Persistent postsurgical pain: risk factors and prevention

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Acute postoperative pain is followed by persistent pain in 10–50% of individuals after common operations, such as groin hernia repair, breast and thoracic surgery, leg amputation, and coronary artery bypass surgery. Since chronic pain can be severe in about 2–10% of these patients, persistent postsurgical pain represents a major, largely unrecognised clinical problem. Iatrogenic neuropathic pain is probably the most important cause of long-term postsurgical pain. Consequently, surgical techniques that avoid nerve damage should be applied whenever possible. Also, the effect of aggressive, early therapy for postoperative pain should be investigated, since the intensity of acute postoperative pain correlates with the risk of developing a persistent pain state. Finally, the role of genetic factors should be studied, since only a proportion of patients with intraoperative nerve damage develop chronic pain. Based on information about the molecular mechanisms that affect changes to the peripheral and central nervous system in neuropathic pain, several opportunities exist for multimodal pharmacological intervention. Here, we outline strategies for identification of patients at risk and for prevention and possible treatment of this important entity of chronic pain.

Despite our ability to control pain during and immediately after surgery with local anaesthetic agents, opiates, and cyclo-oxygenase (COX) inhibitors, pain that persists after the surgical wound has healed is a major, if largely unrecognised, clinical problem. Known as persistent postsurgical pain, such discomfort usually lasts for more than 3–6 months after surgery.[1] Table 1[2–14] shows the estimated incidence of chronic postoperative pain and disability, based on studies of six common surgical procedures. Alongside these proportions are figures for US hospital discharges for the same procedures. Taken together, these data suggest that an alarmingly high number of patients develop chronic pain after routine surgery.

We assert here that postsurgical chronic pain is the consequence either of ongoing inflammation or, much more commonly, a manifestation of neuropathic pain, resulting from surgical injury to major peripheral nerves. By virtue of the size of the surgical patient population, the scale of the associated morbidity bears comparison with classic forms of neuropathic pain, such as postherpetic neuralgia and post-stroke pain, in which the proportion of patients with chronic pain is in the order of 5–10%.[15,16] We describe the clinical presentation of postsurgical chronic pain and explain its pathophysiology, based on the peripheral and central neuroplastic changes that arise in response to tissue and nerve injury. Given that only a subset of surgical patients develop chronic pain, we then outline factors that might predispose an individual to develop chronic pain. Finally, we review the options, current and prospective, for treatment and prevention.

Search strategy and selection criteria

Because of the many features of basic pain physiology and acute and chronic pain covered in the Review, we did not do a formal literature search. We based the Review on work published mostly within the past 5 years from the major anaesthesiology, surgical, pain, and neurophysiology journals and systematic reviews where appropriate. Recent articles that provided comprehensive overviews are included where appropriate instead of multiple references of original work.

Clinical presentation (table 2)

Although pain is a psychological sensory experience, it is caused by various factors—eg, nociceptive, inflammatory, and neuropathic pain.

Nociceptive pain is the pain that results from activation of high threshold peripheral sensory (nociceptor) neurons by intense mechanical, chemical, or thermal noxious stimuli. This pain is the pain that results, for example, from a scalpel blade cutting through skin. It signals the presence, location, intensity, and duration of a noxious stimulus and fades once the peripheral driving force is removed.

Inflammatory pain is the heightened pain sensitivity that occurs in response to tissue injury and inflammation. It results from the release of sensitising inflammatory mediators that lead to a reduction in the threshold of nociceptors that innervate the inflamed tissue (peripheral sensitisation). As a consequence of an increase in the excitability of neurons in the central nervous system (central sensitisation), inflammatory pain is also associated with exaggerated responses to normal sensory inputs. These phenomena, although evoked within a matter of minutes, can outlast the precipitating tissue injury for several hours or days. However, the changes are generally reversible and normal sensitivity of the system is eventually restored. Inflammatory pain is the pain that, in the absence of any peripheral nerve damage, drives acute postoperative pain until the surgical wound has healed. If a focus of ongoing inflammation persists, however, so will the pain.

Finally, neuropathic pain, which is the pain that arises after injury to nerves or to sensory transmitting systems in the spinal cord and brain. A key feature of neuropathic pain is the combination of sensory loss with paradoxical hypersensitivity. Damage to the afferent transmission system causes partial or complete loss of input to the nervous system, leading to negative sensory phenomena, such as loss of touch or temperature or pressure

sensations. Nerve injury is the starting point for reactive changes that sweep centrally to produce abnormal neural function. In addition to sensory loss, which is a universal response to nerve damage, there can in some individuals be development of so-called positive phenomena, including spontaneous pain, dysaesthesia, and hypersensitivity, including allodynia—in which pain is evoked by innocuous stimuli such as light touch or gentle pressure to deep tissue—hyperalgesia—an exaggerated or amplified response to a noxious stimulus—and hyperpathia—an explosive abnormal pain that outlasts a stimulus. The hypersensitivity located within and beyond the damaged nerve innervation territory can mask the sensory loss. There is no specific diagnostic method or test to unequivocally show the presence of neuropathic pain, so a grading system has been suggested (panel).[17]

In the immediate postoperative period, with direct activation of nociceptors, inflammation, and in some cases injury to nerves, the clinical picture is dominated by spontaneous resting and breakthrough pain referred to the site of surgery and the surrounding tissues. Movement or touching of the wound site, breathing, coughing, and gastrointestinal motility can all evoke flares of pain. Stimulus-evoked hypersensitivity is present both in the injured area and the surrounding non-injured tissue. Most patients respond well to opiates and COX inhibitors. If nerves are injured during surgery, a neuropathic component of the pain might develop immediately and then persist in the absence of any peripheral noxious stimulus or ongoing peripheral inflammation. This pain, once established, is likely to be resistant to COX inhibitors.

Surgical nerve injury

In most affected patients, postsurgical chronic pain closely resembles neuropathic pain.[3,18] Major nerves trespass the surgical field of most of the surgical procedures associated with chronic pain, and damage to these nerves is probably a prerequisite for the development of postsurgical chronic pain. In a subset of patients, a continuous inflammatory response, such as after inguinal mesh hernia repair, can contribute to a maintained inflammatory pain.[8] Differentiation of neuropathic from non-neuropathic causes of postsurgical pain is essential for the design of effective strategies to prevent and treat the conditions. Signs of neurological damage, in the form of hypoaesthesia, have been reported after mastectomy,[3,19] hernia repair,[18] and mandibular osteotomy.[20] Extensive nerve damage is frequent in thoracotomy, since use of a rib retractor blocks intercostal nerve conduction by 50–100% in segments close to the incision, according to the findings of late intraoperative electromyography.[21] Furthermore, the degree of nerve damage, as assessed by changes in sensory threshold and somatosensory evoked responses to electrical stimulation in the thoracotomy scar area, correlates with intensity of chronic pain.[22]

	Estimated incidence of chronic pain	Estimated chronic severe (disabling) pain (>5 out of score of 10)	US surgical volumes (1000s)†
Amputation[2]	30–50%	5–10%	159 (lower limb only)
Breast surgery (lumpectomy and mastectomy)[3]	20–30%	5–10%	479
Thoracotomy[4–7]	30–40%	10%	Unknown
Inguinal hernia repair[8–10]	10%	2–4%	609
Coronary artery bypass surgery[11–13]	30–50%	5–10%	598
Caesarean section[14]	10%	4%	220

*Gall bladder surgery not included, since preoperative diagnosis of pain specifically from gall bladder is difficult and persistent postoperative pain could therefore be related to other intra-abdominal disorders. †National Center For Health Statistics, Ambulatory and Inpatients Procedures, USA, 1996.

Table 1: **Estimated incidence of chronic postoperative pain and disability after selected surgical procedures***

	Neuropathic pain	Inflammatory pain
Positive symptoms and signs		
Spontaneous pain in damaged area	Yes	Yes
Heat hyperalgesia	Rarely	Often
Cold allodynia	Often	Rarely
Hyperpathia (increased threshold and explosive suprathreshold pains)	Often	Never
Aftersensations	Often	Rarely
Paroxysms	Often	Rarely
Burning pain	Often	Rarely
Throbbing pain	Rarely	Often
Negative symptoms and signs		
Sensory loss in damaged nerve territory	Yes	No
Motor deficit in damaged nerve territory	Often	No

Table 2: **Characteristic features of neuropathic and inflammatory pain**

Panel: **Diagnosis of definite neuropathic pain**

All factors must be present

- Pain in a neuroanatomically defined area—ie, corresponding to a peripheral or central innervation territory
- A history of relevant disease or lesion in the nervous system, which is temporally related to development of pain
- Partial or complete sensory loss in all or part of the painful area
- Confirmation of a lesion or disease by a specific test—eg, surgical evidence, imaging, clinical neurophysiology, biopsy

In addition, acute and chronic pain is expressed against a complex physiological, genetic, and psychosocial background, which contributes not only to the conversion of somatosensory activity into a pain experience, but also to the amplitude of and reaction to the sensation, and to related changes to mood and behaviour.

Neuronal plasticity and pain (figure)

There are then two kinds of plasticity. One is associated with essentially reversible changes in the software of the system and operates during inflammatory pain; in the other, after nerve injury, the hardware itself is altered. There is consequently no simple continuum from acute

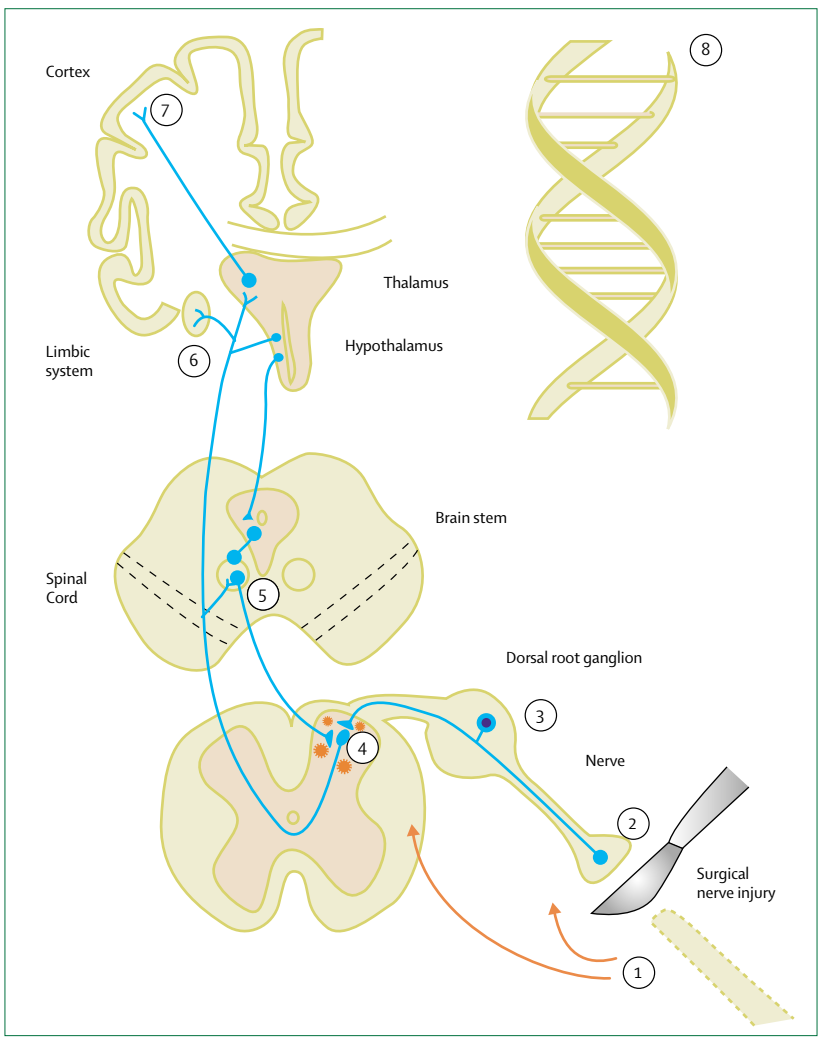

Figure: **Sites and mechanisms responsible for chronic postsurgical neuropathic pain**
(1) Denervated Schwann cells and infiltrating macrophages distal to nerve injury produce local and systemic chemicals that drive pain signalling. (2) Neuroma at site of injury is source of ectopic spontaneous excitability in sensory fibres. (3) Changes in gene expression in dorsal root ganglion alter excitability, responsiveness, transmission, and survival of sensory neurons. (4) Dorsal horn is site of altered activity and gene expression, producing central sensitisation, loss of inhibitory interneurons, and microglial activation, which together amplify sensory flow. (5) Brainstem descending controls modulate transmission in spinal cord. (6) Limbic system and hypothalamus contribute to altered mood, behaviour, and autonomic reflexes. (7) Sensation of pain generated in cortex (past experiences, cultural inputs, and expectations converge to determine what patient feels). (8) Genomic DNA predispose (or not) patient to chronic pain and affect their reaction to treatment.

to chronic pain that correlates with the duration or intensity of peripheral injury.

Nociceptive and inflammatory pain

Reversible changes in the properties of the peripheral and central nervous systems produce the increased pain hypersensitivity characteristic of inflammatory pain.[23] Peripheral sensitisation results from the local action of inflammatory mediators, including prostanoids released from injured and inflammatory cells, on the peripheral terminals of high-threshold nociceptor sensory neurons. These actions activate intracellular signalling pathways that lead to the phosphorylation of ion channels and receptors on the nociceptor terminal membrane, reducing threshold and increasing excitability.[24,25] This hypersensitivity reduces the intensity of the peripheral stimulus needed to activate nociceptors at the site of inflammation (primary hyperalgesia). Once the active source of mediators subsides, with healing, so does this form of local hyperexcitability.

Central sensitisation is a form of synaptic plasticity in the spinal cord that amplifies pain signalling.[26] The plasticity is produced first by the barrage of action potentials evoked by intense noxious peripheral stimuli, such as surgery, and the consequent synaptic activity generated in dorsal horn neurons, as well as by humoral signals released from inflamed tissue that act on the central nervous system.[27] Via activation of intracellular kinases, alterations in pre-existing proteins in dorsal horn neurons are produced, increasing the trafficking of ion channels and receptors to the membrane and changing their function. Some hours after tissue injury, there is altered gene transcription in sensory neurons and in the spinal cord that augments the release and action of excitatory transmitters and reduces inhibitory transmitters, including induction centrally of COX-2.[27,28] The net effect is short latency (minutes) changes in neuronal excitability that, although fairly long lasting (days), are reversible. After induction of central sensitisation, the responsiveness of the neurons increases sufficiently that normally ineffective synaptic inputs, including those elicited by innocuous stimuli, activate pain transmission neurons.[29] Central sensitisation constitutes an abnormal perceptual response to a normal sensory input and results in the spread of sensitivity well beyond the peripheral site of injury (secondary hyperalgesia).[30]

Nerve injury

Unlike the plasticity produced by inflammation, lesions to the peripheral nervous system can produce persistent maladaptive plasticity. Injured primary sensory neurons and their immediate non-injured neighbours begin to fire action potentials spontaneously as a result of increased or novel expression and altered trafficking of sodium channels.[31–33] This ectopic pacemaker-like activity contributes to spontaneous pain and, by inducing central sensitisation, further heightens pain sensitivity and produces tactile allodynia.[34] Additionally, there are changes in the expression of synaptic transmitters and receptors and many other genes that modify transmission and responsiveness.[35] These include a marked up-regulation of the $\alpha_2\delta$ subunit of voltage-gated calcium channels, the binding site for gabapentin and pregabalin,[36] which is also involved in nerve injury-induced central sensitisation.[37]

Peripheral nerve injury also results in neuroimmune interactions. When an axon is cut, its distal end degenerates and is engulfed by inflammatory cells. This action releases pain-producing signal molecules, such as

tumour necrosis factor (TNF) α that act on axons to increase ectopic activity.[38] Microglia, central macrophage-like cells, are massively activated in the spinal cord and produce signal molecules that act on dorsal horn neurons to produce pain hypersensitivity.[39–41]

Alterations in gene expression result in changes in the function of neurons that last for considerable periods, but once an mRNA transcript returns to basal levels, proteins have a half-life of some days and the changes they produce will reverse. However, some changes are irreversible. Most notable among these is loss of neurons. If contact of the injured axon with its target is not restored after peripheral nerve injury, small nociceptor sensory neurons with unmyelinated axons start, after many weeks, to die,[42] and the sensory inflow to the central nervous system is permanently disturbed. The synaptic circuitry and connectivity in the spinal cord is also modified[43] and there is death by apoptosis of neurons in the dorsal horn.[44] This event seems to be an excitotoxic response to the ectopic input and a swamping of the system's capacity to deal with glutamate release. The neurons that die include inhibitory interneurons so that peripheral nerve lesions result in a marked and possibly irreversible reduction in local segmental inhibitory transmission in the dorsal horn.[44] Changes are not limited to the spinal cord: profound alterations in functional topography occur in the cortex, and cortical gray matter is lost.[45] The reciprocal connections between the spinal cord and brain are altered with an increase in descending facilitatory influences and a reduction in inhibitory ones.[46]

Risk factors

An ideal model for studying the development of chronic pain in surgical patients, and establishing predictive factors for the condition, would include preoperative and postoperative assessment of psychological and neurophysiological factors, detailed intraoperative data on handling of tissue and nerves, and detailed early and late postoperative pain data, as well as a thorough clinical investigation to exclude other causes of the chronic pain state. No such study has been reported. However, many surgical patients present with signs of neurological damage but without pain.[18] After mandibular osteotomy, for instance, only about 10% of patients with severe intraoperative nerve damage go on to develop clinically significant neuropathic pain.[20] Thus, although nerve damage seems to be necessary for the development, in most cases, of postsurgical persistent pain, it is not sufficient.

Genetic susceptibility

Sensitivity to physiological nociceptive and clinical pain differs considerably between individuals. Increasingly, this inconsistency is recognised as an indication of differential heritable susceptibility both to the generation and experience of pain, as well as to the response to analgesics.[47–51] Functional genetic polymorphisms of catecholamine-O-methyltransferase (COMT) are associated, for example, with altered sensitivity to pain induced in an experimental environment.[49,50] High COMT activity correlates with a risk of developing chronic temporomandibular joint pain.[50] By use of quantitative trait locus mapping, the melanocortin-1 receptor gene, associated with red hair and fair skin, has been identified as one that confers greater female-specific κ-opioid analgesia.[51] Results of studies in rodents indicate that the susceptibility to develop neuropathic pain has a strong heritable component, but the genes responsible have yet to be identified.[52–54] Given the complexity of neuropathic pain, many genes might contribute, and a familial trait is difficult to identify. Nevertheless, studies are underway to correlate single nucleotide polymorphisms (SNPs) in multiple candidate genes with the risk of developing post-injury neuropathic pain.

Preceding pain

Previous pain correlates with the development of chronic neuropathic pain. Severe postherpetic neuralgia is often preceded by severe zoster pain.[55,56] Amputees with severe phantom limb pain have more often had intense and enduring preamputation pain than amputees with less intense phantom pain.[57,58] A similar association is noted between the intensity of acute postoperative pain and subsequent development of chronic pain after breast surgery,[59] thoracotomy,[60] and inguinal hernia repair.[61] However, whether this association is an indication of the extent of neuroplastic changes induced by the operation, lack of adequate analgesia, or preoperative predisposing factors has not been clarified.

Psychosocial factors

In chronic pain of non-surgical origin, psychological, social, and economic factors play a major part.[62] Expectation of pain, fear, past memories, social environment, work, and levels of physical activity, all affect the response to noxious stimuli.[63,64] Theories about the development of chronic pain have shifted from a biomedical model to a biopsychosocial one, in which pain is thought to be the result of an interaction between biological and psychological variables.[65] In a study[66] of 70 lower-limb amputees, psychosocial variables, such as catastrophising—a tendency to exaggerated pessimism about outcome—perceived social support, and solicitous responding 1 month after amputation, predicted phantom pain up to 2 years after amputation. Preoperative anxiety is correlated with postoperative pain experience.[67,68] Fear of pain in the postoperative setting and the avoidance of such pain might also have a negative effect on how pain is perceived and resolved.

Age and sex

In postherniorrhaphy pain, older patients have a reduced risk of developing chronic pain.[8,9] This finding is by

contrast with postherpetic neuralgia, where increasing age is a risk factor.[56] Findings of several studies[67,68] show that women have higher postoperative pain than men.

Predicting postsurgical chronic pain

A combined scoring system based on age, sex, type of surgery, extent of preoperative pain, and level of anxiety has been developed in an attempt to predict the severity of early postoperative pain.[69] Large cohort studies are needed to validate the approach in individual procedures.

In studies in which a preoperative nociceptive stimulation test was undertaken, either with a heat stimulus before knee surgery or caesarean section[70,71] or an ice water test in patients undergoing laparoscopic cholecystectomy,[72] a positive correlation was noted between the preoperative pain response and degree of early postoperative pain. Also, a preoperative score of catastrophising correlated with the intensity of acute,[72] but not of chronic, postoperative pain.[73]

These clinical experiments emphasise the potential for identifying people likely to respond badly to postoperative pain with a preoperative assessment. Since the intensity of the acute postoperative pain correlates with the risk of chronic postsurgical pain,[4,5,61,73] preoperative tests, including nociceptive responsiveness and detection of pain-protective or pain-enhancing gene haplotypes, identified by SNPs, could help predict patients at risk for developing persistent pain. Once such patients can be identified, a model for the study of preventive approaches, including intensified long-term multimodal analgesia, can be developed.

Potential for prevention

Surgical technique

Since many of the operations that produce persistent pain are associated with risk of damage to major nerves, techniques to avoid such damage merit investigation. Such techniques include, for example, laparoscopic herniorrhaphy, which can decrease the risk of nerve damage and pain compared with open surgery.[8,74] The value of a more precise dissection of the inguinal area to avoid nerve damage during open surgery has never been assessed, but elective division of the ilioinguinal nerve does not alter the risk of chronic pain.[75] The use of a light-weight mesh for repair of the inguinal hernia with presumed less inflammatory response might also reduce the risk of chronic pain.[76] In mastectomy, preliminary observations suggest that preservation of the intercostal brachial nerve could decrease chronic pain.[4,5,56] The increased use of sentinel lymph node biopsy might reduce the need for axillary dissection and thereby intercostal nerve damage. Minimally invasive thoracoscopic techniques might spare intercostal nerves,[4,5] compared with the damage inflicted by rib retractors on these nerves during conventional open surgery.[21] The use of an intracostal suture technique to avoid direct nerve compression could also decrease persistent pain after thoracotomy.[77] Additionally, muscle-sparing thoracotomy results in less nerve damage and chronic pain than a posterolateral approach.[22] Minimally invasive techniques in other procedures, such as nephrectomy (nervi dorsalis) and sternotomy (intercostal nerves), might offer similar benefits.

Pre-emptive and aggressive multimodal analgesia

Findings of studies in animals and in people indicate that some of the acute neuroplastic responses (central sensitisation) that follow tissue injury can be prevented by aggressive early pain relief,[78] and this technique might also work for neuropathic pain. However, whether techniques such as pre-emptive or preventive analgesia produce a clinically meaningful reduction in the intensity or duration of postsurgical pain remains unclear.[6,79] The data from randomised clinical studies are not generally favourable,[6,80–88] although a few positive studies have been reported.[6,87,88] Among the weaknesses of research to date is a lack of reporting, when neural blockade techniques are used, of the adequacy of the afferent blockade. Moreover, whether such blockade alone is sufficient, given that inflammation produces humoral signals that operate on the central nervous system, is unclear.[27] Even more pertinent is the fact that most researchers have not recognised that nerve injury is the major factor in establishing, in susceptible patients, chronic or persistent pain and that pre-empting neuropathic pain will need approaches quite different from those needed for preventing inflammatory pain and the transient plasticity that drives it. Thus, a relatively short blockade in the perioperative period, COX inhibitors, and opiates might be suitable for alleviating the inflammatory pain, but not for preventing neuropathic pain. An 18-h epidural blockade of the afferent input to the central nervous system is clearly insufficient to prevent development and maintenance of postamputation pain.[82] Multimodal approaches that use ketamine[89] or other N-methyl-d-aspartate receptor antagonists[90]—gabapentin or pregabalin[91]—COX inhibitors, steroids, and afferent neural blockade in the perioperative period have the potential to prevent central neuroplasticity and merit further investigation. Promising results have been obtained in the reduction of chronic pain after breast surgery with perioperative administration of venlafaxine,[92] mexilitine with gabapentin,[93] a eutectic mixture of local anaesthetics (EMLA),[94] and a combined treatment with EMLA and gabapentin.[95] All these treatments are of neuropathic, rather than inflammatory, pain. Importantly, future studies of the effect of pre-emptive or preventive analgesia on the risk of persistent pain should focus not on the timing of analgesia but on the completeness and appropriateness of the intervention.[6,80]

New targets for prevention and treatment

The primary focus for prevention needs to be an increased awareness among surgeons of ways to avoid intraoperative nerve injury—eg, by careful dissection, reduction of inflammatory responses, and use of minimally invasive surgical techniques.

There are two potential approaches for the management of neuropathic pain: symptom control and disease modification. Only symptom control is possible at the moment—that is, treatment that reduces pain while the medication is administered. By identifying the sequence of pathophysiological events that produce persistent alterations in the sensitivity of the somatosensory system after peripheral nerve injury, and the risk factors involved in the expression of these mechanisms, we might be able to develop rational strategies to prevent the establishment of persistent postsurgical neuropathic pain in high-risk patients.

What might this treatment involve? Long-term interruption of sensory inflow from the site of nerve injury with local and regional anaesthesia has the potential to prevent activity-dependent changes in the central nervous system. Administration of growth factors, such as glial cell line-derived neurotrophic factor (GDNF), could prevent injury-induced transcriptional changes in sensory neurons. Other treatment modalities could include the prevention of microglial activation with drugs like minocycline, and neuroprotective strategies designed to prevent apoptosis in the dorsal root ganglion or dorsal horn. Pharmacological targets might include blockade of the $Na_v1.3$, $Na_v1.7$, and $Na_v1.8$ sodium channels, potassium channel openers in sensory neurons, P2X4 and P2X7 purinergic receptor antagonists in microglia, use-dependent N-type calcium channel $Ca_v2.2$ blockers, $\alpha_2\delta$ binding drugs that decrease transmission, and those that activate glutamate transporters and inhibit caspases to decrease excitotoxicity. Treatments that recruit or augment descending inhibition—eg, dual uptake inhibitors of monoamine transporters—might also be useful.

Neuropathic pain, including most cases of postsurgical chronic pain, is a neurodegenerative disease that requires neuroprotective treatment. Such treatment might well depend on a combination of therapies, directed at both the injured nerve and at the neuroplastic changes subsequently induced in the central nervous system. What is clear is that aggressive suppression of the symptom of pain at the time of surgery is probably inadequate: treatment needs to be targeted at the progression of mechanisms, not just the disturbances in sensation that they produce.

Conclusions

Postsurgical persistent pain is a major, largely unrecognised clinical problem, which is distressing and reduces the quality of life of patients. Iatrogenic neuropathic pain is probably the most common type of postsurgical persistent pain and, as such, surgical techniques that avoid nerve damage should be used wherever possible. Despite advances in the understanding of the processes that lead to persistent pain and the increasing ease of identification of patients at risk of developing such pain, the management and prevention of postsurgical persistent pain remains inadequate.

Contributors

H Kehlet, T S Jensen, and C J Woolf contributed equally to the idea, outline, and writing of this manuscript, selection and analysis of the references, and revision of the Review.

Conflict of interest statement

H Kehlet, T S Jensen, and C J Woolf have been consultants for various pharmaceutical companies and members of scientific and clinical advisory boards, they have received speakers' fees, participated in meetings supported by unrestricted grants from industry, and have received sponsored research funding from several companies. All three authors state that none of these declarations presents a conflict of interest in relation to the content of this Review.

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