Chapter 7
Acute Perioperative Pain: Mechanisms and Management

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Overview

Most patients anticipated some degree of postoperative pain as an associated feature of surgery and a consequence of performing a surgical incision. However, with better anesthesia and analgesia, many patients have now come to expect less pain than previous generations endured. This in itself is an important consideration, as anticipation of the extent of the pain may modify the actual perception of pain, and additionally, patient "satisfaction" with medical/surgical treatment may be heavily contingent upon their prior expectation of the intensity of pain they might suffer when agreeing during "informed consent" to a procedure. Realistically, however, some pain is usually expected, by most patients, with most surgical procedures. In effect, with much improved analgesia (thankfully), we also inadvertently "raise the bar" of patient and community expectation for "pain-free" surgical and anesthetic care. Despite the enormous advances in anesthesia and analgesia over the last 50 years, some postoperative pain is still experienced by many patients, and the overall aim is therefore to make the patient as comfortable and as least distressed by the pain, as possible. Indeed, the so-called "breakthrough" pain is important for the surgical diagnosis of postoperative

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complications, such as vascular compartment syndrome in a limb or following an undetected gastrointestinal perforation or an anastomotic leak. Not infrequently, pain precedes surgery, especially with acute surgical conditions or following trauma, and so the postoperative pain potentially arising from surgery is often a mix of preoperative pain, any intraoperative pain, and the postoperative pain induced by surgical intervention. Indeed, for many patients in pain prior to surgery, postoperative pain is a lesser and a much preferable option. Postoperative pain as a pathophysiological response is therefore important but must be managed appropriately to reduce the amount of distress and discomfort to acceptable levels for the patient and in a safe manner. This chapter focuses on some of the underlying mechanisms, types of pain experienced by patients, pain associated with complication following surgery, and its possible management.

Introduction

International Association for the Study of Pain (IASP) has defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (Merskey 1979). An inability to verbally communicate does not mean that an individual is not experiencing pain and does not negate the need of suitable pain-relieving treatment. This is important for certain situations or conditions including intensive care, coma, during anesthesia, dementia, retardation, dysarthria, and in pediatric patients. Noxious stimuli in the absence of tissue damage usually result in temporary acute pain, as a physiological "warning system." However, in the presence of tissue damage, a complex pathophysiological process results in inflammation and other changes associated with acute pain. Also, the injury response and acute pain impact on all organ systems. As is the case with all clinical pain, there are physical, psychological, and environmental factors that may be involved to varying degrees in individual patient's experience of acute pain. Recently, it has emerged that, following trauma or surgery, a considerable percentage of patients with acute pain progress to persistent (chronic) pain.

Pain Transduction and Transmission

The nociceptor relays information on thermal, mechanical, and chemical noxious stimuli via slower unmyelinated (C) fibers and small, lightly myelinated (A-delta) fibers to the dorsal horn of the spinal cord at the respective corresponding segmental level or rostrally and caudally passing through Lissauer's tract. Modulation of this signal at the dorsal horn involves both inhibitory and excitatory mechanisms through local and supraspinal inputs, before transmission to supraspinal structures involved in the perception of pain (Siddall and Cousins 2009). The discovery of transduction mechanisms for heat/capsaicin ($TRPV_1$) and for chemical stimuli (ASIC) has been a major advance that opens up new avenues for peripheral blockade of acute pain (see Siddall and Cousins 2009).

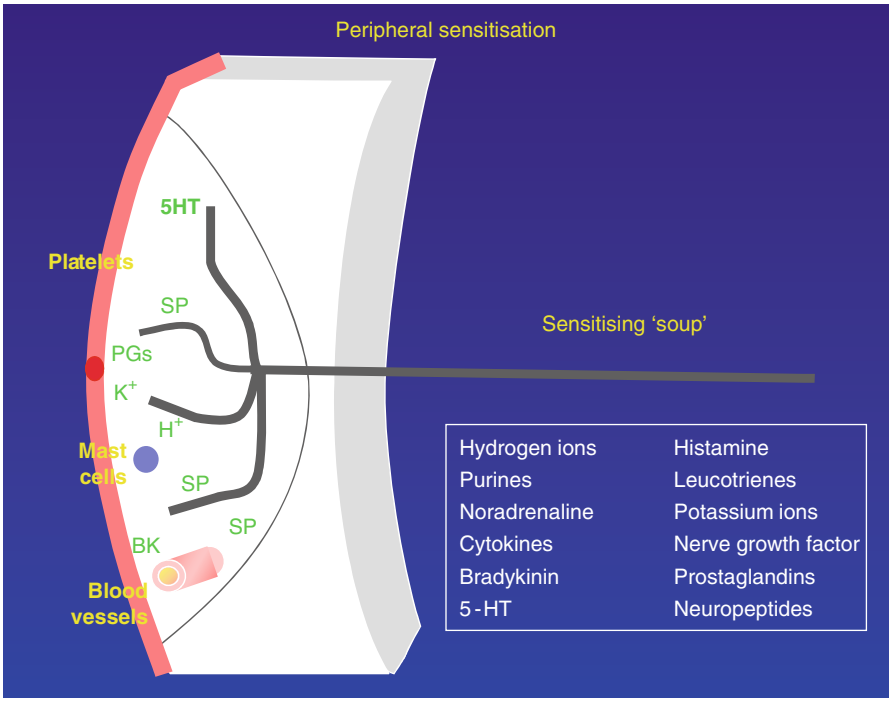

Fig. 7.1 Peripheral sensitization following injury. Injury results in release of potassium (K^+) from damaged cells, as well as prostaglandins. K^+ strongly activates nociceptive free nerve endings (**Aδ**- and C-fibers). Prostaglandins sensitize nociceptors to activators such as K^+. Antidromic stimuli in collaterals activate release of substance P (SP) (and calcitonin-gene-related peptide [*CGRP*]; not shown), which plays a pivotal role at three sites: SP (and CGRP) increase capillary permeability, thus allowing the peptide bradykinin to cross capillary walls and strongly activate nociceptors, in turn releasing more SP; SP acts on platelets to release 5-hydroxytryptamine (*5HT*), which sensitizes nociceptors, again releasing more SP; and SP acts also on mast cells to release histamine, sensitizing nociceptors. The foregoing three SP processes set up vicious circles of increasing sensitization. *PGs* prostaglandins

Peripheral Sensitization

Surgical trauma or the noxious stimuli associated with pain are associated with an inflammatory response. A complex range of mediators is released from damaged tissue and inflammatory cells. In addition, nociceptive stimulation activates the neuronal release of substance P, CGRP, and neurokinin A, causing neurogenic inflammation through action on blood vessels and further increased mediator release from inflammatory cells. This "inflammatory soup" induces a phenotypic change within the nociceptor leading to peripheral sensitization (Fig. 7.1), where low-intensity non-noxious stimuli may be perceived as painful. This zone of *primary hyperalgesia* is also marked by a reduction in thermal threshold detection, which will differentiate it from secondary hyperalgesia (Siddall and Cousins 2009).

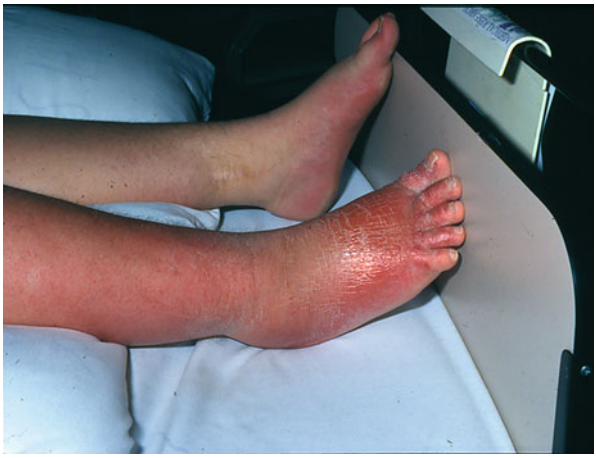

Fig. 7.2 Sympathetic nervous system and acute pain. Patient with CRPS

Sympathetic Nervous System

The sympathetic nervous system is also implicated in maintenance of acute pain. Inflammation can result in the sensitization of primary nociceptive afferent fibers by prostanoids that are released from sympathetic fibers (Levine et al. 1993). Furthermore, activation of alpha-adrenoreceptors on afferent fibers and innervation of the dorsal root ganglia by sympathetic terminals (McLachlan et al. 1993) can lead to sympathetically mediated pain. Pain syndromes, like complex regional pain syndrome, are associated with features of autonomic dysfunction including vasomotor, sudomotor, and trophic changes (Fig. 7.2) (Binder and Baron 2009).

Central Sensitization

A zone of secondary hyperalgesia with normal thermal threshold in undamaged tissue cannot be explained by peripheral sensitization. Rather, afferent noxious stimuli induce changes in the dorsal horn spinal neurons. This is marked by changes in neuropeptide, neurotrophins, and cytokine levels; receptor activation; and expression, especially the NMDA receptor. Anatomical changes have also been implicated in the pathogenesis of severe central sensitization, with cell death and axonal sprouting. There is also evidence that NMDA receptors are involved in a number of phenomena that may contribute to the medium- or long-term changes that are observed in the transition from acute to chronic pain states. These phenomena include the development of "windup" (Davies and Lodge 1987) facilitation, central sensitization (Woolf and Thompson 1991), changes in peripheral receptive fields, induction of oncogenes, and long-term potentiation (Fig. 7.3) (Collingridge and Singer 1990). Long-term potentiation, in particular, refers to the changes in synaptic efficacy that occur as part of the process of memory and may play a role in the development of a

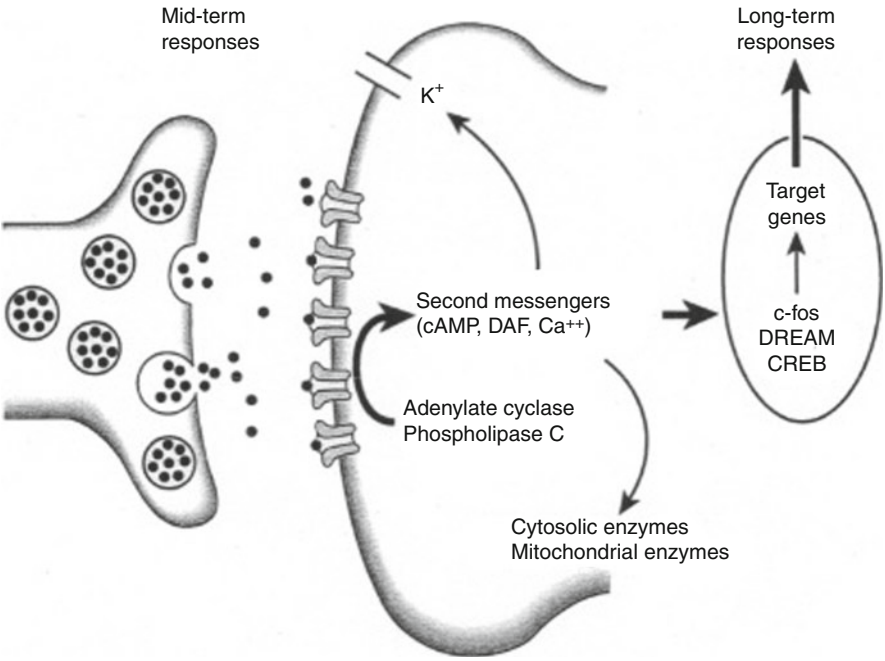

Fig. 7.3 Neurotransmitter release from the central terminal of peripheral afferents results in activation of receptor sites on the postsynaptic membrane. Activation of phospholipase C and adenylate cyclase leads to the production of the second messengers cyclic adenosine monophosphate (cAMP) and diacylglycerol (DAG). Mobilization of these second messengers may result in a decrease in potassium (K^+) efflux and elevation of intracellular calcium. The increase in intracellular calcium results in the induction of the proto-oncogene c-Fos, production of Fos protein, and a presumed action on target genes to alter long-term responses of the cell to further stimuli. *DREAM* downstream regulatory element antagonist modulator, *CREB* cyclic adenosine monophosphate (cAMP) response element-binding protein

cellular "memory" for pain or enhanced responsiveness to noxious inputs. Furthermore, it appears that NMDA antagonists can attenuate these responses (Woolf and Thompson 1991), indicating a role for NMDA antagonists in the treatment of acute pain and in the prevention of chronic pain states.

The activation of NMDA receptors appears to set in train a cascade of secondary events in the cell which has been activated. These events lead to changes within the cell, which increase the responsiveness of the nociceptive system and lead to some of the phenomena described above (Dickenson 1996). The NMDA receptor calcium channel in its resting state is "blocked" by a magnesium "plug." Priming of the NMDA receptor by co-release of glutamate and the peptides acting on the neurokinin receptors leads to removal of the magnesium plug and subsequent calcium influx into the cell leading to secondary events such as oncogene induction (Morgan and Curran 1986), production of nitric oxide (NO), (Garthwaite et al. 1988), and activation or production of a number of second messengers including

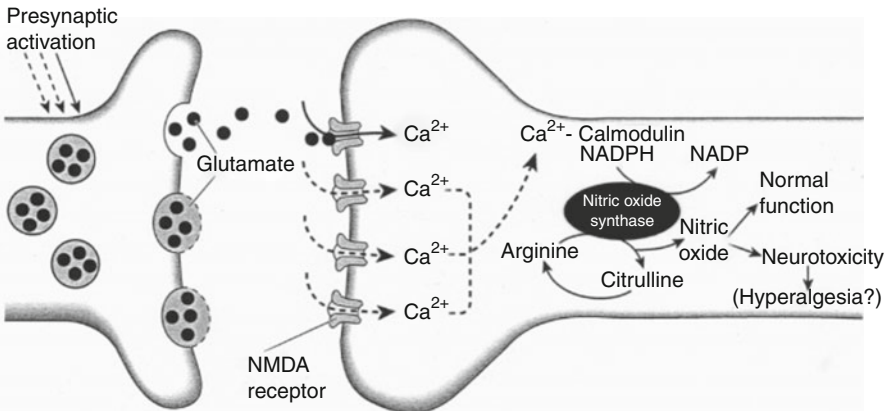

Fig. 7.4 Diagram illustrating postsynaptic events following release of glutamate from central terminals of primary afferents in the spinal cord. Following priming of the N-methyl-D-aspartate (NMDA) receptor complex, subsequent glutamate release results in NMDA receptor activation with subsequent calcium influx. Intracellular calcium then acts on the calmodulin-sensitive site to activate the enzyme nitric oxide synthase (NOS). In the presence of a cofactor nicotinamide adenine dinucleotide phosphate (NADPH), NOS uses arginine as a substrate to produce nitric oxide and citrulline. Nitric oxide has a role in normal cellular function, but increased production may be involved in hyperalgesia and may lead to neurotoxicity

phospholipases, polyphosphoinosites (IP_3, DAG), cyclic guanine monophosphate (cGMP), eicosanoids, and protein kinase C. These second messengers then act directly to change the excitability of the cell or induce the production of oncogenes, which may result in long-term alterations in the responsivity of the cell. Prolonged stimulation, presumably through sustained and therefore excitotoxic release of glutamate, may result in cell death (Fig. 7.4).

The exact role of NO in nociceptive processing is still unclear (Malmberg and Yaksh 1993). However, the production of NO is implicated in the induction and maintenance of chronic pain states (Meller and Gebhart 1993) and may be one of the factors responsible for the cell death and reduced GABA inhibition which has been demonstrated to occur under these conditions. It has been suggested that NO acts as a positive feedback mechanism in the maintenance of pain. The changes in nociceptive processing, gene expression, and others to be described below form a continuum with the early effects of nociception. Thus, it is no longer logical to view acute, subacute, and chronic pain as being entirely separate.

The production of arachidonic acid metabolites as part of the cascade that occurs following NMDA receptor activation also raises an interesting potential avenue of intervention that is already being explored (Eisenach 1993). Although the peripheral effects of NSAIDs have been emphasized in the past, it appears that there may be a role for the spinal administration of NSAIDs. Spinal NSAIDs act either directly on receptors, such as the strychnine-insensitive glycine site of the NMDA receptor complex, or influence the production of metabolites within the cell.

Descending Inhibition

The foregoing processes mostly result in enhanced peripheral and spinal cord nociception with the potential to progress to persistent pain. Fortunately, a powerful descending modulatory process "descending inhibition" provides potent inhibitory input at various levels, including the dorsal horn, via release of gamma-aminobutyric acid (GABA) and other inhibitory neurotransmitters.

Visceral Pain

Visceral pain differs in many distinct ways to somatic pain. For instance, visceral pain does not always indicate tissue damage, is poorly localized, can show a referred component, and can be associated with autonomic and affective components. Distension and spasm of visceral hollow organs can produce pain. Nonspecific visceral receptors that use an intensity coding mechanism convey afferent impulses via a limited number of autonomic afferent fibers to the dorsal horn, where they branch, forming synapses with dorsal horn neurons at different segments. The visceral structures represent a large percentage of the body surface area and however represent only 10 % of the fiber types in the dorsal horn. Therefore the somatotopic map of the viscera is poor leading to indistinct localization of pain. The convergence of visceral afferents onto dorsal horn neurons (viscero-somatic convergence) supplied by cutaneous and deep somatic afferents gives rise to the characteristic referral pattern of visceral pain. Similarly, augmentation of pain due to sensory interaction between different visceral structures that share afferent circuitry (viscero–viscero convergence) can occur.

The Pain Response

Injury Response

The pathophysiology of the injury response is wide-ranging, resulting in impairment of homeostasis, brought about by the neuroendocrine release and local cytokines. A hypercatabolic state ensues, with mobilization of glucose stores, protein and fat breakdown, and electrolyte and water flux (Carli and Schricker 2009).

Neuroendocrine and Metabolic Response

Catabolic

- Increase in ACTH, cortisol, ADH, GH, catecholamines, renin, angiotensin II, aldosterone, glucagon, and interleukin-1

Anabolic

- Due to decrease in insulin and testosterone

Metabolic

Carbohydrate

- Decrease in insulin secretion/action
- Hepatic glycogenolysis (epinephrine, glucagon)
- Gluconeogenesis (cortisol, glucagon, growth hormone, epinephrine, free fatty acids)
- Hyperglycemia, glucose intolerance, and insulin resistance

Protein

- Muscle protein catabolism and increased synthesis of acute-phase proteins
- Due to increase in cortisol, epinephrine, glucagon, and interleukin-1

Fat

- Increased lipolysis and oxidation
- Due to increase in catecholamines, cortisol, glucagon, and growth hormone

Water and Electrolyte Flux

- Retention of H_2O and Na^+, increased excretion of K^+, and decreased functional extracellular fluid with shifts to intracellular compartments (data from Kehlet (1989))

Cardiovascular Response

Sympathetic stimulation results in increased cardiac output and peripheral vascular resistance. In the compromised heart, this increased cardiac workload together with the reduction in myocardial oxygen supply through the decreased diastolic filling time will be deleterious (Wu and Liu 2009). The relationship between postoperative pain and noxious stimuli has been illustrated by the effect of epidural analgesia in preventing and reversing these cardiovascular abnormalities (Sjogren and Wright 1972; Hoar and Hickey 1976; Kumar and Hibbert 1984; Wu and Liu 2009). There is impressive evidence from animal studies that noxious stimulation results in coronary artery vasoconstriction and potential for myocardial ischemia. This has been supported by evidence in recent systematic reviews with reduction in cardiac morbidity associated with epidural analgesia, particularly in intra-abdominal aortic surgery (Wu and Liu 2009).

Respiratory Response

Respiratory dysfunction results through a variety of mechanisms. Noxious stimuli can evoke both involuntary spinal reflexes with muscle spasm and voluntary reduction in muscle movement due to perception of pain. This muscle splinting impacts

on ventilatory parameters, leading to small airway closure, and impairment of cough, leading to atelectasis and ensuing hypoxia (Wu and Liu 2009). Substantial correction of the majority of the abnormalities in pulmonary function can be obtained with effective pain relief associated with epidural block (Bowler et al. 1986; Scott and Kehlet 1988). The cumulative evidence of many clinical trials, when subjected to meta-analysis, has confirmed the superiority of epidural over systemic opioid administration in minimizing postoperative pulmonary morbidity.

Gastrointestinal Effects

Increased sympathetic activity results in decreased bowel motility and increased intestinal secretions, although this can also be attributed to opioid effects. There is some evidence that pain relief with neural blockade may reduce the transit time of x-ray contrast media through the gut, from up to 150 h in a control group to 35 h in a group receiving epidural analgesia (Ahn et al. 1988). There is also evidence that the pain-related impairment of intestinal motility may be relieved by epidural local anesthetic, but not by epidural opioid (Scheinin et al. 1987; Thoren et al. 1989, 1992; Wattwil et al. 1989; Liu et al. 1995a, b; Wu and Liu 2009). Interestingly, there is good evidence that the systemic, intravenous, administration of lignocaine speeds the return of bowel function after radical prostatectomy, as well as reducing pain and shortening hospital stay (Groudine et al. 1998).

Immunological Effects

Immunological effects with suppression of humoral and cellular immunity and coagulation abnormalities have also been recognized (Wu and Liu 2009). Changes in coagulation and fibrinolysis associated with major surgery may be partly modified by pain relief with neural blockade (Jorgensen et al. 1991). However, interpretation of these results is complex, because factors other than pain may be involved. Also, the absorption of local anesthetics associated with neural blockade may result in an antithrombotic effect (Kehlet 1998). Encouragingly, a clinical study comparing the effects of epidural and general anesthesia in peripheral vascular surgery has found that the epidural group needed fivefold fewer repeat operations for graft failure within 1 month (Christopherson et al. 1993). Changes in immunocompetence and acute-phase proteins are well documented in association with surgical trauma. Pain relief with neural blockade has a mild influence on various aspects of the surgically induced impairment of immunocompetence. The mechanism has not been completely elucidated, but may be partly explained by the concomitant inhibition of various endocrine metabolic responses. It is currently not clear if the mechanism of this effect is predominantly a result of blockade of nociception. Elucidation of this mechanism is important because posttraumatic immunodepression has been impossible to modulate by other therapeutic measures (Kehlet 1998; Wu and Liu 2009).

Attenuation of the Injury Response

Adequate management of postoperative pain is essential to attenuate the injury response. The role of different factors in the modification of the injury response is reviewed by Kehlet (1996, 1998), Liu et al. (1995b), and Wu and Liu (2009). While favorable data exist for effects on outcome of neural blockade using local anesthetic and opioid for lower-abdominal and lower-extremity procedures, less convincing effects are seen for upper abdominal and thoracic procedures.

Psychological Factors Affecting the Acute Pain Response

There is now considerable evidence that psychological factors account for a significant proportion of the variance in pain response. In addition, unrelieved pain leads to psychological changes, with increased anxiety, sleep disturbances, low morale, loss of control, and inability to think and interact (Cousins et al. 2004; Katz and Melzack 2009). Anxiety is the psychological variable which is most reliably related to high levels of pain. Circumstances associated with acute postoperative pain are probably some of the most potent in aggravating such fears. Fear of the unknown is also a major component of the general anxiety which patients experience. Hospitalization itself produces many threats, including possible disability, loss of life, coping with a new situation, loss of normal freedom, and separation from one's family and normal routine (Johnson 1980; Katz and Melzack 2009).

- Preoperative anxiety has been shown to be associated with higher levels of pain in the early postoperative period after abdominal (Caumo et al. 2002), coronary artery bypass surgery (Nelson et al. 1998), and 1 year after total knee replacement (Bradner et al. 2002).
- Higher preoperative pain catastrophizing scores correlated with higher pain scores immediately postoperatively after anterior cruciate repair and breast surgery (Pavlin et al. 2005; Jacobsen and Butler 1996).
- Higher preoperative pain catastrophizing scores correlated with higher analgesic use after breast surgery (Jacobsen and Butler 1996).
- Preoperative depression and neuroticism are predictors of early postoperative pain after surgery (Kudoh et al. 2001; Bisgaard et al. 2001).

The effects of situational or environmental variables have been shown to be important, as exemplified by the powerful effect of anxiety and perceived control over the situation (Peck 1986). Some patients may interpret the use of sophisticated monitoring equipment as implying that their situation is one of the imminent disasters (Cousins 1970). The anxiety experienced by family members is often transferred directly to the patient and serves to reinforce or reactivate his or her own fears. Another important area of investigation has been the interaction between individual and situational variables, such as the interaction between coping style and the control the patient has over the situation (Andrew 1970).

Placebo and expectation effects can sometimes play a very powerful role. One aspect of these effects is the patient's confidence and belief that the healthcare professional will be able to provide pain relief, and clearly such a placebo response is augmented by a positive doctor–patient or nurse–patient relationship (Dimatteo and Di Nicola 1982).

Studies suggest that the initial relief experienced in a new situation may be an important determinant of future relief, because the patient's expectations may be conditioned at that time. On the other hand, inadequate relief may condition a negative expectation, which could adversely affect later pain control. This indicates the importance of providing adequate pain control as quickly as possible and conveying the expectation that the pain control procedures will continue to provide effective pain relief (Voudoris and Peck 1985; Katz and Melzack 2009).

Acute Postoperative Neuropathic Pain

Neuropathic pain is pain initiated or caused by a primary lesion (or dysfunction) in the nervous system (Merskey and Bogduk 1994). In the postsurgery or posttrauma patient, neuropathic pain may have an early onset within the first 24 h; this is contrary to classic teaching. There may also be a delayed onset of the order of 10 days. Numerous physiological and structural changes occur following nerve injuries and have been summarized in several review articles (Siddal and Cousins 2008; Woolf and Manion 1999). Experimental evidence concerning the mediators involved in nerve injury and central sensitization is numerous. Injured sensory neurons undergo Wallerian degeneration with myelin sheath disruption, invasion by immune cells, and distal degeneration of the axon before regeneration can occur. Many changes have been implicated including neuroma formation, increased or novel expression of sodium channel subtypes leading to ectopic pacemaker-like activity, upregulation of voltage-gated channel expression, and neuro-immune interactions both peripherally and centrally. These afferent barrages, alterations in inhibitory and anatomical changes, lead to marked changes in the dorsal horn neurons that may lead to persistent central sensitization. Recognition of neuropathic pain and early aggressive treatment are therefore paramount to prevent long-term problems. Features suggestive of neuropathic pain are:

- Pain in the absence of ongoing tissue damage.
- Pain in an area of sensory loss.
- Paroxysmal or spontaneous pain.
- Allodynia (pain in response to non-painful stimuli), e.g., "tingling" and "pins and needles."
- Hyperalgesia (increased pain in response to painful stimuli).
- Dysesthesias (unpleasant abnormal sensations).
- Characteristic of pain different from nociception: burning, pulsing, stabbing pain
- Sometimes a delay in onset of pain after nerve injury (*note*: some neuropathic pain has immediate onset).

Table 7.1 Neuropathic pain screening tools

Pricking, tingling	+	+
Electric shocks or shooting	+	+
Hot or burning	+	+
Numbness	−	+
Pain evoked by light touch	+	+
Other symptoms	Autonomic changes	Temporal and referred patterns Pain evoked by hot/cold
Clinical examination	Brush allodynia raised Pinprick threshold	

Bennett et al. (2007)

- Hyperpathia: increasing pain with repetitive stimulation; "after response" (continued exacerbation of pain after stimulation); and radiation of pain to adjacent areas after stimulation.
- Tapping of neuromata (spontaneously firing growth buds from damaged peripheral nerves) produces a radiating electric shock sensation in the distribution of the nerve (Tinel's sign).
- Poor response (not unresponsiveness) to opioids.
- Presence of a major neurological deficit (e.g., brachial plexus avulsion, spinal injury).

(Adapted from Acute Pain Management: scientific evidence NHMRC 1999)

Despite these features neuropathic pain remains a significant diagnostic challenge. There is no single diagnostic test for neuropathic pain. Nerve conduction velocity tests and electromyography provide information about large myelinated fibers, but not about the small nociceptive afferents. Quantitative sensory testing is a psychophysical test that informs about large and small fiber function through subjective appreciation of detection thresholds to touch, pain, thermal, and vibration stimuli. Its use is limited in daily clinical practice due to the specialized equipment and training needed. Many neuropathic assessment tools have been validated for the discrimination of neuropathic pain. The S-LANSS (Leeds Assessment of Neuropathic Symptoms and Signs pain scale) score is a simple and valid seven-item self-reporting tool with sensitivity of 74 % and specificity of 76 % (Table 7.1). While these tools can aid in diagnosis, the "gold standard" at present is clinical history and examination.

Persistent Postsurgical Pain

Persistent postsurgical pain is present in at least 10–50 % of individuals after operations such as inguinal hernia repair (10 %), breast surgery (up to 30 %), thoracotomy (up to 50 %), leg amputation, and coronary artery bypass grafting (Macrae 2001). Given the sheer volumes of patients undergoing these procedures and minimal incidence of 5–10 % of severe persistent pain, it represents a major clinical

problem. Many of these patients tolerate and endure their pain, and most of this morbidity goes largely undetected by their attending medical practitioners, except through pain clinics or when a specific enquiry is made to the patient or their family. Surgical incision/trauma leads to an acute inflammatory process that activates and sensitizes the peripheral nociceptor. This increasing afferent input to the spinal cord can lead to central sensitization; however, as tissue healing occurs, the changes usually stabilize back to normal. Persisting pain may be attributable to chronic inflammation, but nerve injury is undoubtedly one of the major contributors (Perkins and Kehlet 2000; Shipton 2008). Much of the evidence pertaining to treatment focuses on surgical technique to minimize tissue and nerve trauma. However, though nerve damage seems to be necessary for pain development, it is just one of many risk factors. Unfortunately, there are no studies to date that address in full, preoperative and postoperative assessment of neurophysiologic and psychological, intraoperative technical data or detailed postoperative pain data. Recent studies report the potential effect of neurectomy and mesh removal for post-inguinal hernia persistent pain (Aasvang and Kehlet 2009).

Genetic Susceptibility

There is a marked variation among patients in the sensitivity to noxious stimuli and response to analgesia. This has evoked interest in studies of genetic susceptibility. Single-gene mutations are seen in disorders such as hereditary sensory and autonomic neuropathy, familial hemiplegic migraine, and a number of other chronic pain conditions. Heritability studies have shown strong associations in pain states such as migraine, low back pain, sciatica, and carpal tunnel syndrome. Even gender differences in pain perception and behavior are seen due to sex-specific quantitative trait loci in different genes. Identification of candidate genes and association studies with single nucleotide polymorphisms (SNP) have led to interest in a pain-susceptible phenotype. SNPs encoding for COMT, m-opioid receptor, and melanocortin receptor have been identified that impact on pain sensitivity. Interestingly tetrahydrobiopterin (BH4, a cofactor in nitric oxide, serotonin, and catecholamine production) and its synthesizing enzyme GTP cyclohydrolase have a role in increased pain sensitivity (Tegeder et al. 2006). Elevated levels of BH4 are associated with increased pain sensitivity. SNPs in the regulatory region of the gene for GTP cyclohydrolase have been identified with a pain-protective haplotype identified in 15 % of the population studied showing decreased postsurgical pain and acute mechanical experimental pain.

Pain Intensity, Pain Assessment, and Pain Scores

Severe pain preoperatively and postoperatively has been implicated in the etiology of persistent surgical pain. Correlation between phantom limb pain and preamputation pain has been noted (Jensen et al. 1985; Nikolajsen et al. 1997). Severe

postoperative pain has been shown to correlate with the development of chronic pain after inguinal hernia repair, breast surgery, and thoracotomy (Callesen et al. 1999; Katz et al. 1996; Tasmuth et al. 1996; Macrae 2001; Kehlet et al. 2006). Pain can be assessed by direct reporting by the patient and rated as none, mild, moderate, and severe; or on a visual-analogue scale from 0 (no pain) through five (moderate pain) to ten (worst pain imaginable); or simply rated against previous pain – better, same, or worse – than before. This evaluation is particularly useful for tailoring analgesia type and dose and to assess the effectiveness of previous and ongoing pain relief therapy. The duration of pain relief (relative time when pain comes back after the last dose) may constitute an important factor for effectively "titrating" the dose(s) of analgesia.

Surgical Factors

Clinical observation suggests that the following operations are particularly prone to be associated with long-term pain in or near the surgical incision: lateral thoracotomy, cholecystectomy, nephrectomy (flank incision), radical mastectomy, vein stripping (especially long saphenous because of proximity to saphenous nerve), inguinal herniorrhaphy, episiotomy, various operations on the arm and hand, and facial surgery (Litwin 1962; White and Sweet 1962; Applegate 1972; Lindblom 1979; Tasker et al. 1983; Kitzinger 1984; Macrae 2001). The type of incision selected, and care to avoid entrapment or injury to nerves during surgery or during surgical closure of the wound, is particularly important to consider. For example, lower midline incisions are usually less painful and tender than upper midline incisions and produce less respiratory compromise, while subcostal and thoracoabdominal incisions are more commonly associated with nerve injury and entrapment problems. New minimally invasive techniques using laparoscopy, lightweight mesh, and dissolving mesh fixation methods may show benefit in addressing potential nerve injury and persistent inflammation in inguinal hernia surgery. Previous use of non-soluble clips, staples, and screws to fix mesh in position for hernia repair has been associated with nerve injury or entrapment. Approaches to thoracic surgery using thoracoscopes, intercostal suturing techniques, and muscle-sparing thoracotomy have been advocated to avoid intercostal nerve damage (Kehlet et al. 2006).

Psychosocial Factors

Concepts of chronic pain have shifted from a purely biomedical to a biopsychosocial concept. Past pain experience, anxiety, fear, social, and cultural issues all affect the response to a noxious stimulus. Psychological vulnerability and compensation issues have predicted phantom limb pain up to 2 years after lower-limb amputation

(Hanley et al. 2004). As previously detailed, psychological factors have a marked impact on the acute pain experience which itself predicts chronic progression (Katz and Melzack 2009).

Postamputation Pain

Postamputation pain is a common problem with an incidence that varies from 3 to 85 % among studies, with between 5 and 10 % experiencing severe pain. Much of the long-term pain and disability is attributed to phantom limb pain, where pain is present in a body part that no longer exists. Though no long-term prospective studies exist, a retrospective study of British veteran amputees showed that in 33 % a marked decrease in pain occurs over time with complete resolution in 16 % of patients. The condition remained the same in 44 % and increased in only 3 % (Wartan et al. 1997). Although pain may diminish over time, a significant proportion will continue to suffer. This condition should not be confused with non-painful phantom limb sensations and stump pain, although a positive correlation exists between phantom limb and stump pain. Stump pain usually commences in the early postamputation period and subsides over time as tissue healing occurs. However, in 5–10 %, this pain persists, interfering with the rehabilitation period. Nociceptive stump pain originates from the local structures within the stump, and management should be directed to vascular insufficiency, badly fitting prosthesis, adherent scars, skin irritation, etc. Neuromata within the stump can give rise to neuropathic pain. Surgical removal is inconclusive due to regrowth of the neuromata, and so local anesthetic injections and pharmacological treatments could be considered. The mechanisms of phantom limb pain have not been completely elucidated with both peripheral and central dysfunction implicated. The occurrence of phantom limb pain is independent of age, gender, level of amputation, and reason for amputation. As with other persistent postsurgical conditions, pain intensity pre- and postsurgery and psychological variables have a role in the progression to chronicity. Unfortunately, data supporting the effective management of phantom limb pain is sparse. Early interventions using epidural analgesia showed inconsistent results. Regional nerve blockade provided improved acute pain scores however provided no long-term benefit (Flor et al. 2001). A study that used the NMDA receptor antagonist, Memantine, in addition to brachial plexus anesthesia for traumatic finger or hand amputation reported a significant reduction in reports of phantom limb pain after 1 year (Weich et al. 2001), although a later controlled trial showed no effect (Maier et al. 2003). Gabapentin, opioids, ketamine, dextromethorphan, and early intravenous calcitonin therapy are effective treatments for phantom limb pain (Bone et al. 2002; Wu et al. 2002; Abraham et al. 2003; Nikolajsen 1996, 1997; Jaeger and Maier 1992). Although proven in other neuropathic pain states, no studies have proven a role for amitriptyline. Non-medication approaches have shown promise. Myoelectric prosthesis and sensory discrimination training have reduced phantom limb pain and reduced cortical reorganization (Lotze et al. 1999). Visual feedback

Table 7.2 Diagnostic criteria for complex regional pain syndrome

Diagnostic criteria (see Binder and Baron 2009)	
Continuing pain, which is disproportionate to any inciting event	
Symptoms/signs	
Sensory	Hyperalgesia (to pinprick)
	Allodynia (to light touch)
Vasomotor	Temperature asymmetry
	Skin color changes/asymmetry
Sudomotor	Edema
	Sweating changes/asymmetry
Motor/trophic	Decreased range of motion
	Motor dysfunction (weakness, tremor, dystonia, neglect)
	Trophic changes (nail, skin, hair)

with mirror boxes has been used to eliminate painful phantom limb spasms (Ramachandran and Rogers-Rmachandran 2000). TENS applied to the ear and the stump has shown inconsistent results. The lack of side effects of these non-medication techniques makes them a viable treatment option despite the lack of controlled data.

Complex Regional Pain Syndrome

Complex regional pain syndrome is a chronic pain condition that follows an initiating noxious event. Diagnostic criteria rely on the presence of a constellation of symptoms and signs that include pain, sensory, vasomotor, sudomotor, and motor signs and symptoms, with exclusion of other causes. Two subtypes exist, CRPS 2 where nerve lesion is the underlying trigger and CRPS 1 where no nerve lesion can be identified. Research and clinical criteria for diagnosis differ in respect to the number of signs and symptoms needed to make the diagnosis. The patient must report at least one symptom in each of the four categories and display one sign in at least two of the categories for research purposes, with three categories of symptoms and two categories of signs for clinical diagnosis (Harden et al. 1999; Binder and Baron 2009) (Table 7.2).

Controversy exists in all areas of the condition, in its diagnostic classification, division into subtypes based upon nerve injury, and evidence of beneficial treatments (Binder and Baron 2009; Bruehl et al. 2009). No specific diagnostic techniques exist. Quantitative sensory testing can be used to evaluate altered detection and pain thresholds to a variety of stimuli (pressure, temp). Thermography, or at least spot temperature, can be used to document vasomotor abnormalities, and sudomotor abnormalities can formally quantified using quantitative sudomotor axon reflex testing. Although bone changes do occur in this condition, the utility of radiological investigations such as triple-phase bone scan is questionable. The primary goal in treatment is restoration in physical function. All other treatment modalities such as pharmacotherapy, interventional, and psychological therapies

are aimed at improving the ability to cope with a functional restoration program. Pharmacological therapy using intravenous sympatholytic agents such as guanethidine and phentolamine lacks convincing evidence. Bisphosphonates, particularly when administered intravenously, have been thoroughly studied with statistically significant improvements in active movement and motor function (Vareena et al. 2000; Adami et al. 1997). Due to the lack of sufficient quality controlled trails, anecdotal evidence from other neuropathic pain states guides use of pharmacological therapies in CRPS.

Lumbar sympathetic and stellate ganglion local anesthetic blockade continues to be widely practiced. These provide short-term pain relief which may be beneficial in expediting improvement and assessment in physical therapy. Although this procedure can be repeated, it is thought that the efficacy reduces over time (Cepeda et al. 2002). Interestingly, there is evidence that a good response to sympathetic block may predict the likelihood of success with spinal cord stimulation. Chemical and surgical sympathectomy can be associated with a significant rate of complications with worsening of pain or production of a new pain syndrome.

A randomized controlled trial by Kemler et al. looked at the management of severely disabled, treatment refractory CRPS patients randomized to spinal cord stimulation (SCS) with physical therapy or physical therapy alone. These patients were followed up at 2 and 5 years. Initial evaluation pointed to marked reduction in pain with SCS. On 2-year follow-up, pain intensity and quality of life measures were improved with SCS although no difference in function was present. Five-year follow-up revealed that pain relief with SCS had diminished over time and was not significant after 3 years (Prager and Stanton-Hicks 2009).

Multimodal Analgesia and Multidisciplinary Treatment

The treatment of pain relies on appropriate management of physiological, psychological, and environmental factors. This multidisciplinary approach has demonstrated efficacy in the management of chronic pain. However, as detailed above, the psychological factors in acute pain contribute not only to acute pain, but also to the progression into chronic pain. Psychological methods for reducing pain have been discussed by Peck (1986), Melzack (1988, 1993), and Katz and Melzack (2009). There is now good evidence that patients benefit from the use of multimodal, or balanced, analgesia after surgery. Multimodal analgesia employs a variety of drugs, given perhaps by different routes and/or different timing, to achieve analgesia, with a reduction in the incidence and severity of side effects, especially those seen with opioid administration. After bowel surgery, multimodal analgesia comprising epidural analgesia using a mixture of local anesthetics and low-dose opioid provides excellent analgesia and hastens the rate of recovery of gastrointestinal function after surgery of the colon, especially if systemic NSAIDs are used to avoid the need for opioid administration after the epidural has been ceased (Liu et al. 1995a). It is possible to eliminate pain after surgery using multimodal analgesia with a significant

reduction in total opioid consumption (Schulze et al. 1988; Dahl et al. 1990). However, the effect on morbidity and mortality has been disappointing in some studies (Moiniche et al. 1994), demonstrating that very good pain control is not automatically associated with an improvement in outcome. Recent research has suggested, however, that the use of multimodal analgesia after major surgery may improve recovery and thus reduce costs (Brodner et al. 1998). Kehlet has proposed that the "pain-free state" should be employed as a fundamental component of an aggressive regimen of postoperative mobilization and early oral feeding in a process of acute rehabilitation after surgery (Kehlet and Dahl 1993), to enable "fast-track" surgery and reduce hospital stay (Kehlet 2008; Kehlet and Wilmore 2008).

Preemptive/Preventive Analgesia

The recognition of the spinal changes that occur with sustained noxious input causing central sensitization and experimental evidence (Woolf 1983) reporting attenuation when analgesia was administered prior to acute pain stimulus (preemptive analgesia) evoked much clinical interest. Unfortunately, clinical studies and two recent systematic reviews (Moiniche et al. 2002; Ong et al. 2005) show contrasting results. Studies have typically looked at the timing of the intervention between pre- and post-incision, termed *preemptive analgesia*. In a review of 80 studies, Moiniche et al. (2002) were unable to demonstrate any clinically significant effects of preemptive analgesia with peripheral local anesthetic, neuraxial blockade via the epidural and caudal route, intravenous opioids or ketamine, and nonsteroidal anti-inflammatory medications. The most recent systematic review by Ong et al. (2005) which reviewed 66 studies showed consistent improvement in postoperative pain score, analgesic consumption, and time to rescue analgesia with epidural analgesia. Decreased analgesic consumption and increased time to rescue analgesia were evident with local anesthetic wound infiltration and nonsteroidal anti-inflammatory medications (Aasvang and Kehlet 2005). No positive effects were found with systemic NMDA antagonists or opioids. As noxious input exists not only on surgical incision but throughout the postoperative period, the administration of an agent pre- or postoperatively ("preemptive") may only temporarily reduce central sensitization. Studies of "preventive" methods aim to provide continuous modification of central sensitization postoperatively, by various regimens, and to compare this with placebo/no treatment of this type. Outcomes evaluated include pain and "rescue analgesic" medication as well as development of persistent pain. A systematic review by McCartney et al. (2004) showed significant preventive benefit for NMDA receptor antagonists, which concurs with basic science knowledge of the NMDA receptors' role in central sensitization. Severity of acute pain has been found to be associated with development of persistent pain (Perkins and Kehlet 2000), and there is some evidence that early intervention may attenuate the risk of persistent pain. Epidural analgesia initiated prior to thoracotomy and continued postoperatively resulted in significant reduction in reports of pain after 6 months in comparison to intravenous patient-controlled analgesia morphine (Senturk et al. 2002). Unfortunately, no such evidence is available for preoperative epidural use in phantom limb pain (Halbert et al. 2002).

Table 7.3 Commonly used classes and examples of agents with analgesic or anti-inflammatory properties

Analgesic agent	Example(s)
Opioids	Morphine, fentanyl, pethidine, methadone, buprenorphine, codeine, oxycodone, tramadol, dextropropoxyphene
Hypnotics	Benzodiazepines (diazepam, baclofen) for muscle spasm
Neuropathic drugs	Amitriptyline (noradrenergic and Na^a channel), ketamine (NMDA), gabapentin, pregabalin ($\alpha_2$delta site of Ca++ channel), duloxetine (noradrenergic and serotonergic)
Simple analgesics	Paracetamol (oral or intravenous)
Nonsteroidal anti-inflammatories (NSAIDs)	Aspirin, ibuprofen, piroxicam, indomethacin, celecoxib, naproxen, ketorolac
Steroids	Dexamethasone, cortisone
Local anesthetics	Lignocaine injection or gels, bupivacaine injection
Anti-gout	Allopurinol, colchicine

Commonly Used Analgesics

Some representative examples of commonly used analgesics and pain modifying agents are given in Table 7.3.

Combination or mixed agents (e.g., paracetamol/codeine; paracetamol/dextropropoxyphene) are also used, as are combinations dosing of separate agents. These agents are used according to the intensity of pain and causation and are frequently used in combination where appropriate to maximize the efficacy. For example, a short half-life, rapidly acting opioid analgesic might be selected initially for control of wound pain postoperatively as an intravenous infusion for patient-controlled analgesia (fentanyl), then followed by a longer half-life intermittent subcutaneously injected opioid (morphine) a few days later, and an anti-inflammatory agent (ibuprofen) might be combined with a simple analgesic (paracetamol) later during the mobilization and recovery period. Epidural or spinal anesthesia/analgesia or a regional block (e.g., caudal axillary or sciatic block) may be utilized to reduce the opioid requirement or decrease the risk of respiratory, cardiovascular, or other complications.

In addition, it is important to consider the mode of administration, as opioids may be delivered by the intravenous, subcutaneous, intramuscular, epidural, and spinal routes, and local anesthetics can be administered by topical, intradermal/subcutaneous injection, and perineural (for regional neural blockade), epidural, and spinal injections. Paracetamol (and some NSAIDs) may be administered orally or intravenously.

The management of pain is considered in more detail in a number of excellent publications including the Australian and New Zealand College of Anaesthetists' and Faculty of Pain Medicine, NHMRC (National Health and Medical Research Council of Australia), endorsed *Acute Pain Management: Scientific Evidence*, Australian and New Zealand College of Anaesthetists, (June) 2005 (New Version late 2009) www.anzca.edu.au/resources/books-and-publications, and in Macintyre and Schug. *Acute Pain Management: A Practical guide*. 3rd Ed, (2007).

Summary

Although pain is a natural consequence of tissue trauma, including from acute trauma, acute surgical pathology, and surgical intervention, it can usually be minimized or alleviated with adequate planning, consideration, and utilization of a multimodality approach. Not only is the aim to prevent or diminish the acute pain in the perioperative period, but avoidance of prolonged or chronic pain should also be an objective of pain management at the time of surgery. As demonstrated above, this has anesthesia, psychological, and surgical components to reduce the experience of excessive pain in the perioperative period and to reduce the risk of events during surgery and wound closure, such as nerve entrapment or injury. As the mechanisms for induction of pain become more precisely and clearly understood, better agents and techniques for acute and chronic pain management should become available to assist us.

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