Pain and Analgesia

Secondary article

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The accepted definition of pain is 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage'. Analgesia is the alleviation or the absence of pain.

Article Contents

Introduction

Pain is a multidimensional experience that is essential for the maintenance and preservation of an individual. It warns of the danger of bodily harm and alerts to trauma and injury. Pain is a specific enteroceptive sensation; it can be perceived as arising from a particular portion of the body, its temporal properties can be detailed, it can be differentiated qualitatively (for example, as stinging, pricking, burning, throbbing, dull or aching), and it involves dedicated subsets of peripheral and central neurons. The experience of pain has a distinctly unpleasant character, that is, an affective or motivational aspect that can be distinguished from its discriminative sensory aspects and from the long-term emotional experience of 'suffering'. The unpleasantness ranges in intensity from the discomfort of a cold room, fatigued muscles or colonic tension to the excruciating agony of a severe burn, toothache, gallstone or migraine. Under normal circumstances, primary afferent pain fibres activate particular central pathways that engage protective mechanisms at several functional levels: autonomic, homeostatic, motoric, behavioural and mnemonic. However, injury or disease can alter the balance of this system and result in persistent, pathological pain. Analgesic substances, such as aspirin and morphine, that interact with the transmitters and modulators of the pain system are helpful for many people with pain, but there is a great need for the development of better methods for the alleviation and control of both acute (immediate) and chronic (long-term, pathological) pain.

Nociceptors and the Organization of Nociceptive Processing in the Spinal Cord

Primary afferent sensory nerve fibres with cell bodies in the dorsal root ganglia innervate all tissues of the body. Among the small myelinated (Aδ) and the unmyelinated (C) sensory fibres are those that respond selectively to noxious or potentially damaging stimuli, which are called nociceptors. The receptive elements are free nerve endings. The Aδ nociceptors (which innervate a spot-like receptive field) in the skin may respond only to noxious mechanical stimuli (e.g. pinch) or to both noxious mechanical and heat stimuli. Some C-fibre receptors (which have a 1–4-mm^2 receptive field) are similarly submodality selective, whereas others are polymodal, responsive to several forms of noxious mechanical, thermal and chemical stimulation (apparently by separate biophysical transducers). Adequate chemical (i.e. metabolic) stimuli can include acidic interstitial pH, bradykinin, serotonin, hypoxia and hypoglycaemia. C-fibre receptors in muscle (also known as group IV receptors) can be activated by dynamic exercise, fatigue or ischaemia.

The perceptual thresholds for pain vary with body region, time of day and sex. The mean threshold for mechanical cutaneous pain is approximately 10 g of force (per millimetre of circumference of a flat probe), and the mean heat and cold cutaneous pain thresholds are about 45°C and 15°C, respectively. The physiological thresholds for activation of nociceptors in all tissues extend over a broad range encompassing these stimulus intensities, yet the nociceptors are clearly distinct from other somatosensory receptors responsive to innocuous mechanical stimuli or cool or warm, both in their thresholds and their activity patterns, and especially in their central effects. Some nociceptors are normally insensitive ('silent') and respond only subsequent to inflammation or actual tissue damage. The discharge activity of nociceptors is slow (few C fibres fire faster than 20 Hz), and microneurographic C-fibre recordings in humans show that central temporal and spatial summation is required to produce a sensation of pain. Above threshold, the intensity of pain is directly correlated with the number of action potentials the nociceptors fire. Activity in Aδ nociceptors is associated with a rapid stinging or pricking sensation called 'first' pain, and activity in C nociceptors is associated with a

slower, burning sensation (or from deep tissues, a dull, aching or cramping sensation) called 'second' pain.

The central axons of the small-diameter nociceptive primary afferent fibres enter the spinal cord through the medial portion of the dorsal roots, and their collaterals extend one to three segments longitudinally in the Lissauer tract. Cutaneous C fibres arborize and terminate in lamina I and outer lamina II (the substantia gelatinosa) of the superficial dorsal horn of the spinal cord, and the Aδ fibres terminate in lamina I and deeper in lamina V (the neck of the dorsal horn). Nociceptive afferents from muscle, joint and viscera terminate in lamina I and may also reach laminae V and X (near the central canal). Nociceptive cells in laminae I and V are the main second-order pain projection neurons that send ascending axons to the brain; cells in lamina II are generally interneurons which project at most two to three spinal segments. Nociceptive neurons in lamina I have little or no ongoing activity, and they respond specifically to noxious stimuli within a small receptive field (in skin, muscle or viscera). Nociceptive neurons in lamina V have considerable ongoing discharge, respond to both nonnoxious and noxious mechanical stimuli (hence, called 'wide dynamic range' cells) and have large receptive fields. Both types of nociceptive cells encode the intensity of stimulation with the frequency of their discharge. Both can respond to A fibre only or to both A and C fibre input (monosynaptically in lamina I, polysynaptically in lamina V). Two distinct functional types of nociceptive cells with different morphological characteristics are present in lamina I, one dominated by Aδ input and the other by C-fibre input. Nociceptive information is conveyed to spinal autonomic systems mainly by lamina I cells and to spinal motoric systems mainly by lamina V cells. Nociceptive cells that respond to visceral stimulation usually also have a cutaneous receptive field. This convergence may be the basis for referred pain, in which pain originating from nociceptors in deep tissues is localized to a cutaneous zone represented in the same spinal segments, for example the pain referred to the left shoulder in angina pectoris.

Multiple Pathways that Transmit Pain Messages to the Midbrain, Thalamus and Cortex

Ascending projections of spinal nociceptive neurons terminate in several regions that reflect a hierarchical organization of the various reactions to a painful stimulus. Within the spinal cord, lamina I (and some lamina V) cells project to the sympathetic preganglionic regions in the thoracolumbar cord, as well as to parasympathetic regions in the sacral cord and the spinomedullary junction. In the lower brainstem, lamina I terminations occur bilaterally in several autonomic sites, including the major catecholamine cell groups in the ventrolateral medulla and the dorsolateral pons. These projections provide a basis for the somatoautonomic reflex responses in cardiorespiratory function caused by noxious stimuli or adverse tissue metabolic changes. Lamina V cells provide diffuse input to the reticular core of the brainstem that may affect somatomotor integration and behavioural state. There are dense projections from lamina I cells (and a few lamina V cells) to the parabrachial nucleus at the pontomesencephalic junction, a major viscerosensory (homeostatic) integration site that is interconnected with the periaqueductal grey, hypothalamus, amygdala and preautonomic cortical regions. This provides an indirect spinal pathway to the central amygdala which appears to be involved in fear-associated conditioning by nociceptive activity as well as morphine analgesia. There is a similar spinal input to the periaqueductal grey, which is the major mesencephalic site for homeostasis, defence reactions and vocalization. The hypothalamus receives nociceptive activity by way of the parabrachial nucleus and from noradrenergic cells in the caudal ventrolateral medulla (and perhaps by a direct input from spinal neurons) that may affect goal-directed aversive and feeding behaviours, neuroendocrine and immune responses, and thermoregulatory and osmoregulatory control.

The main ascending pathway for pain sensation is the crossed lateral spinothalamic tract, which courses in the middle of the lateral funiculus and consists primarily of lamina I axons (**Figure 1**). This terminates in three regions of the thalamus: (1) a dedicated nociceptive- and thermoreceptive-specific relay nucleus in the posterior thalamus, which projects topographically to the parietoinsular cortex and has a collateral projection to the fundus of the central sulcus; (2) a ventral portion of the main somatosensory thalamic relay nucleus, which projects to the second somatosensory region in the parietal operculum of the lateral sulcus; and (3) a posterior portion of medial thalamus, which projects to the anterior cingulate cortex. In addition, axons of lamina V cells that ascend in the anterior spinothalamic tract constitute a second major component of the pain pathway; they terminate in patches in the main somatosensory relay nucleus around immunohistochemically distinct cells which project to the superficial layers of the primary somatosensory cortex in the postcentral gyrus. There are nociceptive spinothalamic cells in the spinal intermediate zone as well, especially at upper cervical segments, which project to the medial thalamus and to motor thalamus; these and other multisynaptic pathways may provide ancillary pain information to the forebrain.

Accordingly, four main regions of the human cerebral cortex are activated by pain in functional imaging studies: the insula, the anterior cingulate, and the primary and secondary somatosensory areas. These areas may subserve different roles in pain. Possible associations are: the insula

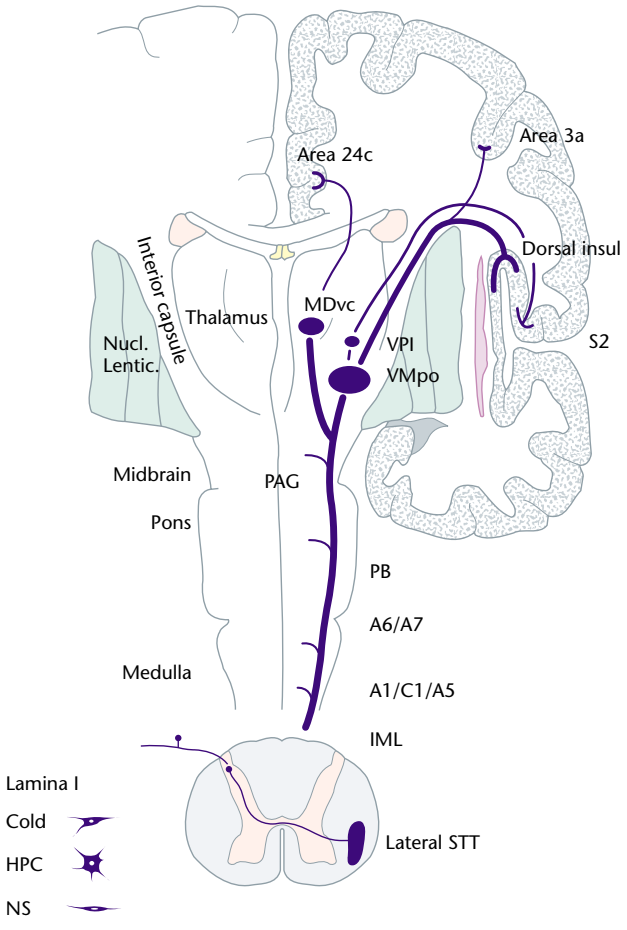

Figure 1 The anatomy of the spinal cord at the cervical level depicting the Aα, β, δ and C fibres and their potential target regions mediating the nociception. MDvc, ventral caudal part of the medial dorsal nucleus; VPI, ventral posterior inferior nucleus; VMpo, posterior part of the ventral medial nucleus; PAG, periaqueductal grey; PB, parabrachial nucleus; IML, intermediolateral cell column; HPC, polymodal nociceptive cell ('heat, pinch and cold'); NS, nociceptive-specific cell; STT, spinothalamic tract.

with qualitative differentiation, homeostasis and memory; the anterior cingulate with motivation and attention; and the somatosensory areas with discrimination and motoric integration. The anterior cingulate appears particularly important, because its activation is selectively associated with the perception of pain and unpleasantness from thermal stimulation (Craig *et al*., 1996;Rainville *et al*., 1997). Other forebrain regions activated by painful stimuli include dorsolateral prefrontal cortex, striatum, cerebellum, hypothalamus, amygdala and periaqueductal grey. Many of these areas are interconnected, and the experience of pain clearly involves multiple forebrain regions that interact within a complex network. Thus, the effects of lesions in any one of these regions are equivocal. Lesions involving posterolateral thalamus, the insula and parietal operculum can abolish pain and temperature sensation, but can also result in the central pain syndrome. Large lesions of the postcentral gyrus have no effect on pain, but small lesions (which include the fundus of the central sulcus) can reduce pain. Lesions of the anterior cingulate have had various effects, including blunting the emotional aspect of pain, but anatomical variability has been a serious confound.

Neurotransmitters Involved in Peripheral and Spinal Pain Processing

Nociceptive primary afferent fibres communicate with second-order dorsal horn cells by release of neurotransmitters, neuromodulators and trophic agents. They contain glutamate and/or aspartate, which are major excitatory amino acid (EAA) neurotransmitters also used by primary afferents mediating other somatic modalities, such as touch and vibration. The terminals of EAA-containing primary afferent fibres are located throughout the dorsal horn. Approximately 50% of the terminals on spinothalamic cells contain glutamate. Nociceptive afferent fibres may corelease adenosine triphosphate (ATP), and some nociceptors, particularly those with C afferent fibres, may also contain one or more peptides, including substance P, calcitonin gene-related peptide (CGRP), neuropeptide Y and galanin. Substance P, for example, is found in a subset of small dorsal root ganglion cells that have unmyelinated (C) or small myelinated (Aδ) axons. It can appear alone or be colocalized with other peptides. Most fibres that contain substance P are also sensitive to capsaicin (the pungent ingredient in hot peppers), a characteristic of heat-sensitive nociceptors (Caterina *et al*., 1997); however, the peptide cotransmitters otherwise do not appear to be associated selectively with particular subtypes of nociceptors. Nearly all cells that are immunopositive for substance P are also immunopositive for one of the EAAs. Glutamate and substance P can be found not only in the cell bodies and central terminals of nociceptive fibres, but also in their peripheral terminals. The release of co-contained neurotransmitters may be under differential, independent control.

Once released, EAAs act on several types of receptors in the dorsal horn, which include both ionotropic and metabotropic EAA receptors. Binding of an EAA to an ionotropic receptor, such as the α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionate (AMPA) and *N*-methyl-D-aspartate (NMDA) receptors, opens cation channels in the postsynaptic cell leading to the influx of Na^+ through the AMPA receptor, or Na^+ plus Ca^{2+} through the NMDA receptor. Both ligand-gated channels produce a fast-onset depolarization. Blockade of AMPA, but not NMDA receptors leads to inhibition of acute pain. Depolarization is required to remove the Mg block on NMDA channels but, following NMDA receptor activation, the depolariza-

tion is slightly more prolonged, and second-messenger systems are activated which can lead to long-term changes within the neuron. Activation of postsynaptic NMDA receptors seems to be an essential initiating step in the development of central hyperexcitability and chronic pain (Woolf and Thompson, 1991). Administration of NMDA receptor antagonists (such as MK-801 or dextromethorphan) has been highly successful in blocking inflammatory or nerve injury-induced pain in animal studies, and in limited clinical trials it has been effective for refractory cases of chronic pain, although the effects are not selective for pain processing. These agents also synergize with spinal morphine and reduce the development of opiate tolerance. Metabotropic EAA receptors, which are located on glia as well as on neurons, work via G protein-coupled receptors and the second-messenger protein kinase C (PKC). Blockade of these receptors (in particular, metabotropic glutamate receptor 1 (mGluR1)) can also reduce or inhibit nocifensive responses.

Substance P is thought to exert its effect by binding to one of several neurokinin receptors, especially the neurokinin 1 (NK1) receptor. This G protein-coupled transmembrane receptor is located predominantly on lamina I neurons, but may also be found on certain lamina III–V neurons. There are several actions subsequent to binding at the NK1 receptor, including a delayed, long-lasting (tens of seconds) depolarization that can summate. Activation of PKC following NK1 receptor activation results in phosphorylation of the NMDA receptor complex, rendering it more active. Abolition of NK1 receptive neurons or of PKC-γ in the dorsal horn can reduce chronic pain sensitivity in animal models (Malmberg *et al*., 1997; Mantyh *et al*., 1997).

Unlike substance P and the EAAs, which are synthesized in both primary afferent neurons and spinal cord neurons, the inhibitory neurotransmitters are found only in intrinsic spinal cord neurons. Small spinal inhibitory interneurons that act to modulate the pain message are found in the highest concentrations in laminae II and III. The two inhibitory amino acids, γ-aminobutyric acid (GABA) and glycine are often colocalized (Todd *et al*., 1996). These agents work by several mechanisms, both presynaptically to reduce neurotransmitter release from the primary afferent fibres and postsynaptically to hyperpolarize the neurons and reduce the evoked responses. There are also interneurons containing endogenous opioids (enkephalin, dynorphin) in the superficial dorsal horn as well as in lamina V. Interestingly, intrinsic substance P-containing cells in the dorsal horn always contain enkephalin, although enkephalin is found in some cells that do not contain substance P. The inhibitory interneurons can be activated by descending catecholamine pathways, by serotonin and by ATP. There is also evidence that the metabolic product of ATP, adenosine, has presynaptic and postsynaptic inhibitory effects on nociceptive processing in the superficial dorsal horn.

Role of Primary Afferent Fibres in Inflammation

Tissue damage elicits a local injury response. Cell injury results in the production of arachidonic acid metabolites (from cell membrane fatty acids), including prostaglandin (PG) E_2, leukotrienes (LT) B_4 and platelet-activating factor. Bradykinin is formed by plasma kallikrein; leucocytes and mast cells secrete lactic acid (lowering the local pH) and superoxide free radicals, as well as serotonin, histamine and various proinflammatory cytokines (e.g. interleukin (IL) 1β and tumour necrosis factor (TNF) α). All of these inflammatory (and antibacterial) mediators have direct effects on nociceptors, resulting in activation or sensitization. In addition, neurogenic inflammation is generated by the peripheral effector action of the activated nociceptor nerve terminals. Action potentials in the primary afferent nerve fibres are conducted not only into the spinal cord, but also to the neighbouring terminal branches of the same nerve fibres, some of which arborize widely (over centimetres) in the tissues. This causes neurotransmitters to be released into the peripheral tissue, including glutamate, substance P, neuropeptide Y, CGRP and ATP. These agents diffuse through the tissue and enhance inflammation through a variety of actions on sympathetic efferents, mast cells and small blood vessels, causing vasodilatation and increased permeability between capillary endothelial cells. This allows proteins and fluid to leak from the blood vessels (plasma extravasation), which in small quantities results in erythema (redness or flare) and in larger quantities in oedema (swelling). PGE_2 and LTB_4 also increase vascular permeability, and IL-1β and TNFα act on capillary endothelium to attract several types of leucocytes including neutrophils. These blood cells infiltrate the tissue, along with plasma containing cytokines, complement agents and more bradykinin, serotonin, glutamate and other substances by the extravasation. Collectively, these varied agents act to sensitize local nociceptive nerve terminals, thus creating a cascade of inflammatory events spreading out from the point of original damage. Nerve growth factor and other trophic factors that are induced and released can have longer-term effects on the expression of chemicals and receptors in the peripheral and central afferent nerve terminals, and these may play a role in lasting, neuropathic changes in addition to their role in regeneration and healing.

Hyperalgesia: Peripheral Sensitization and Central Hyperexcitability

Tissue injury or inflammation results in release of several different classes of chemicals that affect nociceptive terminals, as described above. Many of these agents

produce pain when injected into skin, and all lower the threshold of the nociceptors. Lowered threshold to pain and increased pain to a given stimulus are called collectively hyperalgesia. An example of hyperalgesia is the increased sensitivity following a sunburn, where light touch or a warm temperature on the burned area can hurt (lowered threshold) and a hot shower is more painful than it is normally. Inflammatory hyperalgesia is involved in the pain of many diseases. For example, in arthritis, nociceptors in the joints that fire little if at all during normal movement are exquisitely sensitive to flexion or extension, causing severe pain. The role of prostaglandins in hyperalgesia is the basis for the effectiveness of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) in relieving such pain (see below).

Hyperalgesia results from the peripheral sensitization of the nociceptors and also from increased excitability of central nociceptive neurons. Sustained activity in nociceptive C-fibre afferents produces postsynaptic biochemical changes in dorsal horn neurons, and they become hyperresponsive. Other manifestations of central hyperexcitability include increased spontaneous activity, an enlarged receptive field, and a lowered threshold to peripheral stimulation such that mechanoreceptive Aβ fibres can drive nociceptive dorsal horn cells; this may be the basis for the tactile allodynia that is a hallmark of neuropathic pain. In many cells, this is dependent on activation of NK1 and NMDA receptors, with subsequent mobilization of PKC. Repeated bursts of afferent C-fibre activity lower the threshold throughout the extent of the receptive field of the nociceptive dorsal horn cells. Thus, in cells that receive convergent cutaneous and visceral inputs, cutaneous hyperalgesia can occur as a referred symptom of visceral pain, as, for example, the trigeminal (facial) hyperalgesia that can accompany a toothache. Prevention of the central sensitization initiated by afferent barrages of C-fibre nociceptive activity is the justification for preemptive analgesia, in which prophylactic local and systemic analgesics are used before major surgery.

Descending Inhibitory Control Systems

The time required for healing following traumatic injury or inflammation, coupled with the interrelationship between nociception and integrative homeostasis, implies the need for central neural controls on pain transmission. In addition, fast endogenous antinociceptive circuits are thought to have evolved to enhance survival by facilitating defence and escape behaviours. The two classic examples supporting the existence of endogenous central pain control systems are the observations of soldiers with massive wounds who did not complain of pain and the well-documented occurrence of placebo effects in patients with organic causes of pain. Several inhibitory mechanisms have been recognized.

First, there are fast inhibitory mechanisms on C fibre ('slow') pain initiated by low-threshold A-fibre activity (e.g. rubbing, vibration) and by Aδ nociceptor activity (e.g. counterirritation) which can be shown definitively during a progressive pressure block of peripheral nerve conduction. These effects, which suggested the gate control theory of pain integration (Melzack and Wall, 1965), occur partially at the spinal segmental level and partially at the cortical level. Dysfunction of these mechanisms may underly touch-evoked neuropathic pain. These mechanisms may be engaged by transcutaneous electrical nerve stimulation (TENS) and by dorsal column stimulation, procedures used by some clinicians for pain control.

Second, there is a cross-modal interaction between innocuous thermosensory (cool–warm) activity and C fibre-evoked pain. Therapeutic cold or warmth has a peripheral palliative effect on inflammation and on sensitized nociceptors; in addition, there is a central inhibitory effect on pain that occurs in the forebrain. The thermal grill illusion of pain, in which a painful ice-like burning sensation is elicited by spatially interlaced innocuous warm and cool stimuli, demonstrates this interaction by showing that the reduction of cooling-induced thermosensory activity (by the simultaneous warming) can unmask the noxious (burning) sensation normally caused by noxious cold. This disinhibition, or reduction of the normal inhibition of pain by cooling, is associated with lamina I spinothalamic activation of the anterior cingulate cortex (Craig *et al*., 1996). A conduction block of peripheral nerve A fibres (by maintained pressure) that eliminates cooling sensibility (conveyed by Aδ fibres) enables an innocuous cool stimulus to produce the same burning sensation (via C-fibre nociceptors). The intense burning sensation caused by putting warm water on feet that are numbed by cold, an unmistakable thermoregulatory distress signal, is probably based on the same mechanism.

Third, there are several sites in the brain from which analgesia can be produced by the electrical or chemical activation of descending and ascending pathways, known as stimulation-produced analgesia. Clinically, deep brain stimulation of the periaqueductal grey can alleviate certain kinds of chronic pain, and stimulation in the hypothalamus and other forebrain sites can also be antinociceptive. The descending pathways activated by stimulation of the periaqueductal grey originate from serotonergic and peptidergic (substance P) neurons in the rostroventral medulla and the midline nucleus raphe magnus, and also from noradrenergic and enkephalinergic neurons in the dorsolateral pontine tegmentum (Basbaum and Fields, 1978). These cells project directly to the spinal dorsal horn, where they inhibit nociceptive neurons. Accordingly, such antinociception can be partially blocked by intrathecal α_2-adrenergic antagonists or serotonin antagonists, and may

be enhanced by agonists. These descending systems are also activated by systemic opiates. Just as pain has direct effects on cardiorespiratory activity, these descending bulbospinal antinociceptive pathways also have direct actions on sympathetic preganglionic neurons and other brainstem autonomic sites. None the less, stimulation-produced analgesia in human patients is often reported to be selective, in that pain relief occurs without any autonomic changes or sensory experiences.

These endogenous pain control systems can be naturally activated by stressors ('stress-induced analgesia') and by environmental danger signals, which can be classically conditioned or learned. Recently, it has been recognized that there are also endogenous antianalgesia circuits that can be activated by learned safety signals which predict that danger will not occur. These powerful circuits appear to be distinct from the analgesia circuits and can reverse their effects at the spinal level. Learned safety signals cause the spinal release of peptides, such as cholecystokinin, that effectively block analgesia produced by stress, danger or even morphine. Such antianalgesia mechanisms may therefore play a key role in chronic pain and in the development of morphine tolerance.

Influence of Disease and Stress on Pain Perception

Pain is an aspect of enteroception (the sense of the condition of the body) and, accordingly, it is influenced by many of the other processes of physiological homeostasis. For example, pain sensation is reduced by cold or warmth, by hypertension and by food intake. Nociceptive neurons at spinal and higher levels have receptors for circulating compounds that are involved in homeostasis and released by stressors, such as corticosteroids, catecholamines and oestrogen, and most brain areas associated with pain are interconnected with autonomic areas; for example, spinal lamina I neurons receive descending projections from the 'master autonomic control centre', the paraventricular hypothalamus.

Significantly, generalized illness and immune system challenges (infection, inflammation, injury) can induce hyperalgesia. Circulating proinflammatory cytokines released by activated immune cells (such as the interleukins and TNF) have direct effects on nociceptive primary afferent fibres and on central neurons. This may be one reason for increased headache and migraine incidence during a systemic immune response, because there is evidence that illness-induced hyperalgesia can be blocked by drugs that disrupt proinflammatory cytokines. An exaggerated pain state may be a natural concomitant of immune-activated, neurally organized illness behaviour (including fever, decreased activity and food and water intake, increased sleep) and consistent with the role of C-fibre afferents in metaboreception. Analysis of the integration of neural activity with immune function is only just beginning; none the less, the available evidence supports the view that pain sensation can be strongly influenced by the general health of the body, as well as by hormone levels, nutrition and behaviour (Maier and Watkins, 1998). Pain is also influenced by several psychological factors, such as culture, context, emotional status, previous experience and patient history, and thus appropriate behavioural therapy for pain is an important aspect of clinical team management.

Conversely, pain itself can have strong negative effects on health. Pain, like stress and surgery, can inhibit immune function, enhance tumour growth, and increase morbidity and mortality rates. Unrelieved pain usually leads to sleep disturbance, loss of appetite, depression, immobilization, severe impairment of general health and suicide. Pain can kill. Management of patients with chronic, intractable pain presents a great challenge.

Neuropathic Pain

Only the epineurium surrounding peripheral nerves and the meninges surrounding the brain are innervated by C-fibre afferents, and the brain itself is insensate; however, injury to the nervous system can cause pathological pain by several means. Peripheral nerve damage due to trauma (e.g. in carpal tunnel syndrome, neuroma) or to pathogenic processes (e.g. in diabetic neuropathy, postherpetic (viral) neuralgia or rheumatoid inflammation) can initiate cellular changes in primary afferent fibres that result in ectopic neural activity, molecular phenotype changes and anatomical sprouting in the spinal dorsal horn. Antibodies to gangliosides that are present on primary afferent fibres or cytokines (TNFα) or agents of the immune complement cascade (C3a) may cause activation of C nociceptors (Xiao *et al*., 1997); systemic lignocaine (lidocaine) and gabapentin may relieve neuropathic pain by interfering with these mechanisms peripherally or centrally.

Peripheral neuropathies can also initiate changes in central neural function to varying degrees. For example, the deafferentation pain of a brachial plexus root evulsion can be treated effectively by a lesion of the dorsal root entry zone, which eliminates hyperactivity in the dorsal horn of the cervical spinal cord. A particularly complex syndrome is reflex sympathetic dystrophy, also known as 'complex regional pain syndrome' or causalgia, in which nociceptive afferent fibres may become sensitive to circulating adrenaline or efferent sympathetic activity, and trophic changes (hair loss, inappropriate sweating, cold limbs) may arise. Phantom limb pain, which can result following amputation, particularly if there was significant preoperative pain, may involve changes in both peripheral nerve and brain function.

Damage to the central nervous system can also result in intractable pain. In Wallenberg syndrome (anaesthesia dolorosa), an infarct in the caudal medulla produces loss of evoked pain and temperature sensation in the ipsilateral face and the contralateral body, and ongoing pain arises in these regions. A central pain syndrome can also result following a spinal lesion (as in multiple sclerosis), or following stroke-induced damage in the posterolateral thalamus or the parietoinsular cortex, if the lesion eliminates normal temperature and pain sensation in the contralateral body. Such pain is often burning, and pain from innocuous cooling or touch (allodynia) is typical. This must result from the release (disinhibition) of activity elsewhere in the brain, perhaps by the loss of endogenous analgesia mechanisms such as the normal inhibition of pain by cold. Central pain is usually unresponsive to opiates, but tricyclic antidepressants (amitriptyline) can be efficacious (Pagni, 1998).

Aspirin, Opiates and Other Analgesics

Aspirin, or acetylsalicylic acid, was originally derived from the bark of the willow tree. It has several actions, including permanent inhibition of cyclooxygenases (COXs), the enzymes that catalyse the production of prostaglandins from arachidonic acid (a fatty acid component of cell membranes). Prostaglandins do not activate nociceptors, but they cause sensitization, decreasing their thresholds so that they are activated by mechanical, thermal or chemical stimuli that are normally innocuous. Thus, blocking the peripheral production of prostaglandins during inflammation reduces ongoing pain and hyperalgesia and, by interfering with neurogenic inflammation, also reduces the concomitant flare and swelling. Similar agents such as paracetamol (acetaminophen), ibuprofen and naproxen, which are collectively termed NSAIDs, exert their peripheral analgesic effects via the same mechanism. Corticosteroids have a similar effect by preventing the induction of COX as well as proinflammatory cytokines.

Aspirin and NSAIDs permanently inhibit both the COX-1 (constitutive) and COX-2 (inducible) isozymes, which produce different prostaglandins and are localized in different tissues. COX-1 is essential for the health of the stomach and kidney, where chronic high doses of aspirin cause damage. Because the prostaglandins made by the inducible COX-2 primarily cause inflammation, sensitization and fever, selective COX-2 inhibitors ('superaspirins') are being developed that are relatively free of the side effects of aspirin.

NSAIDs also have central effects. During chronic pain states, prostaglandins are released in the spinal cord, where they contribute to central sensitization in a manner analogous to their effect in the periphery, for example by increasing neurotransmitter release from primary afferent terminals. Spinal administration of small amounts of NSAIDs eliminates this enhanced release and, in addition, reduces peripheral neurogenic inflammation by eliminating pathological activity carried in nociceptive fibres antidromically (in a reverse direction) into the peripheral tissue. Systemic NSAIDs may also produce central analgesic effects by interacting with endogenous pain control mechanisms in the periaqueductal grey matter, an action that can synergize with opioid actions (Vaughan *et al*., 1997).

The opioids, which include the classic opiates such as morphine and also peptides with similar actions, are potent analgesics with both peripheral and central actions. Peripheral opioid injections may affect inflammatory pain by reducing activity in sensitized nociceptive primary afferent fibres and affecting immune cell activity. In the spinal cord, opioids produce presynaptic inhibition of nociceptive afferents (by inhibition of calcium entry) and postsynaptic inhibition of nociceptive dorsal horn cells (via a G protein-coupled potassium conductance increase). In contrast to NSAIDs, both sensitized release and normal pain transmission are reduced by opiates. All three types of opiate receptors (μ, δ and κ) are involved, but epidural (or intrathecal) injections of fast-acting μ-selective opiates (such as fentanyl) are clinically most effective. Such injections usually include bupivacaine, a long-lasting local anaesthetic that blocks small-diameter primary afferent fibres, which reduces the dosage of opiate needed and the danger of respiratory depression due to rostral spread.

Systemically administered opiates engage endogenous pain control mechanisms in the forebrain, particularly in the brainstem periaqueductal grey matter and the amygdala. μ-Selective agonists cause disinhibition of the descending pathways involving serotonergic and noradrenergic fibres which can be activated during stimulation-produced analgesia. Another antinociceptive pathway that is normally activated by endogenous β-endorphin in the periaqueductal grey is not engaged by morphine. Aspirin can synergize with the effects of morphine in the periaqueductal grey. Opiates have traditionally been underprescribed clinically for acute or postoperative pain relief, because of fears of dependency, but their usage is now strongly recommended, based on studies showing that less than 1% of patients are at risk. The coadministration of adjuvants that help prevent the development of tolerance (the pharmacological need for larger doses) has further encouraged increased clinical use of opiates, for example in bedside pumps for patient-controlled analgesia.

Summary

Pain is an important sensation that alerts to a threatening condition in the body's tissues. Like hunger or thirst, it is a motivational somatic state that drives appropriate beha-

vioural responses, but chronic pathological pain can also completely dominate attention and consciousness and cause intolerable suffering. Our knowledge of the representation of pain in the peripheral nerves, the spinal cord and the brain is increasing, and we are becoming aware of the many neurochemicals involved and the critical interactions with other systems, such as the thermoregulatory, sympathetic and immune systems, that make pain an integrated physiological phenomenon. The clinical treatment of pain has improved with the advent of local and spinal analgesia, with the use of stimulation in the periphery, the spinal cord and the brain, with the identification of new pharmacological tools such as serotonergic and adrenergic agonists, and with the combination of behavioural and organic therapies. Accelerating advances in our knowledge in each of these directions suggest that there is hope that chronic pain, which causes enormous costs to our society in care and lost effort, may some day be alleviated.

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