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Somatic pain—pathogenesis and prevention

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Although we use the term pain to define all sensations that hurt or are unpleasant, actually two quite distinct kinds of pain exist. The first is the pain that is only elicited when intense, that is noxious stimuli threaten to damage normal tissue. This pain can be termed *nociceptive*, because of its direct link with noxious stimuli, or *physiological* because it is a key component of the body's normal defence mechanisms, protecting the body from a potentially hostile external environment by initiating behavioural and reflex avoidance strategies. This protective mechanism operates as a result of the presence of a specific set of primary sensory neurones which encode the intensity, duration and quality of any noxious stimulus and, by virtue of their topographically organized projections to the spinal cord, its location [108]. Absence of these nociceptors, as in patients with congenital analgesia or peripheral neuropathies, is associated with tissue damage and poor healing as a consequence of the absence of the normal protective reflexes and behavioural responses elicited by the nociceptors. This "ouch" pain is, therefore, an important and adaptive element of the normal nervous system which, clinically, only needs to be temporarily suppressed or disabled during surgical procedures where damage is deliberately produced.

The nociceptors terminate in a highly ordered way in the dorsal horn of the spinal cord with the thinly myelinated A ending in laminae I and V and the unmyelinated C-fibres in lamina II. These high threshold sensory fibres activate a large number of second order interneurones and projection neurones in the spinal cord, some of which are activated exclusively by noxious stimuli (*nociceptive specific*) and others which are activated by low and high intensity stimuli (*multireceptive or wide dynamic range neurones*). The activity generated by nociceptor input is transferred, after complex active processing in the dorsal horn, directly, or via brainstem relay nuclei, to the thalamus and then onto the cortex, where the sensation of pain is generated [108]. Parallel outputs from the dorsal horn go to the ventral horn and activate flexor motor neurones generating the withdrawal flexion reflex, so that both the sensation of physiological pain and the flexion withdrawal reflex occur together [107].

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Clinical pain

Clinical pain is present when ongoing discomfort and abnormal sensitivity are a feature of a patient's symptomatology. There are usually three general features of clinical pain, spontaneous pain which may be dull, burning, or stabbing, exaggerated pain in response to noxious stimuli (hyperalgesia) and pain produced by stimuli which would never normally do so (allodynia). It is useful to analyse clinical pain both from the perspective of the injured tissue; inflammatory pain which is associated with tissue damage, inflammation, or both and neuropathic pain which is that pain that results from a lesion to the peripheral or central nervous systems; and from a temporal perspective; acute and chronic pain.

ACUTE PAIN

Acute pain typically results from soft tissue injury or inflammation and, although sharing many of the sensory characteristics of chronic pain, can be considered to have an adaptive or biologically useful function. This function is protective, not in the same way as nociceptive pain, because tissue damage has already occurred and therefore cannot be prevented, but by enabling healing and repair to occur undisturbed. In other words it has a reparative function. This is achieved by making the injured/inflamed area and surrounding tissue hypersensitive to all stimuli so that contact with any external stimulus is avoided. This manifests as a tenderness of the injured part. Clinically, acute pain manifests in response to trauma and inflammation and is typically seen, for example, postoperatively. Since the pain is reparative it is important to address the issue of whether it is appropriate clinically to completely eliminate such pain or whether it is sufficient to reduce it to a level where it is no longer distressing but can still fulfil a protective function. In patients who have undergone abdominal surgery, for example, the advantage of early mobilization and easier breathing must be tempered against risks of wound dehiscence as a result of excessive movement

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[113]. Similarly consumption of non-steroidal anti-inflammatory agents before excessive exercise may prevent or reduce the development of muscle / joint pain, but does it increase the risk of damage to these tissues?

CHRONIC PAIN

Chronic pain can be a sustained sensory abnormality occurring as a result of an ongoing peripheral pathology, such as chronic inflammation, or it can be autonomous, independent of the trigger that initiated it [82]. In the latter case it is the changes in the nervous system that have become the pathology and the pain is maladaptive offering no survival advantage [114]. Chronic pain may be either spontaneous or provoked. Spontaneous pain occurs in most chronic pain conditions but is a particular feature of denervation syndromes, where the sensory channel from the periphery to the CNS is disrupted (e.g. anaesthesia dolorosa, phantom limb pain, brachial plexus avulsion injuries). Provoked pain is elicited by a peripheral stimulus but the response is typically exaggerated in amplitude or duration. The pain may be generated by stimuli quite unlike those which would normally be required to elicit pain. Patients with causalgia, post-herpetic or trigeminal neuralgia, for example, experience excruciating pain in response to the lightest of touches to the skin.

A distinctive feature of clinical pain then is sensory hypersensitivity, comprising both an exaggerated or increased response to suprathreshold stimuli and the production of pain by low intensity or formerly subthreshold stimuli. In both cases the responsiveness of the "pain" system is dramatically altered, an increase in gain in the former case and a reduction in threshold in the latter. How does this occur?

Peripheral sensitization

One explanation for post-injury pain hypersensitivity states is that the transduction sensitivity of the high threshold nociceptors changes. This view was vigorously proposed by Thomas Lewis in the 1930s, who suggested in addition, that the axon reflex was responsible for the spread of sensitivity from the zone of tissue damage (zone of primary hyperalgesia) into neighbouring areas where sensitivity is present but no tissue damage (the zone of secondary hyperalgesia) [53]. In the mid 1960s Bessou and Perl [4] demonstrated directly in studies on single polymodal nociceptors, that an intense noxious heat stimulus altered the sensitivity of a proportion of the sensory fibres to subsequent heat stimuli. This work has been extensively replicated and there is now no doubt that tissue damage, and the inflammatory response it provokes, initiates a local change in the sensitivity of sensory fibres, the phenomenon of peripheral sensitization [35, 101]. These changes have been most clearly demonstrated for thermal stimuli, although local mechanical hypersensitivity has also been described [18].

A great deal of work has been devoted to elucidating what triggers the peripheral sensitivity changes since this would provide a potential avenue for the production of analgesic drugs. The results have turned out to be rather complex in chemicals which might be expected to be responsible for peripheral sensitization because they are released during painful inflammatory conditions, such as potassium and hydrogen ions, 5-HT, histamine, bradykinin, purines, cytokines, substance P, calcitonin gene-related peptide (CGRP) and the eicosanoids tend to act synergistically together rather than individually, so that the optimal way of producing peripheral sensitization is to use a "soup" or "cocktail" of these different mediators [35,10l]. This implies that a single antagonist, for example a bradykinin-receptor antagonist, may not be sufficient to prevent peripheral sensitization if other mediators are present, even though it can block any hyperalgesic action of bradykinin.

The non-steroidal anti-inflammatory agents are assumed largely to produce their analgesia in the periphery as a result of the inhibition of prostaglandin production by the enzyme cyclo-oxygenase (COX). There is, however, a mismatch between the anti-inflammatory potency of these drugs and their analgesic activity and many turn out to be relatively more selective for the constitutive form of COX (COX1) than the form of the enzyme that is induced during inflammation (COX2) [104]. These drugs may act in part on the central nervous system [60].

PAIN HYPERSENSITIVITY AND PERIPHERAL SENSITIZATION

What has become clear in recent years is that while peripheral changes in sensitivity do occur, they cannot account for all the hypersensitivity changes associated with acute tissue injury. Two aspects of post-injury pain hypersensitivity in particular cannot be accounted for by a simple change in the transduction sensitivity of high threshold primary sensory nociceptors. The first is the spatial extent of the hypersensitivity and the second the capacity of low threshold mechanoreceptors to produce pain.

As indicated earlier, two zones of hyperalgesia occur after tissue damage, that of primary and secondary hyperalgesia. Although peripheral sensitization has been well documented in the zone of primary hyperalgesia [5, 12, 18], where the damaged or inflamed tissue is located, no change in transduction sensitivity of nociceptors has ever been found in the zone of secondary hyperalgesia [5, 48, 76]. Peripheral changes in transduction sensitivity have a role in the thermal hypersensitivity associated with burn injuries [126] and contribute to the mechanical hypersensitivity present in inflamed joints [84], a primary role for peripheral sensitization in clinical pain appears to be limited to rare conditions where C-afferent fibres become spontaneously sensitized producing a burning sensation [12].

Mechanical hypersensitivity is a very prominent feature of inflammatory pain manifesting, for example, as pain in response to normal ranges of movement of joints in patients with arthritis or exquisite tenderness to touch at the site of a cutaneous inflammatory lesion. Such tenderness to

movement or contact is often the most distressing feature of clinical pain states for patients, preventing normal functioning. While a reduction in the mechanical sensitivity of nociceptors occurs, and has been particularly well described for joint afferents [84], these changes cannot completely account for the mechanical sensitivity seen clinically. One reason is that the mechanical sensitivity is actually mediated by large low threshold mechanoreceptive A -primary sensory neurones. A -primary sensory fibres, which innervate specialized end organs in the periphery, normally only elicit innocuous sensations such as touch, vibration, pressure or movement of hairs [100]. However, when the excitability of the spinal cord is increased as part of the syndrome of central sensitization [109, 110], activation of these low threshold sensory fibres begins to produce pain. This has been demonstrated using conduction block of the large myelinated afferents where, in parallel with a disappearance of action potential conduction of the A fibres, mechanical sensitivity disappears, even though conduction in the A and C-nociceptors remains intact. The specific involvement of A - fibres in mechanical hypersensitivity has been shown following the application of chemical irritants [46, 47, 48]. A more direct demonstration has come from a study where single A -afferents were recorded and stimulated in volunteers, using microneurographic techniques [99]. After the afferents' receptive field has been defined, usually as a small area on the skin, the electrode was changed to a stimulating mode and using very low currents the same afferent could be activated electrically which elicited, as expected, a simple innocuous sensation which was interpreted by the subject as arising from the receptive field. The investigators then injected capsaicin, the pungent ingredient of red peppers, into the skin adjacent to the receptive field. The capsaicin produced a period of intense pain followed by the appearance of a zone of secondary hyperalgesia where light touch began to produce pain. Provided the single afferent's peripheral receptive field fell within this zone of secondary hyperalgesia, then stimulating it again began to produce pain. As the, mechanical hypersensitivity disappeared, the electrically evoked sensation returned to an innocuous one.

Mechanical pain sensitivity is largely, therefore, the consequence of a misinterpretation of normal inputs which are not part of the nociceptive or physiological pain system and which never normally generate pain, and this is the consequence of the generation of central sensitization [109, 110].

Central sensitization

In the early 1980s, a study on central plasticity in the somatosensory system led to the discovery that tissue injury triggered an increase in the excitability of neurones in the spinal cord [109], a phenomenon that has become known as central sensitization [26, 101, 111] It was then found that central sensitization was generated by C-afferent fibres [105, 124] and that the changes are expressed as alterations in the spatial extent, responsiveness and threshold of the receptive fields of dorsal horn neurones [16] as a consequence of the recruitment) of subthreshold synaptic potentials [115, 116]. The pharmacology of central sensitization has been explored, leading to the discovery that NMDA (N-methyl-D-aspartate) [56, 122] and tachykinin [57] receptors are involved, and that morphine pretreatment prevents its establishment [125].

Central sensitization has been documented in a large number of laboratories in a wide variety of species [14, 16, 25, 33, 34, 36, 38, 67, 72, 77, 83, 89, 109], including humans [46, 49, 99] and is now accepted as a major contributor to post-injury pain hypersensitivity. One direct implication of this work is that interventions that prevent the establishment of central sensitization in patients may have a therapeutic role; the concept of pre-emptive analgesia [113]. We have recently demonstrated, for example, that preoperative administration of morphine reduces postoperative analgesic requirement and local wound hypersensitivity, compared with the same dose at the end of the operation [81]. This, together with related work by others [27, 28, 41, 44, 66, 79, 87, 102], indicates that pre-emptive analgesia and NMDA-receptor antagonists may have a contribution to make in reducing acute pain [15].

MECHANISMS OF CENTRAL SENSITIZATION

Small diameter primary afferents produce slow synaptic potentials which summate temporally on low repetition rates leading to a non-linearly increasing cumulative depolarization [90, 96, 97]. This is mediated by NMDA and tachykinin receptors [64, 65, 97] and is accompanied by calcium entry via NMDA channels [62] which activates protein kinase C [13] and, by a phosphorylation of the NMDA channel [9], relieves the Mg^{2+} block of the ion channels [62], increasing glutamate sensitivity. This cumulative depolarization is responsible for the windup of action potential discharge in spinal neurones [97] but more importantly, is likely to be the trigger for prolonged alterations in membrane excitability, which manifest at a cellular level as heterosynaptic facilitation [98] and at a system level as central sensitization [112].

Central sensitization provides an explanation of how low threshold A -mechanoreceptors, which normally generate only innocuous: sensations [69, 103], begin to produce pain after acute C-fibre inputs in humans [46, 49, 99] and in animals [16, 121]; by the recruitment of previously subthreshold inputs to nociceptive dorsal horn neurones as a result of an increase in membrane excitability.

CENTRAL SENSITIZATION AND INFLAMMATORY PAIN

Two simultaneous processes may be occurring to produce and maintain a central component of inflammatory hypersensitivity. The first is an ongoing generation of central sensitization by nociceptors activated and sensitized by the inflammation. The second is a change in the phenotype of sensory neurones innervating the inflamed area as a result of

an upregulation of target-related neuroactive factors, leading to altered or augmented central actions of afferents. An increasing number of growth factors and neuropoietic cytokines including the neurotrophin nerve growth factor (NGF) and the neurokine leukaemia inhibitory factor/cholinergic differentiation factor (LIF/CDF) have been shown to interact directly with primary sensory neurones via specific high affinity receptors [23, 42, 52, 54, 73, 78, 86, 95, 106] and produce changes either locally or after retrograde transport [17, 22] by modification of transcription in the dorsal root ganglion (DRG) soma [22]. Inflammatory cytokines such as interleukin (IL)-1 , tumour necrosis factor (TNF) and , or transforming growth factor (TGF) also act on DRG neurones but usually via intermediary inflammatory target or Schwann cells [42, 50, 55, 61], stimulating the release of sensitizing inflammatory mediators [29] or neuroactive growth factors/neurokines [71]. The presence of these neuroactive cytokine/growth factors in peripheral targets may contribute to the maintenance of the normal phenotype of the cells, but a relative decrease or an increase after axotomy or during inflammation [30, 31, 37, 43, 106, 118] induce changes in phenotype. Changes in phenotype may contribute to pain hypersensitivity by modifying levels of neuromodulators such as the tachykinins or CGRP, upregulating novel peptides with particular central actions, for example galanin or cholecystokinin (CCK) [37], modifying presynaptic receptors (opiate and GABA), peripheral transducing elements and receptors (e.g. adrenergic or capsaicin receptors), altering ion channels and growth status.

To examine this we have recently investigated whether inflammation changes the levels of growth factors known to act directly or indirectly on neurones. We have first confirmed that inflammation elevates NGF concentration in the periphery [23, 118] and extended this by showing that neutralizing anti-NGF antibodies prevent both inflammatory hypersensitivity and the upregulation of neuropeptides in primary sensory neurones produced by inflammation *in vivo* [118]. This finding is in keeping with previous studies that NGF influences the sensitivity of primary sensory neurones [52] and has major implications for the understanding of the pathophysiology of inflammatory pain. It raises the possibility, moreover, that anti-NGF compounds could be candidates as novel analgesics for inflammatory pain, provided they do not disrupt essential NGF-mediated functions.

Neuropathic pain

Neuropathic pain, the pain produced by damage to the nervous system, is also characterized by central changes in sensitivity including A -mediated pain [6, 32, 70]. This may be the consequence of three different kinds of pathological change produced by nerve lesions [114]. First, a maintained state of central sensitization in response to ongoing ectopic C-fibre input either from the site of the injury [3, 19, 32] or the DRG [20] (the generator model). Second, decreased inhibition due to impaired inhibitory transmission [19, 123], as a result of either a decrease in GABA levels [8] or an excitotoxic loss of inhibitory neurones [3] (the disinhibition model). We have recently shown that disinhibition results in a central hypersensitivity phenomenon [91]. Finally, A -mediated pain might be the consequence of a reorganization of synaptic connections in the spinal cord (the structural model). The latter possibility has emerged from work in my laboratory showing that axotomized A -fibres sprout from their normal site of termination in the deeper laminae of the dorsal horn into laminae I and II [98, 119], which are normally occupied only by A - and C-fibres [108]. This work has recently been confirmed in the cat [45]. We have also shown that the sprouted central terminals make novel synaptic connections in the superficial laminae [120]. The sprouted terminals may drive cells which normally receive C-nociceptor input [63] and in this way, contribute to touch-evoked allodynia.

After nerve injury, sympathetic fibres sprout around large dorsal root ganglion cells [58], and consequently sympathetic activity.after nerve injury may begin to activate A fibres, providing a unifying explanation for sympathetic and A fibre-mediated neuropathic pain.

It is likely that neuropathic pain in humans involves various combinations of these and other maladaptive changes that occur in response to nerve damage [2, 32], some of which may resemble inflammatory changes and others which will be quite different. What will be critical now, is to establish what initates which change and when, and to determine if the changes are reversible. It is particularly encouraging that neuropathic pain in laboratory animal models can be prevented by some manipulations such as preventing an injury discharge with local anaesthetic blocks [24, 85], NMDA receptor antagonists [59] or morphine [75] and that this is also true for patients with intercostal neuralgia [80] and phantom limb pain [39].

Conclusions

Although inflammatory and neuropathic pain are generally different in their presentation and natural history, related general pathophysiological mechanisms may be involved. These include alterations in chemical expression or phenotype [23, 37, 54, 68, 93] and growth status of primary sensory neurones [51, 92, 117] and increases in excitability or disinhibition of dorsal horn neurones [3, 21, 91, 123]. There are important differences though; nerve injury but not peripheral inflammation is associated with the development of ectopic activity [11, 20, 40], adrenergic sensitivity [10, 73, 82], dorsal root ganglion cell death [1, 78], transganglionic atrophy [1, 7] and possible transynaptic degeneration after nerve damage [94], whereas inflammation involves alterations in structurally intact neurones, including changes in the afferent and efferent functions of the peripheral terminal. Painful conditions such as vertebral disc prolapse, cancer and soft tissue trauma are likely to involve combinations of inflammatory and neuropathic pain, while others like arthritis or

diabetic neuropathy will be predominantly inflammatory or neuropathic. Fibromyalgia, where there is no apparent peripheral pathology, may be a clinical manifestation of altered central processing.

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