When does acute pain become chronic?

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Summary. The transition from acute to chronic pain appears to occur in discrete pathophysiological and histopathological steps. Stimuli initiating a nociceptive response vary, but receptors and endogenous defence mechanisms in the periphery interact in a similar manner regardless of the insult. Chemical, mechanical, and thermal receptors, along with leucocytes and macrophages, determine the intensity, location, and duration of noxious events. Nocuous stimuli are transduced to the dorsal horn of the spinal cord, where amino acid and peptide transmitters activate second-order neurones. Spinal neurones then transmit signals to the brain. The resultant actions by the individual involve sensory-discriminative, motivational-affective, and modulatory processes in an attempt to limit or stop the painful process. Under normal conditions, nocuous stimuli diminish as healing progresses and pain sensation lessens until minimal or no pain is detected. Persistent, intense pain, however, activates secondary mechanisms both at the periphery and within the central nervous system that cause allodynia, hyperalgesia, and hyperpathia that can diminish normal functioning. These changes begin in the periphery with upregulation of cyclo-oxygenase-2 and interleukin-1β-sensitizing first-order neurones, which eventually sensitize second-order spinal neurones by activating N-methyl-D-aspartic acid channels and signalling microglia to alter neuronal cytoarchitecture. Throughout these processes, prostaglandins, endocannabinoids, ion-specific channels, and scavenger cells all play a key role in the transformation of acute to chronic pain. A better understanding of the interplay among these substances will assist in the development of agents designed to ameliorate or reverse chronic pain.

Keywords: analgesia; cyclo-oxygenase-2; hyperalgesia; microglia; neuroplasticity; nociception; pain; postoperative pain; post-surgical chronic pain; sensitization

Mechanism for acute pain generation: peripheral effects and spinal and central effects

The generation of acute surgical pain can be summarized in the following way. Surgery-associated tissue injury is interpreted neuraxially in the same way as trauma-associated injury. Pain sensation varies according to the intensity, quality, and duration of stimuli. Surgery sets off a cascade of inter-related events designed to fight infection, limit further damage, and initiate repair. It involves nociception, inflammation, and nerve cell remodelling. Pro-inflammatory cytokines, chemokines, and neurotrophins induce both peripheral and central nerve sensitization to heighten pain awareness in order to limit further injury to the affected area. In the generation of pain, multiple pain systems are known to be activated.
It is the activation of nociceptors in the periphery, and their ongoing activation, through processes such as peripheral and ultimately central sensitization, that underlies one mechanism of the transition to the chronic pain state. Nociceptors are free nerve endings, with no extracellular matrix capsule or epithelial cell adherent to the neurone, and respond to stimuli that damage or threaten to damage tissue. Nociceptors are present in skin, muscle, joints, and viscera, with varying degrees of density. It is this density of population that allows for differential sensory ability, for example, the difference between the finger tip and the back. Nociceptors are the primary afferent terminals of nerves that generate impulses to the spinal cord, and are categorized by their receptive modality and by their response to that stimulus.

A-δ fibres are fast-conducting myelinated nerves activated by heat by mechano-thermal receptors and high-threshold mechanoreceptors. The degree of the stimulus is translated into a proportional intensity of firing. In contrast, C-fibres are non-myelinated, slow-conducting, fibres with receptive fields smaller than those of A-δ nociceptors. In the non-sensitized state, they have higher thresholds for activation when compared with A-δ fibres or A-β fibres. These fibres represent the majority of peripheral nociceptors, and most are of the C-polymodal neurone type. Like A-δ fibres, C-fibres respond to thermal and mechanical stimulation. Unlike A-δ fibres, they also respond to chemical stimuli, and produce sensation consistent with itching. A-β fibres are of large diameter and highly myelinated, and convey only proprioception and touch.

Nociceptors are either specific to the type of noxious stimuli, such as mechanical pressure, cold, or hot, or are polymodal nociceptors that respond to mechanical, thermal, and chemical stimuli. Polymodal nociceptors are the most abundant type. By varying both in their threshold to stimuli and their rate of firing to the dorsal horn, action potential processing into the CNS can span a wide range of pain perceptions, both in quality and intensity. Also, by responding differently to stimuli, these nociceptors encode a wide range of sensory phenomena. When a polymodal nociceptor becomes sensitized, it is sensitized to all modalities it conveys.

A-δ and C-fibre innervation of the dorsal horn terminates superficially in laminae I–II with a few connections to deeper laminae, whereas A-β fibres predominantly terminate in laminae III–VI. Centrally, within the laminae of the dorsal horn, receiving neurones are specific to either A-δ and C-fibre input, to A-β input, or are wide dynamic range neurones receiving input from all three. These second-order neurone connections can be influenced by both excitatory glutamatergic and inhibitory GABAergic interneurones, or by astrocytes and microglia, particularly under pathological states. Within lamina I, approximately 80% of these cells express the neurokinin 1 receptor for substance P. These cells project to the thalamus, periaqueductal grey (PAG), and the parabrachial area. Hence, lamina I cells play a strong role in processing spinal input to inhibitory and facilitatory descending pathways from higher CNS centres.

The CNS can alter the afferent nociceptive information it receives by a descending or modulatory system. This system arises out of several regions of the CNS, including the somatosensory cortex, hypothalamus, PAG, pons, lateral tegmental area, and raphe magnus. These structures communicate with laminae I and V via the dorsolateral funiculus. Stimulation of these areas, or of their common outlet path via the dorsolateral funiculus, inhibits nociceptive impulses promoting an analgesic effect. Descending inhibition largely involves the release of norepinephrine in the dorsal horn from the locus coeruleus, acting at α2-adrenoceptors, to inhibit primary afferent terminals and suppress firing of projection neurones. Descending facilitatory pathways, primarily involving a serotonergic mechanism, are also involved and appear to play a greater role in the development of chronic pain. Thus, in terms of central sensitization, the spinal cord is an important pain processing crossroad receiving input from peripheral neurones, interneurones, astrocytes and microglia, and descending modulatory controls.

Five events are needed for a nociceptor to relay pain information to the CNS; signal transduction, action potential generation, transmission of the action potential to the CNS, second-order neurone activation to transmit the signal to the thalamus, and third-order neurone transmission of the signal to the cerebral cortex, where the nociceptive stimulus is perceived as pain. Each process is controlled by a distinct set of receptor proteins amenable to a wide variety of therapeutic interventions, some of which will be briefly reviewed below.

As free nerve endings, nociceptors are chemosensors that react to cellular damage by responding to a wide range of inflammatory molecules. These include adenosine-5′-triphosphate (ATP), nerve growth factor (NGF), tumour necrosis factor-alpha (TNF-α), bradykinin, prostaglandin E2, serotonin, and protons (H+), which are released by epithelial cells, mast cells, macrophages, etc. Given the abundance of ligands and voltage-gated ion channels, nociceptive transmission involves multiple rather than only one voltage- or ligand-gated channels. Nociceptors are also capable of amplifying local inflammation by releasing such compounds as substance P, which can activate local mast cells and cause vasodilation by the release of calcitonin gene-related peptide (CGRP). After tissue damage, increased density of several transducers, phosphorylation of these transducers, and activation of receptors such as transient receptor potential type V1 (TRPV1) results in an increased channel activity and sensitivity to noxious stimuli (sensitization). For example, changes in the expression, trafficking, and distribution of Na+ channels after inflammation or nerve injury contribute to unstable oscillations of membrane potential, abnormal firing, and the generation of ectopic activity in afferent nerves.

In addition to the generation of ongoing spontaneous ectopic activity through the accumulation and clustering of
Na⁺ channels, these neurones can exhibit ephaptic transmission both between peripheral fibres and their cell bodies within the dorsal root ganglion. Along with changes within nociceptive fibres, sympathetic efferents become able to activate nociceptive fibres via poorly characterized α-adrenoceptors. In relation to this generation of spontaneous activity, the Na⁺ channel subtype is thought to play a key role. Knockdown of this receptor in mice produces a marked reduction in abnormal responsiveness.

Understanding the endogenous mediators and factors that contribute to sensitization in a synergistic fashion might provide a better understanding of how acute pain may transition to a chronic physiological pain state (Fig. 1). Blocking these receptors might attenuate or prevent acute pain, or if a chronic pain state has already developed, might ameliorate or even reverse such a pathophysiological state.

The stimuli sufficient for the activation of nociceptors appear to be tissue-specific, and tissue damage is not always required. For example, the sensitization process in the masseter muscle has been found to involve a decrease in a specific voltage-gated K⁺ channel. Similar mechanisms of a decrease, or increase, in specific ligand-gated or voltage-gated channels have been found in the sensitization process of other tissues. Additionally, so-called ‘sleeping’ nociceptors can become activated after exposure to inflammation and other endogenous mediators, and might represent as much as 15% of all C-fibres, contributing to a significant increase in peripheral input to the CNS.

**Neuroplasticity**

Neuroplasticity, or the physical remodelling of neuronal cytoarchitecture, occurs shortly after the onset of persistent acute pain and leads to the transition from acute pain into a chronic pain state. As a result of a peripheral lesion that persistently generates pain impulses to the spinal cord, inhibitory interneurones responsible for modulating painful nerve transmission impulses eventually die. Furthermore, glial cells remodel neuronal synapses to intensify nociceptive transmission. These pain-transmitting neurones become more sensitive, react more intensely to stimuli, and grow more connections to second-order neurones within the CNS. In short, this process of neuroplasticity leads to central sensitization in which activity dependent phenotypic changes are seen in the dorsal horn neurones and other CNS structures, including higher centres.
Whereas primary hyperalgesia occurs in the periphery, secondary hyperalgesia occurs within the CNS and precedes long-term central sensitization. Most of the treatments for postoperative pain have only minimal analgesic effects on secondary hyperalgesia. As secondary hyperalgesia is felt to be a source for chronic postsurgical pain, developing agents to better treat secondary hyperalgesia might be more effective in preventing chronic postsurgical pain, and treating acute postoperative pain.28 29

Post-procedural pain

The factors contributing to post-procedural pain can broadly be divided between patient and surgical factors. Patient factors include psychosocial status, pre-existing pain conditions, genetic predisposition to exaggerated pain response, and gender. Surgical factors include the type of anaesthesia administered (general vs regional technique) and surgical approach including the ability to identify and avoid nerve injury when possible. Additional surgical factors include the postoperative period and the type of pain treatment and duration, and full assessments of the pain, its consequences, and neurophysiological examination.30–32

The mechanisms of post-procedural pain and chronic postsurgical pain are complex and poorly understood. Many of the syndromes are, at least in part, neuropathic that result from neuroplastic changes after injury.33 After surgical intervention, patients experience ongoing pain or are sensitive to incidental, normally non-painful stimulation. This period of time varies, and with uncomplicated wound healing this pain progressively attenuates and disappears. The patient population with persistent post-surgical pain experience deep pain or referred pain that lasts months or years. The International Association for the Study of Pain defined post-procedural pain as a persistent pain state that is apparent more than two months after operation and cannot be explained by other causes. The nature and properties of this pain are poorly characterized, without a distinct transition period from acute to chronic pain. It is unclear whether the chronic condition constitutes merely an extension of perioperative pain.34 To give an example of the magnitude of the problem, after procedures such as thoracotomy, mastectomy, and amputation, as many as 50–70% of patients continue to experience pain for at least 6 months, with approximately 10% reporting severe pain.32 35–37 Post-procedural pain is also common 1 yr after lower abdominal surgery, sternotomy, hysterectomy, and herniorrhaphy with rates of 25% or greater.38–63 This problem is not restricted to major surgeries; after minor procedures, approximately 5% of patients suffer severe chronic post-surgical pain.32 The wide variation in the incidence of chronic post-surgical pain is probably owing to differences in surgical techniques, study design, patient populations, and differing definitions of chronic pain.33

From the perspective of patients’ overall assessments of their health, even low levels of residual pain significantly affect social and physical function. From the perspective of the medical profession, it is encouraging that it is now recognized that ‘chronic pain is the most common and serious long-term problem after repair of an inguinal hernia,’ showing a heightened awareness of this important issue in the last decade.33 44

Surgery causes the release of inflammatory and other mediators. Initially, these mediators activate nociceptors, however during persistent pain nociceptors become sensitized. If this persistent pain resolves in the process of normal wound healing, this process of sensitization and facilitation of synaptic transmission to the CNS reverts to normal intrinsic nociceptor activity. For many surgery-related reasons, such as prolonged inflammatory states with the insertion of mesh materials or chronic nerve stretching in bunionectomy, this process of sensitization and facilitation can cause phenotypic and pathophysiological changes in nociceptors. These include changes in gene expression, receptor translocation to the cell membrane, sustained activation of inflammatory and glial cells, and spinal inhibition and facilitation. Once these structural changes occur, chronic pain pathophysiology becomes established. These changes are seen in animal models of incisional injury, which predisposes animals to enhanced pain sensitivity when a second injury is applied several weeks later.36 45 46

Though a compelling hypothesis, the benefits of preoperative, intra-operative, and postoperative analgesic interventions in an attempt to reduce the incidence of chronic postsurgical pain have not proved unequivocally effective.35 47 48 It is likely that the pathogenic mechanisms leading to post-procedural pain are multiple. More rigorous study designs will be required to better understand how the problem evolves and who is at greatest risk.30

The factors that predispose one to chronic pain include gender, psychosocial issues, preoperative pain at the site of surgery or in other body regions, the type of surgical trauma, nerve damage, severity of acute postoperative pain and inflammatory responses, perioperative analgesia, type of disease, younger age (increasing age-reducing risk), length of surgery (operations lasting more than 3 h), recurrence of malignancy, and radiation therapy.30 32 49 50 Chemotherapy and age as risk factors have been controversial (Table 1).33 51 52 For the most part, trauma pain is akin to post-procedural pain.

Given the numbers of patients at risk each year, the economic consequences, and the effect on quality of life, the issue of chronic post-surgical pain is a major public health issue.31 As chronic post-surgical pain is, at least in part in some syndromes, neuropathic, its prevention is important owing to the difficulty of its treatment.33

Neuropathic pain

Nerve injury causes both neural and immune changes that give rise to neuropathic pain. At the cellular and tissue levels, redistribution of the Na+,1,8 voltage-gated Na+ channel subtype in nociceptors expressing neuropathic physiology and microglial activation in the ipsilateral dorsal horn of the spinal cord occur. These changes facilitate the
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Development of persistent pain as they provoke long-term changes including altered gene expression in the dorsal root ganglia and the spinal cord, central sensitization, and trans-synaptic neurodegeneration. Injuries and diseases of the nervous system that result in neuropathic pain promote the presence of inflammatory mediators within the spinal cord. Hence, blocking peripheral inflammation alone would not deal with this central inflammatory state unless the analgesic mediators readily crossed the blood–brain barrier. There are clearly both peripheral and central inflammatory components in neuropathic pain. It is not yet clear whether ongoing inflammation or inflammatory mediators maintain chronic neuropathic pain. In short, neuropathic pain requires ongoing sensitization caused either by constant afferent stimulation from injured nerves or functional changes in dorsal root ganglion as seen in sympathetic sprouting.

There is a large body of evidence that shows the pathophysiology of different pain types such as inflammatory, neuropathic, or cancer-related pain is distinct from one another. For example, distinct pathophysiological features exist in murine models of inflammatory, neuropathic, and cancer pain. Increases in substance P, CGRP, protein kinase C, and the substance P receptor were observed in the spinal cord in inflammatory pain. In neuropathic pain, significant decreases in substance P and CGRP and increases in galanin and neuropeptide Y were observed in both primary afferent neurones and the spinal cord. In cancer-related pain, there were no detectable changes in any of these markers in either primary afferent neurones or the spinal cord; rather there was massive astrocyte hypertrophy without neuronal loss, increased neuronal expression of c-Fos, and increased number of dynorphin-immunoreactive neurones in the spinal cord ipsilateral to the limb with cancer. Differences were also found for microglial cells, in which the marker complement receptor type 3 (C3) was increased only in the neuropathic pain model. Many patients with post-procedural pain report both sensory abnormalities and localized stimulus-evoked pain, suggesting that both abnormal sensory nerve function and ongoing nociception play a role. Effective treatment for these two interwoven yet distinctly different pain syndromes is unlikely to be solved using a single therapeutic strategy for one or the other.

### Epidemiology of chronic pain

In a 1999 study of chronic pain in the community, 46% of the general population had chronic pain. Backward stepwise logistic-regression modelling identified age, female gender, housing tenure, and employment status as significant predictors of the presence of chronic pain. A 2006 study found a similar prevalence in any chronic pain of 48%, however the prevalence of pain of predominantly neuropathic origin was 8%. This study showed that chronic pain with neuropathic features appears to be more common than previously thought. This finding is especially important in light of the fact that pain with neuropathic features is more severe and difficult to treat. Chronic neuropathic pain patients had similar risk factors as described before (with the addition of no educational qualifications, no longer married, and smokers). Moreover, pain of predominantly neuropathic origin was independently associated with older age, gender, employment (being unable to work), and lower educational attainment.

### Development of chronic pain

Changes in nociceptor function can be broadly divided into modulation or modification. Modulation represents reversible changes in the excitability of primary sensory and central neurones mediated by post-translational modification of receptors and ion channels by activation of intracellular signal-transduction cascades. Modification represents long-lasting alterations in the expression of transmitters, receptors, and ion channels or in the structure, connectivity, and survival of neurones, such that the cytoarchitecture is modified altering normal stimulus-response characteristics. Modification is the more plausible link to the transition from acute to chronic pain. With an array of chemical mediators that interact with nociceptive neurones, it is important to note that each sensitizing signal molecule might act on different receptors, but collectively they produce similar end results by activating the same intracellular signalling cascades leading to the activation of protein kinase A (PKA) or protein kinase C (PKC). Thus, inhibiting a single sensitizing agent is unlikely to completely eliminate peripheral sensitization. This argues the use of multimodal

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<th>Table 1 Predisposing factors for chronic post-procedural pain</th>
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<td><strong>Preoperative factors at the site of surgery or other body regions</strong></td>
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<td>Psychosocial factors</td>
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<td>Coping skills</td>
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<td>Surgical factors</td>
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<tr>
<td>1. Nerve damage (complicated aetiology likely than just nerve injury alone)</td>
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<td>2. Factors predisposing to prolonged inflammatory states (foreign materials)</td>
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<td>3. Volume of surgeries performed per year for given operation</td>
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<td>4. Recurrence of operation</td>
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<td>5. Type of surgery</td>
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<td>6. Length of surgery</td>
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<tr>
<td>Genetic predisposition</td>
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<tr>
<td>Acuity of postoperative pain</td>
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<td>Prolonged postoperative pain/inflammatory responses</td>
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<td>Duration of postoperative pain treatment</td>
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<td>Anaesthetic factors (general vs regional, type of general anaesthesia)</td>
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<td>Gender (female)</td>
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<td>Type of disease</td>
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<td>Recurrence of malignancy</td>
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<td>Adjuvant therapy: radiation, chemotherapy (conflicting reports)</td>
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<td>Age (conflicting reports)</td>
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analgesic techniques as a necessity. The process of central sensitization is probably similar in this regard.

As seen in the dorsal root reflex and axonal reflex, action potentials can be initiated in the central terminal, and conducted anterogradely to the periphery. After surgical tissue damage, this mechanism appears to be a significant factor in neurogenic inflammation.65

There is evidence of a possible window in which permanent changes occur in nociceptors after an insult.56 In reference to the development of neuropathic pain, this concept of a window would be important in terms of the timing of the delivery of treatment.

**N-methyl-α-aspartic acid receptors**

Prolonged firing of C-fibre nociceptors causes release of glutamate, the major excitatory neurotransmitter within the CNS, which acts on post-synaptic ionotropic glutamate receptors [N-methyl-α-aspartic acid (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors], and the G protein-coupled metabotropic (mGLuR) family of receptors.10 Presynaptic kainate receptors for glutamate have also been described.67

Glutamate release by sensory afferents acts on AMPA receptors if the impulse is more acute and brief. However, if repetitive and high-frequency stimulus from C-fibres is received, amplification and prolongation of the response occurs in the process known as wind-up through activation of the NMDA receptor. Normally, the NMDA receptor is blocked by its ion channel Mg2+; however, under continuous stimulation it is removed. Relief of the Mg2+ block is probably facilitated by the co-release of substance P and CGRP from C-fibres.68 69 This enhanced NMDA receptor activation plays a role in inflammatory and neuropathic pain states,70 71 and results in the activation and exacerbation of secondary hyperalgesia. They also initiate translational changes of the second-order neurones, which might be a crucial link in the pathogenesis of chronic pain.72–74 NMDA receptors are also required for the descending inhibitory pathway of the CNS within the substantia gelatinosa.75 Though this receptor appears vital for the induction and maintenance of pain, to date, largely owing to side-effects of the currently available drugs (ketamine, dextromethorphan, and memantine), low therapeutic indexes, and lack of specificity for the dorsal horn NMDA receptor (NR2B subtype), most patients cannot achieve complete pain relief with NMDA receptor blockade alone.10 However, low doses of these drugs have been shown to be effective with more tolerable side-effect profiles, hence suggesting their use in multi-modal analgesic approaches to more effectively treat chronic pain.

**Glial cells**

Activation of CNS microglial cells, which are functionally equivalent to peripheral macrophages, plays a central role in pain.76 Glial cells are activated by substances released from primary afferent terminals (substance P, excitatory amino acids) and from second-order transmission neurones (nitric oxide, prostaglandins). Activated glial cells then up-regulate cyclo-oxygenase-2 (COX-2) to produce prostaglandin E2 and release additional neuroactive substances (cytokines interleukin-1, interleukin-6, TNF-α). These substances increase the excitability of second-order neurones, and play a role in axonal sprouting, altered connectivity, and cell death.77 Hence, persistent glial cell activity producing these pro-inflammatory mediators plays a role in the development of a neuropathic pain state.78 79 Post-traumatic models, inflammatory models, central demyelinating disorders, and diabetes mellitus have all demonstrated a role for glial cell activation.78 80–86 Activation of microglia can be followed by increased expression of p38 mitogen-activated protein kinase (MAPK), which participates in a signalling cascade controlling cellular responses to cytokines and stress and is amplified across many painful conditions.87 88

**Cyclo-oxygenase-2**

Both inflammation and nerve injury induce transcriptional changes in dorsal horn neurones, which includes the induction of COX2. The major inducer of central COX-2 upregulation is interleukin-1β. This has been shown through the administration of an interleukin-1β-converting enzyme (ICE) inhibitor, interleukin-1ra, or a COX-2 inhibitor (NS398), which decreases inflammation-induced central PGE2 levels and mechanical hyperalgesia.89 This central mechanism renders peripheral nerve blocks less effective in reducing inflammatory pain and encourages the use of COX-2 inhibitors or non-steroidal anti-inflammatory drugs (NSAIDs). COX-2 in the CNS is a major target for pain control as upregulation of COX-2 expression leads to increased central sensitization and pain hypersensitivity. Intraspinal administration of an experimental COX-2 inhibitor resulted in a significant decrease in centrally generated inflammatory pain hypersensitivity through a cannabinergic mechanism that is described below.90 Thus, inhibitors of COX-2 that can better penetrate the blood–brain barrier should be more efficient analgesics.89–91

Tied to the expression of COX-2 are the CNS effects of PGE2, which include binding to prostaglandin E receptor subtypes EP1 or EP3 on sensory neurones, activation of PKA and PKC, phosphorylation of sensory neurone-specific Na+ channels, reduction in the threshold for sensory neurone activation, increase in neuronal excitability, and the activation and synthesis of interleukin-1β by microglia89–91 (Table 2 and Fig. 2).

**Table 2** Summary of prostaglandin E2 effects in pain development

<table>
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<tr>
<th>Product of the cyclooxygenase-2 pathway</th>
<th>Binds prostaglandin E receptor subtypes EP1 or EP3 on sensory neurones</th>
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<tr>
<td>Activates protein kinases A and C</td>
<td>Phosphorylates sensory neurone-specific Na+ channels</td>
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<tr>
<td>Causes a reduction in the threshold for sensory neurone activation</td>
<td>Causes neuronal excitability</td>
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<tr>
<td>Causes activation and synthesis of interleukin-1β by microglia</td>
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Cannabinoids

Endocannabinoids (eCBs) are derivatives of arachidonic acid. Cannabinoid receptors (CB1 and CB2) are expressed in all nociceptive neuroanatomical pathways of the CNS and peripheral nervous system (PNS). These areas include the PAG zone (CB1), the dorsal horn of the spinal column (CB1), dorsal root ganglion neurones (CB1), peripheral nociceptors (CB1 and CB2), macrophages (CB2), and keratinocytes (CB2). The CB1 and CB2 receptors are G protein-coupled receptors that bind eCBs. They act by retrograde synaptic inhibition to decrease presynaptic Ca\(^{2+}\) concentrations and activate inward-rectifying K\(^+\) channels, thus reducing the release of such neurotransmitters as glutamate from the presynaptic neurone.\(^9^2 - 9^4\) They are involved in descending supraspinal inhibitory modulation via the PAG and rostral ventromedial medulla (RVM).\(^9^5\)

Cannabinoids possess anti-nociceptive properties in acute pain as reported in hot-plate, tail-flick, paw pressure, and formalin (inflammatory) animal models. Numerous models of neuropathic pain have shown a role of the CB1 receptor in suppressing hyperalgesia and allodynia.\(^9^6\) Using a knockout mouse model, the CB1 receptor normally mediates an inhibitory tone on nociceptive activity.\(^9^7\) Intraspinal expression of CB1 receptors occurs predominantly on intrinsic interneurons. Supraspinal CB1 anti-nociceptive mechanisms appear largely mediated through descending anti-nociceptive pathways.\(^9^6\) \(^9^8 - 10^0\)

Known agonists include \(\Delta^9\)-tetrahydrocannabinol (\(\Delta^9\)-THC), which acts at CB1 and CB2 receptors, cannabidiol (CB2), WIN 55,212-2, CP 55,940, HU-210, AM 1241 (CB2), 2-arachidonoylglycerol (2-AG) (CB1 and CB2), and palmitoylethanolamide (CB2). eCBs are not stored in vesicles, but are rapidly synthesized de novo from post-synaptic membrane lipid precursors.\(^10^1\) These eCBs are more prominently produced in microglial cells during neu-roninflammatory conditions, where 2-AG promotes recruitment of microglial cells by activation of CB2 receptors, and the de novo expression of CB2 receptors occurs in central glial cells after peripheral nerve injury.\(^10^2 - 10^6\) Furthermore, CB2 agonists are effective in modulating the inflammatory response.\(^10^5\) eCBs modulate microglial cell migration without disturbing their ability to produce nitric oxide.

The Cannabinoids in Multiple Sclerosis (CAMS) trial, and a follow-up study, confirmed CB efficacy in reducing muscle spasticity and pain levels over a 12-month period.\(^9^2\) \(^10^6\) \(^10^7\) Numerous other clinical and experimental studies have also shown a role of CBs in pain management.\(^9^2\) \(^9^6\) Analgesic synergy has been shown between the cannabinoid and opioid systems, showing promise for the use of cannabinoids in multimodal analgesic regimens.\(^10^8\) As fatty acid amide hydrolase (FAAH) is the major degradation pathway for eCBs, inhibition of this enzyme as a pharmacological target could also prove beneficial in the treatment of chronic pain.\(^10^9\) (Table 3).
Cyclo-oxygenase-2 inhibitors and cannabinoids

The arachidonic acid pathway produces prostanoids that potentiate bradykinin to sensitize C-fibres. COX-2 can metabolize both anandamide and 2-AG to prostanooids that produce this potentiation. Hence, in an inflammatory state in which COX-2 is up-regulated, not only can the antinociceptive effects of eCBs be lost by their metabolism of COX-2, their metabolites can produce a pro-nociceptive effect. Hence, COX-2 inhibitors can block this conversion, and an understanding of the interaction between COX-2 inhibitors and cannabinoids holds promise in the understanding and treatment of chronic pain.96 101 110

This correlation has been shown where anandamide is released in the PAG during noxious peripheral stimulation and correlates with analgesia, and where 2AG has been shown to be responsible for stress-induced analgesia as the primary mechanism for CNS pain control.99 111 The acetaminophen metabolite N-arachidonoyl-4-aminophenol (AM404) blocks the eCB hydrolytic enzyme to prolong eCB analgesic action.112 COX-2 oxidizes 2AG to form PGE2-G, a prostaglandin-like pro-nociceptive compound.113 115 COX-2 inhibitors at low doses do not block COX-2 but block conversion of 2-AG to PGE2-G.115 In a recent rat inflammation study, COX-1 inhibitors, COX-2 inhibitors, and non-selective COX-1/2 inhibitors all attenuated CNS hyperexcitability before and during the development of knee inflammation. However, only the COX-2 inhibitor reversed CNS hyperexcitability once it was established, and only the COX-2 inhibitor prevented the breakdown of 2-AG to PGE2-G (pro-nociceptive). Inhibition of spinal COX-2 not only reduced prostaglandin production but also eCB breakdown. Thus, reversal of inflammation-evoked spinal hyperexcitability by COX-2 inhibitors is more related to endocannabinergic mechanisms than to the inhibition of spinal PG synthesis91 (Table 4). These early findings are encouraging. Of the commercially available coxib compounds, rofecoxib and etoricoxib have good CNS penetration, however valdecoxib and celecoxib penetrate the CNS poorly.116–118

As COX-2 receptors are found predominantly in microglia expressed during pathological conditions, cannabinoid and cannabidiol, which act predominantly at CB2 receptors, could be used to block this migration and reduce central inflammation. These CB2 agonists have been shown to possess antinociceptive effects in acute nociception, inflammatory hyperalgesia, and in animal models of tactile allodynia, and are beneficial in the treatment of chronic diseases such as diabetic peripheral neuropathy.103–119–121 In a murine model, the CB2R agonist, JWH015 reduced postoperative hypersensitivity after paw incision by decreasing microglial and astrocytic activation in the spinal cord.92 122 Peripheral immune cell stimulation of CB2 receptors appears to downregulate the immune response that causes nociceptor sensitization.92 In contrast, CB1 agonists reduce tactile allodynia and thermal hypersensitivity without affecting microglia.103

In summary, cannabinoids are effective as analgesics in the treatment of acute pain, inflammatory pain, and neuro-pathic pain.123 By acting both in the periphery and within the CNS, cannabinoids could inhibit central sensitization by modifying inflammatory input at both locations, hence preventing chronic pain states, especially if delivered during the time of neural injury or disease.

Transient receptor potential cation channel VI

The TRPV1 channel is of specific interest because only painful stimuli activate it. The endogenous ligand for TRPV1 is not known, however the eCB anandamide is a candidate.124–125 Being a polymodal receptor, it is activated by a wide range of compounds such as capsaicin, resiniferatoxin, protons (pH < 5.3), lipids, heat (> 45°C), and is regulated by inflammatory mediators such as bradykinin and PGE2, and neuro-regulators such as NGF.126 TRPV1 is also present on central terminal afferents, where it facilitates the transmission of noxious mechanical stimuli.127 Topical capsaicin binding to TRPV1 desensitizes the nociceptive terminal to all modes of noxious stimuli.128 Intrathecal resiniferatoxin also inhibits TRPV1 in central terminals resulting in sustained pain relief.129 Capsaicin inhibits C-fibres by interacting with the
TRPV1 receptor to provide pain relief for 3–4 days after surgery.130

Activation of the CB1 receptor in cultured primary sensory neurones reduces responses mediated through the TRPV1 receptor and plays a pivotal role in the development of heat hyperalgesia and visceral hyper-reflexia in inflammatory conditions.131 Furthermore, anandamide might inhibit TRPV1-mediated responses in a non-CB1/CB2 receptor-dependent manner in primary sensory neurones in inflammatory conditions.131 Emerging pharmacological treatments are promising, as this receptor is thought to play important roles in neurone sensitization induced by inflammation and nerve injury.132 133

Genetics

Because individual sensitivity and response to clinical pain differs significantly between individuals, genetic factors have been implicated to explain these differences. Devor has suggested that the occurrence of CPSP is higher in some genetically predisposed individuals undergoing coronary artery bypass grafting (CABG), by showing a higher concordance rate of chest and vein harvest site CPSP than would be expected if these procedures were performed separately.134 Clinical conditions such as fibromyalgia syndrome, migraine, irritable bowel syndrome, irritable bladder, backache, and Raynaud’s syndrome might also have an underlying genetic predisposition to the development of chronic post-surgical pain.135–137

Several pain-related gene candidates have been identified including polymorphisms of catechol-O-methyltransferase, genetic variants of voltage-gated Na⁺ channels, GTP cyclohydrolase, tetrahydrobiopterin-related genes, and the μ-opioid receptor.138–140 The roles that these genes play in the development of chronic pain have not been fully elucidated. Several gene candidates that seem to correlate with pain severity and the incidence of chronic pain after different procedures are under study.30 141 As an example, the Na⁺ 1.7 Na⁺ channel is found as a gain of function point mutation in primary erythromelalgia and paroxysmal extreme pain disorder, while functional polymorphism of the μ-opioid receptor gene appears to be less common in chronic pain patients with high opioid analgesic requirements.142 143 Genotypic variation may also play a role in NSAID and COX-2 responses.144

A complete understanding of the role of genetics in chronic pain development is far from being solved, as more than 2000 genes are reprogrammed within the PNS during the chronic pain state and roughly 400 new gene candidates were recently discovered and described.145

Preventing neuroplastic changes

‘Unlearning’ by the nervous system could be an important concept in the future for unravelling the development of chronic pain, but aggressively treating acute pain to prevent the development of chronic pain is an important current strategy in pain management. After breast, thoracic, and hernia surgery, the severity of postoperative pain is a strong predictor of subsequent chronic pain.146 As severe and persistent preoperative pain are reasonable predictors of chronic pain development, aggressive treatment of pain in the perioperative period should be a focus to prevent chronic pain development.146 However, to date, the effectiveness of this approach has been equivocal.

Physical activity or physical therapy is most effective when acute pain is managed optimally.147 Perhaps allowing the nervous system to learn, or relearn, functional skills is the reason why staying active may be so important in the treatment, and prevention, of non-specific low back pain where neuroplastic changes have occurred.148 Other interesting possibilities in preventing neuroplastic changes in the dorsal horn include pharmacological block of 5–hydroxytryptamine-3 (5-HT₃) receptors, which has been shown to have anti-nociceptive effects in humans by the blockade of descending serotonergic facilitatory drive to the dorsal horn laminae.11 Although gabapentin interacts with the auxiliary α₂β₂ subunit of voltage-gated Ca²⁺ channels, there is evidence that the actions of gabapentin depend on the 5-HT₃ receptor as well.149 150

Psychosocial factors

Studies examining the influence of psychological factors on chronic post-surgical pain are few, with contradictory results. Kock has suggested that chronic post-surgical pain can be caused by a hypervigilant state.151 Fear of surgery and anxiety might also be factors.49 Psychological vulnerability, specifically pain-related fear, has also been found to predict the outcome after lumbar spine surgery.146 152 153 Psychosocial factors and personality disorders such as depression and neuroticism might lead to higher incidences of chronic pain after surgery.152 154 One of the difficulties with studies that examined these factors is the ability to tell whether depression (with or without anxiety) and neuroticism lead to chronic post-surgical pain, or whether chronic post-surgical pain can lead to higher incidences of depression and neuroticism. The psychological factors that seem to be the risk factors for acute pain do not show the same association with chronic post-surgical pain.33 Cognitive factors such as fear of pain seem to play a greater role than factors such as pain intensity.155 Given this observation, it appears that psychosocial factors are important in chronic post-surgical pain. Personality disorders might reflect psychosocial vulnerabilities in coping skills that are antecedents to chronic pain.146 156

As it is known that limbic regions of the brain can influence the RVM, a region that has descending projections to modulate activity of the dorsal horn involved in the maintenance of nerve injury-induced pain predominantly via a 5-HT₃ mechanism, emotional factors related to pain might have a neuroanatomic basis in humans.10 157–159

Prevention of microglial activation

Microglia modifying or inhibiting drugs such as fluoracitrate, acetyl-L-carnitine, monocycline, and propentofylline have been shown to ameliorate pain sensitivity.12 160–162 In
diabetic peripheral neuropathy, microglial cells appear to play a prominent role as demonstrated by an increased density in the dorsal spinal cord and thalamic nuclei in diabetic mice. Cannabidiol has anti-nociceptive effects in mice. Specifically, cannabidiol started concomitantly with the evolution of the diabetic neuropathic state was associated with a lesser microglial density in the dorsal spinal cord and blunted elevation in phosphorylated p38 MAPK. This reduction in microglial accumulation and activation in the dorsal spinal cord was associated with limited development of a neuropathic pain state, even after the discontinuation of cannabidiol, although it did not alter the course of the diabetic condition. When the neuropathic state was already established, both CB1 and CB2 agonists demonstrated an anti-nociceptive effect until their discontinuation. These results are exciting in that they suggest early treatment to inhibit microglia migration, and activation in the CNS can help to prevent the evolution of neuropathic pain, at least in diabetes, where approximately 50% of patients experience chronic neuropathic pain.

Microglial activation can also be regulated via receptor modulation. Microglia express upregulated purinoceptors P2X7 and P2X4 during peripheral nerve injury. Deletion of the P2X7 receptor gene produced complete absence of mechanical and thermal pain in mice. Additionally, deletion of the inflammatory chemokine receptor CCR2 gene, which binds monocyte chemotactic protein-1 (MCP-1, also known as CCL2), has been shown to block glial cell recruitment and attenuate neuropathic pain. MCP-1 recruits monocytes, memory T cells, and dendritic cells to sites of tissue injury and inflammation.

Use of a nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) inhibitor, intrathecal pyrrolidine dithiocarbamate, prevented development of nerve injury-induced neuropathic pain by inhibiting the activation of spinal microglia. Another possible target is the activation of extracellular signal-regulated kinases (ERKs), which are expressed during nerve injury and disease in both neurones and microglia. Activation of ERK plays a role in neuroplasticy and maintains microglial expression of the pain phenotype.

**Surgical factors**

Working closely with surgeons to modify surgical approaches could prove beneficial in the prevention of chronic pain development. Lightweight mesh and non-invasive fixation could be more effective for the prevention of chronic pain with laparoscopic hernia repair. Though larger randomized studies are needed, these concepts are in line with the current understanding of inflammatory pain in the development of chronic pain. Intra-operative nerve damage as seen in thoracotomies and mastectomies plays a key role in the development of chronic neuropathic pain, and care should be taken to minimize such neuronal damage. For example, anterior thoracotomies are not as likely to develop intercostal nerve dysfunction or resultant post-thoracotomy pain syndrome. Similar findings have been noted in breast surgery in which attempts to preserve the intercostobrachial nerve are associated with a lower incidence of pain. In hernia and gallbladder surgery, laparoscopic approaches vs open approaches have lower incidence of chronic post-surgical pain. In breast surgery, less-experienced lower volume units had a higher incidence of chronic post-surgical pain than more experienced centres. Patients operated for a recurrence of inguinal hernia are at higher risk for persistent pain.

Though efforts are made to simplify the issue of chronic post-surgical pain by surgical factors such as nerve damage, it is important to note that these issues probably represent a more complicated aetiology. In a study examining post-thoracotomy pain, neurophysiological tests before the operation, before closing the chest, and at 6 weeks and 3 months after surgery, the authors did not find an association between nerve injury measured at the time of thoracotomy and chronic pain or altered sensation at 3 months follow-up. This finding alludes to the complicated aetiology of neuropathic post-thoracotomy pain rather than the simple assumption that damage to the intercostal nerve alone is the causative factor. Likewise, in chronic postsurgical pain after mastectomy, the generally accepted risk factor of damage to the intercostobrachial nerve is not firmly established.

These findings do not dispute that damage to nerves is an important cause of chronic post-surgical pain, but help to refine further investigation, such as how much nerve damage is needed to cause neuropathic pain, what additional factors might play a role, and what role do central vs peripheral changes play.

To date, the only definitive way to prevent chronic post-surgical pain is to reduce the number of surgeries performed. In an age when many procedures are performed for non-medical or cosmetic reasons, such as vasectomies or breast augmentation, with rates of chronic post-surgical pain of 15% and 13–50%, respectively, if more patients were educated about the risks of chronic post-surgical pain, some might choose to forgo truly elective procedures.

**Anaesthetic factors**

Though little is known about the long-term consequences of anaesthesia techniques and their possible links to chronic pain development, halogenated anaesthetics used routinely in anaesthesia activate peripheral pro-nociceptive ion channels, and in doing so enhance neurogenic inflammation. A few studies dealing with pre-emptive analgesia to reduce central sensitization focused on the use of epidural analgesia. They followed patients through the postoperative period and found decreases in the incidence of postoperative pain. Several studies have shown that the use of an epidural block before surgery could reduce the incidence of long-term post-thoracotomy pain at 6 months after operation. For example, Richardson has shown that regional anaesthetic techniques can reduce the incidence.
of chronic post-thoracotomy pain. Likewise, there have been several studies that have shown benefit for regional anaesthetic techniques to reduce chronic post-surgical pain after hysterectomy, Caesarean section, and iliac crest bone harvesting. However, there have also been studies that have not shown this benefit. One possibility for the discordance between reports is the length of analgesic treatment time needed to prevent pain signals from inducing neuroplastic changes within the spinal cord.

**Predicting postoperative pain**

Recently developed preoperative quantitative sensory testing (QST) could possibly be used as a clinical tool to predict postoperative pain, and predict the majority of variance in acute postoperative pain. This assessment can perhaps guide the use of pre-emptive, intraoperative, and postoperative analgesia if patient populations most at risk are identified before surgery, in the hope that outcomes can be improved. Furthermore, it would be helpful if QST could be used to help identify, or further clarify, polymorphisms of candidate pain genes.

The effectiveness of the endogenous analgesia system activated on a previously pain-free state seems to reflect the ability to handle noxious events, and might serve to identify patients at risk for post-procedural chronic pain. This has been shown by testing the endogenous analgesia system using diffuse inhibitory control, and finding a positive correlation for the development of chronic post-thoracotomy pain.

**Clinical evidence of multimodal treatment strategies**

Patients with severe postoperative pain have a greater risk of developing chronic pain. Aggressive treatment of postoperative pain is assumed to reduce the risk of developing chronic pain. Although adequate treatment of acute postoperative pain is a mainstay of postoperative care, there are no large-scale studies that definitively demonstrate the prevention of chronic pain if effective perioperative pain treatment is provided.

Some investigators have demonstrated in limited series of patients that potent analgesia combined with anti-hyperalgesic medications influences the incidence of chronic pain development. The use of pregabalin treatment in the perioperative period in total knee arthroplasty was shown to reduce the incidence of chronic neuropathic pain. However, other studies looking at multimodal analgesic techniques with the use of medications such as gabapentin, venlafaxine, and ketamine have not shown consistent results in the prevention of chronic post-surgical pain. Though timing of analgesic administration in the perioperative period to prevent the development of chronic pain has produced confounding results, a bigger role to better delineate the best treatment options for surgical patients in our care. The increased use of comprehensive standardized pain evaluation and treatment protocols, coupled with the use of multimodal analgesic techniques aimed at both peripheral and central mechanisms, are likely to become the mainstay of complete perioperative analgesia in the prevention of chronic pain.

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