue injury and augments inflammation. Clinical trials have established the efficacy and apparent safety of selective COX-2 inhibitors, but it is still too early to assign a clear therapeutic role to these agents. Other data indicate that NSAIDs act not only on COX-1 and COX-2, but also inhibit the nuclear transcription factor  $\kappa$ B that is critical for cytokine gene expression during inflammation. Inhibition of  $\kappa$ B, related transcription factors, or cytokines themselves, may also have potential for the treatment of acute and chronic inflammatory pain.

**Opioids**—Opioid analgesics are the basis of pharmacological management of postoperative pain, especially in moderate to severe pain. Later in this series McQuay<sup>33</sup> will discuss opioid analgesia. Opioids act on injured tissue to reduce inflammation, in the dorsal

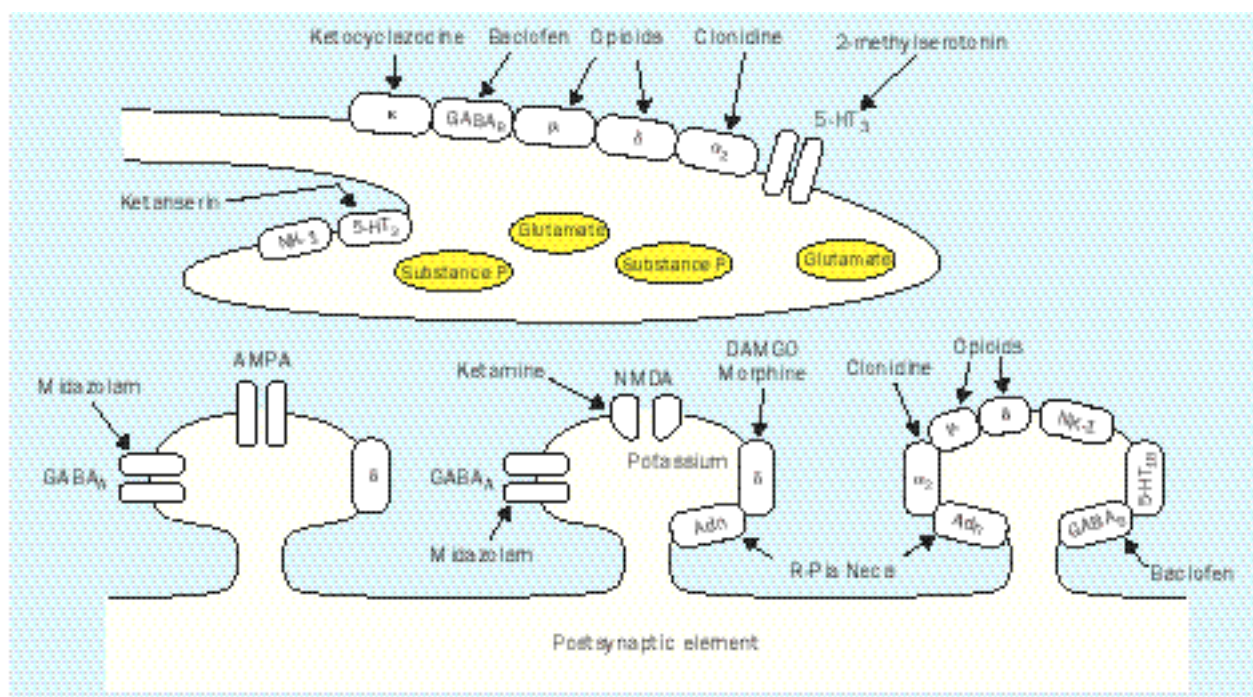


Figure 5: **Neurotransmitters and receptors in the dorsal horn of the spinal cord of current importance in analgesic practice and drug development**

NMDA=N-methyl-D-aspartate; NK-1=neurokinin 1. Adapted with permission from Carr and Cousins.<sup>26</sup>

horn to impede transmission of nociception, and supraspinally to activate inhibitory pathways that descend to the spinal segment. Intravenous patient-controlled analgesia with morphine is available in most US hospitals that care for postoperative inpatients; a minority offer patient-controlled epidural analgesia.<sup>34</sup> Patient-controlled analgesia is an effective way to deliver opioids in patients with moderate to severe acute pain who cannot take oral medication. No advantage accrues from continuous basal drug infusion during patient-controlled analgesia.<sup>35</sup>

Intranasal, transbuccal, periocular, and pulmonary routes to deliver systemic opioids in acute pain supplement more conventional routes, such as oral, intramuscular, subcutaneous, intravenous, and rectal.<sup>31,36</sup> Transdermal on-demand doses of fentanyl are available electrophoretically from a skin patch the size of a large postage stamp. Sustained analgesia can be achieved from a single oral dose of selected opioids (methadone, controlled-release morphine, or oxycodone), but their titration is difficult in the context of fluctuating postoperative analgesic requirements. At the other extreme, intraoperative infusions of short-acting opioids such as alfentanil and remifentanyl may be continued at reduced rates for postoperative analgesia. Such infusions must be titrated carefully and even so can produce side-effects such as nausea or respiratory depression. The discovery that opioids act at peripheral sites of inflammation prompted intra-articular dosing after knee arthroscopy. Intrathecal and epidural routes are widely used to provide sustained postoperative analgesia, but during chronic infusion of opioids for cancer pain systemic and spinal routes are equally effective.<sup>11</sup> However, spinal opioids are now routinely administered with agents such as local anaesthetics in combinations that offer advantages over single agents.<sup>11</sup> Combinations of systemic opioids and NSAIDs are widely used and effective.<sup>31,32</sup>

Partial agonists at the morphine or  $\mu$  receptor (eg, tramadol, buprenorphine) or agents that act upon other opioid receptors such as  $\kappa$  (eg, butorphanol) do not provide better analgesia than morphine, but may produce fewer respiratory, gastrointestinal, or urinary difficulties. Cloning of  $\mu$ ,  $\Delta$ , and  $\kappa$  opioid receptor types has confirmed their identities and stimulated clinical trials of  $\Delta$  receptor-selective opioids.<sup>36</sup> In animals, the latter produce minimum dependence or slowing of gastrointestinal transit but clinical experience with such agents is limited.

**Local anaesthetics**—Local anaesthetics have unique benefit and low risk.<sup>16</sup> Topical application of lidocaine alone or with prilocaine produces cutaneous anaesthesia. Simple techniques of neural blockade—field infiltration, digital nerve block, and trigger point injection—should be known to every practitioner. Complex nerve blocks—intercostal, ankle, and brachial plexus—carry greater risks and benefits, and are best left to those who have had appropriate training. Similarly, spinal administration of local anaesthetics is effective for control of pain after surgery or trauma, but requires expertise and infrastructure to administer and monitor properly.

Systemic infusion of lidocaine can reduce acute pain, but requires continuous monitoring so that resuscitation from seizure or apnoea can be done immediately. Single-enantiomer local anaesthetics, such as ropivacaine or levobupivacaine, offer improved selectivity for sensory over motor block and decreased cardiotoxic potential. The prospect of a local anaesthetic injection that lasts for days is attractive, such as for intercostal block after thoracotomy or ilioinguinal block after herniorrhaphy. Liposomes or polymeric microspheres that slowly release local anaesthetics are under investigation in clinical trials.

**NMDA receptor antagonists**—Several sites on the NMDA receptor complex, activated by the excitatory amino acid glutamate, are analgesic targets.<sup>37</sup> Recognition that ketamine blocks the open calcium channel within this complex has prompted renewed interest in the use of this substance for perioperatively or agent established neuropathic pain. Clinical studies confirm ketamine's merit as an analgesic or coanalgesic (eg, with morphine). Psychotomimetic and other side-effects such as salivation or cardiac stimulation restrict the applicability of standard doses of ketamine and require prophylactic administration of benzodiazepines or anticholinergics. Other compounds target the same site as ketamine (eg, dextromethorphan) or distinct sites on the NMDA receptor complex (eg, glycine). Intracellular effector mechanisms triggered by influx of calcium through its channel in the NMDA receptor complex, such as nitric-oxide synthesis,<sup>19</sup> are also potential targets for new analgesics.

**Adrenergic and cholinergic agonists**—Preclinical evaluations of  $\alpha$  adrenergic agents as analgesics were initiated about 15 years ago as a result of growing interest in spinal analgesia, nearly 100 years after the discovery that spinal application of epinephrine produced analgesia. Clonidine, an  $\alpha_2$  agonist that at high doses also has  $\alpha_1$  receptor stimulating effects, and the more selective  $\alpha_2$  agonist dexmedetomidine produce analgesia and sedation when given systematically, intrathecally, or centrally in rats. There have been extensive reports in clinical trials of analgesia after systemic, epidural, or intrathecal administration of clonidine.<sup>38</sup> Unfortunately, clonidine analgesia tends to be short-lived after single doses, and may be accompanied by side-effects such as sedation, bradycardia, or hypotension (though not respiratory depression). Clonidine is useful to augment morphine analgesia and to extend and intensify local anaesthetic blocks.

Intrathecal administration of acetylcholine also produces analgesia. Side-effects (nausea, epigastric discomfort) limit its use as a single agent, apart from circumstances such as after caesarean section where low intrathecal doses may be adequate.

### Psychological interventions

Surgery or trauma not only damage tissue, but also elicit psychological responses similar to post-traumatic stress disorder.<sup>39</sup> Optimum control of pain lessens psychological injury after an operation or trauma. By contrast, psychological resilience and preparedness make it easier to control pain.<sup>40</sup> High levels of stress, anxiety, or pessimism in preoperative patients predict poor outcomes in measures that range from speed of wound healing to duration of hospital stay.<sup>40</sup> More than 200 studies indicate that pre-emptive cognitive and behavioural interventions in unselected groups of patients decrease anxiety before and after surgery, reduce postoperative pain intensity and intake of analgesic drugs, improve treatment compliance, cardiovascular and respiratory indices, and accelerate recovery.<sup>41</sup> Mechanisms of diverse benefits from such simple, brief, inexpensive efforts, including education alone, range from interpersonal support during such interventions, to neuroendocrine and immune correlates of improved

psychological status. In a landmark study, Egbert and colleagues<sup>42</sup> found that preoperative discussion of likely postsurgical treatments and associated discomfort halved the requirement for postoperative morphine and reduced time to discharge. Patients in that study also received instruction in a relaxation technique. Such strategies, including imagery, have independent benefits upon pain and outcome after surgery and in patients with burn trauma.<sup>26</sup> Distraction is especially effective in children.<sup>43</sup> The seemingly minor environmental factor of a window with a view outside versus a windowless room may shorten postoperative stay and reduce analgesic requirement after cholecystectomy.<sup>44</sup> Despite much evidence that cognitive-behavioural methods to help patients cope with acute pain and anxiety are cost-effective, the pressure of short-term cost savings has eroded the resources to support this approach. As current research elucidates the links between psychological and physiological stress responses, health-care professionals should secure better reimbursement of psychological interventions.<sup>45</sup>

### Pain is a stressor

Stress responses—for example, global endocrinological, immunological and inflammatory consequences of surgery, trauma, and associated pain—impair recovery after surgery or trauma, although such effects presumably confer some natural survival advantage.<sup>46</sup> Limbic input to the hypothalamus, integrated by the paraventricular nucleus, drives classic pituitary-adrenal and sympathomedullary stress responses. Massive tissue injury (eg, burns) generates high circulating concentrations of interleukins, such as interleukin-1 and interleukin-6, that bypass the brain and act directly on the pituitary to stimulate corticotropin and vasopressin secretion.<sup>26</sup> However, pituitary responses are usually governed by the concurrent release of hypothalamic hormones (eg, corticotropin-releasing hormone and vasopressin) that evokes responses in excess of those produced after maximum doses of each separate releasing hormone. Studies of the transition from acute to chronic pain have identified the spinal cord as an important stress-responsive organ with an excellent memory.<sup>10,11,20</sup> Dorsal horn stress responses begin with the postsynaptic actions of substance P and glutamate on multiple receptors. Similar to pituitary stress responses, the duration and magnitude of postsynaptic depolarisation in dorsal horn are substantially greater upon coactivation of substance P and glutamate receptors than after maximum doses of each agent alone. Unlike pituitary-adrenal and sympathomedullary hormone secretion into the circulation, key stress responses within the spinal cord are intracellular and escape detection in blood or urine.<sup>11</sup>

The postsurgical state is characterised by fat and muscle breakdown, hyperglycaemia, and impaired immune function. These perturbations are mostly accounted for by increased plasma concentrations of cortisol,  $\beta$ -endorphine, catecholamines, and other hormones with metabolic as well as immunological actions such as prolactin, growth hormone, and vasopressin.<sup>46</sup> Intraoperative general anaesthesia and an as-needed approach to postoperative pain control evoke higher concentrations of stress hormones, more intense pain, more substantial catabolism, and greater immune impairment than regional local anaesthetic blockade.<sup>18</sup>

Hormone concentrations are not, however, clinical outcomes. Decreases in plasma cortisol during high-dose opioid therapy may simply reflect opioid suppression of corticotropin-releasing hormone secretion, a normal endocrine feedback process. Nausea and vomiting increase plasma concentrations of vasopressin in the absence of any other stressor or pain. Pain may be well controlled by spinal opioids that do little to blunt systemic hormonal responses.

### Pain relief or pain control?

Management of acute pain began in the 1980s when anaesthesiologists started to organise acute pain services,<sup>47,48</sup> and it is now an established component of medical practice. In more developed countries, management of acute pain is likely to grow further in importance as the health requirements of an ageing population increase. Governmental<sup>31,49-50</sup> and professional<sup>51-54</sup> guidelines for acute pain management that can be implemented through various models<sup>48</sup> share key strategies: (1) assess options for pain control with each patient preoperatively and provide instruction in simple, cognitive-behavioural techniques; (2) assess pain routinely, just as one monitors vital signs to discern trends before they become catastrophic; (3) treat pain as early as possible; (4) use non-drug and drug interventions together; (5) select treatment according to the clinical setting and promptly modify it according to the patient's response; and (6) provide continuity of pain control after discharge. The third of these tactics for effective acute management of pain—pre-emptive analgesia—is to be welcomed. Any means to prevent moderate or severe acute pain is desirable. Even when patient-controlled analgesia is in place as a patient wakes from anaesthesia, 30 min may elapse before repeated intravenous bolus doses of morphine control the pain satisfactorily. By that time, the nociceptive cascade is well under way and the patient has already been psychologically assaulted by uncontrolled pain. Dickenson had remarked that seeking synergy between analgesic agents is unnecessary, because all that matters is whether the therapeutic benefit of a combination exceeds that of its components. A similarly practical view is that until some other method is found to quickly suppress moderate to severe pain after surgery and during rehabilitation, pre-emptive preventive strategies should be applied.

Observation of the natural history of acute pain and calculation of manoeuvres to avert it have been advanced by use of standard pain-assessment tools (0–10 scale), increasingly rigorous trials of analgesic methods, and systematic reviews of such trials.<sup>55-57</sup> Synthesis of clinical trials in acute pain relief is aided by the fact that many studies are randomised, controlled, and report quantitative outcomes.<sup>31,32,56,57</sup> The Cochrane Collaboration have responded to increasing professional and consumer interest in relevant systematic reviews and last year registered a review group on pain, palliative and supportive care in 1998.<sup>58</sup> During the next 10 years, collaborations between preclinical and clinical investigators will improve the clinical outcomes and quality of life of patients at risk of acute pain while reducing the cost and social burden of their care.

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