RECENT ADVANCES IN THE PATHOPHYSIOLOGY OF ACUTE PAIN

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The peripheral receptors of the sensory systems have transduction mechanisms that ensure maximal sensitivity to only a small spectrum of the wide range of stimuli that impinge upon them. Because there is a minimal overlap in sensitivity between the receptors of the different sensory systems, each is specialized and possesses its own "specific" or "adequate" stimulus. Maintaining this receptor-generated specificity, sensory pathways in the central nervous system are, to a considerable extent, arranged so that inputs from similar classes of receptor run through neural networks that are closely aligned anatomically. This enables functionally discrete systems such as the visual, auditory and tactile sensory systems to be seen to be structurally distinct. At each level of the neuraxis where sensory information is relayed, complex processing and modulation occurs to assist in defining the location, onset, duration, intensity and dynamic properties of a stimulus. Ultimately, activation of the highest levels of the nervous system may produce a conscious awareness of the stimulus, either as a relatively pure sensation or as a complex hybrid one resulting from parallel sensory inputs. In this way photons falling upon the retina are unambiguously perceived as light, movement of hair cells in the cochlea as sound and deformation of mechanoreceptor terminals in the skin as touch.

Is pain the perceptual consequence of the activation of a specialized sensory system that resembles in its neural organization the visual, auditory or tactile sensory systems? This is not an abstruse academic issue, but the key to understanding the pathophysiology of pain. The current view of many basic scientists and clinicians is that there is a sensory system specific for pain, which has its own receptors, pathways and cortical areas. However, there is evidence that challenges this belief. It suggests that, when pain is viewed from a clinical perspective, it is not the inevitable consequence of the activation of a unique pain system but is, instead, an expression of dysfunction in the somatosensory system.

A major reason for the confusion over the nature of pain is that we have all learnt to use the same word, pain, to label a wide variety of sensations as soon as they become uncomfortable, unpleasant, irritating, disturbing, severe, intense, distressing, intolerable or disabling. We must resist the temptation of thinking that, because we use a single word to describe these sensations, a single neural mechanism is involved. Pain can instead be divided into two distinct and qualitatively different categories. These are what I have chosen to call physiological pain and pathological pain. The distinction between the two depends on the argument that physiological pain is a "normal" sensation, while pathological pain is the consequence of an "abnormal" state [52].

PHYSIOLOGICAL PAIN

This term is used to define the range of transient sensations we experience in response to stimuli that are of sufficient intensity to threaten to damage tissue or produce small localized areas of injury, but which neither provoke an extensive inflammatory response nor damage the nervous system. Sherrington, at the turn of the century, devised the term "noxious" to describe precisely such stimuli [41]. Physiological pain can be elicited by mechanical, thermal or chemical stimuli and clearly defined thresholds can be established experimentally in trained subjects, at which the sensation stops being one of pressure, hot or cold and becomes painful [21]. The intensity of stimuli that reach the pain threshold is almost identical to that which activates the flexion
withdrawal reflex [47]. Further increases in the intensity of the stimulus produce a quantifiable stimulus–response relationship until the pain exceeds a certain tolerance level. Although it is possible, using controlled noxious stimuli in trained subjects, to obtain reproducible and quantitative psychophysical data, physiological pain differs from the sensations produced by innocuous stimuli in being particularly susceptible to interference from psychological factors such as anxiety or suggestion and by being accompanied both by autonomic and affective responses.

The reason for calling the sensation elicited by transient non-tissue damaging noxious stimuli “physiological pain” is two-fold. First, in terms of the sensory apparatus involved and the nature of the stimulus–response relationship there are similarities with other physiological sensations. Second, from a teleological perspective, physiological pain has a protective role: because of the unpleasant nature of the sensations involved, we learn to avoid certain stimuli and, because of the simultaneous activation of the flexion withdrawal reflex there is an automatic removal of the body from the source of the stimulus. Physiological pain is something we all experience frequently in our daily lives by touching hot or cold objects or by exposure to intense external mechanical stimuli that may scratch or prick our skin and, indeed, such pain occurs frequently in the clinical context with interventions such as injections.

**PATHOLOGICAL PAIN**

Pathological pain is that sensation that arises as a consequence of either the inflammatory response that accompanies substantial tissue injury, or damage to the nervous system. Because the natural history, nature and pathophysiology of the pain associated with these two states differs considerably, it is convenient to subdivide pathological pain into inflammatory and neuropathic pain [52]. In spite of their differences, there are important common features in which both types of pain differ from physiological pain. These are:

1. The pain may occur in the absence of any apparent stimulus.
2. The response to suprathreshold stimuli may be exaggerated in either amplitude or duration.
3. The threshold for eliciting pain decreases to a level where what would normally be an innocuous stimulus begins to elicit pain.
4. The sensation of pain may spread from the site of an injury or a lesion to un-injured or unaffected tissue.
5. Pathological interactions between the sympathetic and somatosensory systems may occur.

The presence of all or most of these features (spontaneous pain, hyperpathia/hyperalgesia, allodynia, referred pain, sympathetic dystrophy, sympathetically maintained pain) is what makes clinical pain pathological. Pathological pain involves the disruption of the normal selectivity or specialization of the somatosensory system. Instead there is aberrant convergence and the mismatch of stimulus with response. There is no “adequate” stimulus for pathological pain; it may occur in response to the lightest of touches (e.g. in causalgia) or in response to mildly noxious stimuli; the sensation is excessive and more prolonged than would be expected for the nature of the stimulus, and it may even occur in the absence of any apparent stimulation, as after brachial plexus avulsion injury.

**THE PATHOPHYSIOLOGY OF PAIN**

There is no single pathophysiological mechanism responsible for the production of pain. Physiological pain results from the activation of high threshold receptors in the periphery (nociceptors) which feed in complex ways to a series of ascending pathways that carry information from the spinal cord to the brain. In contrast, inflammatory and neuropathic pain appear to be the consequences of adaptive and maladaptive disturbances which occur within the somatosensory system and can be triggered by a wide variety of different situations. Inflammatory pain retains some teleological resemblance to physiological pain, in that a protective role for the phenomenon can readily be appreciated: tenderness will help to avoid further damage to an injured area while healing takes place. However, neuropathic pain appears to offer no such benefit to the patient and, instead, is the pathological product of a disturbed nervous system.

The differences between the different types of pain are not absolute. In certain circumstances there may be a continuum between them, so that a noxious stimulus which elicits a brief burst of “physiological pain” lasting seconds, may then go on to damage tissue, provoking an inflammatory response setting in train the changes that produce “inflammatory pain” which may last...
from hours to days. Persistent peripheral tissue injury could, in some situations, lead to either a reactive or a direct modification of the nervous system, thereby inducing chronic "neuropathic pain". What has to be decided is if the neural apparatus that is responsible for physiological pain is identical to that which generates pathological pain. Is physiological pain the result of a transient activation of a specific pain system and clinical pain the consequence of a sustained activation of the same system?

The answer to this key question is both yes and no. Yes, in the sense that elements of the nociceptive neural mechanisms that produce physiological pain are involved in the generation of pathological pain. No, because pathological pain results from changes in this and other somatosensory systems, rather than simply from the continued activation of only this system. The nervous system cannot be viewed as a rigid "hardwired" system where certain patterns of input will necessarily produce, in a predetermined fashion, a certain output and all that varies is the amplitude and duration of the signals. Instead, we must recognize that the nervous system is plastic or modifiable and that it is this capacity for change that is responsible to a large extent for the generation of clinical pain states. The plasticity of the nervous system can either be adaptive or maladaptive. Adaptive plasticity underlies the ability of the nervous system to compensate for damage or to produce changes in function appropriate to changes in the environment. Maladaptive plasticity comprises those changes in the nervous system that lead to a disruption of function and, therefore, it may be considered to be a disease state. To a large extent physiological pain is a sensation that reflects certain specific types of peripheral stimuli, while pathological pain is a sensation that is a consequence of changes within the nervous system that result in an alteration in the way in which information from the periphery, some of which may be quite normal, is handled.

There are four categories of change to the nervous system that can result in the pathogenesis of clinical pain:

1. peripheral sensitization of primary afferents
2. central sensitization of dorsal horn neurones
3. abnormal properties in central circuits
4. permanent changes in the nervous system.

The first three tend to occur during inflammatory pain, while the last three tend to occur during neuropathic pain. There are considerable experimental data on the first two phenomena, less on the third and almost nothing on the fourth. This review will, as a consequence, deal only with peripheral and central sensitization and their contribution to acute pain states.

**Peripheral sensitization**

Noctceptors, both A delta and C, are characterized by high thresholds and require intense stimuli to activate them [7, 26, 37]. This property is reflected in the higher intensity of stimuli that are normally required to generate physiological pain, compared with those that elicit innocuous sensations. However, the sensation of pain does not follow the firing pattern of nociceptors in a simple, predictable fashion, and the central processing of the afferent input, in terms of both summation of inputs and inhibitory interactions, is extremely important [1, 21, 35, 37].

After peripheral tissue injury the threshold for eliciting pain decreases both within the area of the injury (primary hyperalgesia) and in the surrounding uninjured tissue (secondary hyperalgesia) [8, 37, 44]. In the zone of the injury, the increased responsiveness is to thermal and mechanical stimuli, whereas in the surrounding zone the sensitivity is exclusively to mechanical stimuli [8]. Contributing to the primary response to heat are changes in the sensitivity of the thermal nociceptors [36]. These include a decrease in threshold, an augmented response to supra-threshold stimuli and spontaneous activity. Similar changes have not so far been found for the mechanonociceptors, even though mechanical hyperalgesia is a prominent feature of tissue injury in man and animals [37, 51]. This means either that the afferents that change after tissue injury have not been found yet, the assumption being that there may be a population of totally insensitive afferents that will not be detected unless their receptive field area is injured, or that the peripheral injury induces alterations in the way that the CNS responds to normal stimuli (see section on central sensitization).

The precise molecular mechanisms responsible for the alteration in the sensitivity of a nociceptor after tissue injury are not known. Many of the biochemicals released directly or indirectly by damaged tissue (bradykinin, histamine, substance P, the leukotrienes, prostaglandins and other arachidonic acid metabolites) have the capacity either to excite nociceptors or to increase their...
sensitivity [3, 22, 37]. Although a role for mast cells in these changes has been recognized, there is recent evidence suggesting that the terminals of post-ganglionic sympathetic efferents are also involved, possibly by the release of a neuropeptide or of ATP [23]. The chemosensitivity of nociceptors may be both a part of the way in which they detect a change in their local environment (e.g. damaged tissue) and the means by which their sensitivity to non-chemical stimuli is altered. If an inflammatory mediator binds to a receptor on an afferent terminal and induces a change in the level of a second messenger in the terminal, this could (without necessarily involving any action potential discharge) result in an alteration in the afferent’s sensitivity by the phosphorylation of a membrane-bound receptor [38].

The spread of the sensitization of primary afferents by the axon reflex is the mechanism which Lewis originally suggested could explain the generation of secondary hyperalgesia in uninjured tissue [24]. Although the antidromic activation of C fibre afferents does occur and contributes to the neurogenic inflammatory response, when peripheral changes in sensitivity in the zone of secondary hyperalgesia are detected [14] they are too small to account for all the injury-induced alterations in either behaviour or sensibility [36]. Consequently we are forced to look centrally for an alternative process which, by acting in concert with peripheral sensitization, can produce the full picture of clinical pain [49, 51].

Central sensitization

The peripheral terminals of primary afferent neurones are specialized to encode particular features of the stimuli that impinge upon the body surface. Centrally, this specialization is maintained by the order in the spatial location and morphology of the central terminals of the afferents [5, 54]. The dorsoventral distribution of the central terminal arbors in the dorsal horn of the spinal cord reflects their modality responsiveness and threshold [5, 25, 42], while their mediolateral and rostrocaudal position is related to the location of their peripheral receptive fields [43]. This somatotopically organized afferent terminal map provides a structural framework for the transfer of the electrical activity generated by cutaneous stimuli to dorsal horn neurones.

The cutaneous receptive fields of dorsal horn neurones, while somatotopically organized [2, 6, 9, 55, 56], do not have the same degree of high spatial order that primary afferents have. Assessment and classification of the cutaneous receptive fields of neurones in the dorsal horn have, however, largely been based on the assumption that the receptive field properties of these neurones are fixed and unchangeable. Nevertheless, spontaneous variation in receptive field properties has been observed [12] in response to descending influences [28], pharmacological agents [39, 65] and as a result of nociceptive afferent input [11, 13, 15, 40, 57, 60]. One of the first indications that afferent input could alter the response properties of spinal neurones for prolonged periods emerged from studies on flexor alpha motoneurones. These neurones are characterized by absent spontaneous activity and discrete high threshold cutaneous receptive fields, stimulation within which evokes a phasic discharge of the motoneurones [10, 59]. Peripheral tissue injury results in the development of a background discharge in the motoneurones, a decrease in the threshold of their receptive fields and a change in the pattern of the reflex from phasic to tonic [49, 50, 58]. These hypersensitivity changes, which resemble pain producing hypersensitivity states after injury in man [37, 52], can be duplicated by brief (20-s), low frequency (1-Hz) trains of electrical stimuli to peripheral nerves, provided that the stimulus intensity is sufficient to activate C fibre afferents [46, 61]. Different C fibre afferents have, moreover, different central effects, depending on the tissue that they innervate, muscle afferents having more prolonged actions than cutaneous ones [46]. The size of the cutaneous receptive fields of the flexor motoneurones expands after peripheral injury or brief C fibre afferent conditioning stimuli, including in many cases the recruitment of novel contralateral inputs [49].

Brief afferent conditioning stimuli have more recently been shown to induce prolonged changes in the receptive field properties of dorsal horn neurones, including a population that projects to the brain [11]. These changes, which have a time course similar to that of the facilitation of the flexion reflex, include both expansions in the size of receptive fields and a change in the types of stimuli that activate these cells. These changes indicate that a static classification of the receptive field of a neurone does not take into account its potential response repertoire. A “nociceptive-specific” neurone in one context may, for ex-
ample, begin to respond to low threshold afferent fibres in another.

Intracellular studies of dorsal horn neurones in vivo reveal the way in which receptive plasticity occurs by demonstrating that, in addition to an impulse firing zone (that area of skin where stimulation generates a discharge of action potentials), the receptive fields of many dorsal horn neurones also contain a subliminal zone (that area of skin where the stimulus only produces subliminal or subthreshold responses). The subliminal responses of dorsal horn neurones represent a reservoir of functional activity that is potentially available, if either the amplitude of the subthreshold inputs or the excitability of the cells, increases [57,60]. Under normal circumstances the postsynaptic potentials generated by primary afferents are too brief to produce anything other than a few hundred milliseconds of perturbation of excitability and this, together with segmental and descending tonic and phasic inhibitory mechanisms, acts to stabilize receptive fields. However, when peripheral injury activates high threshold afferents, they trigger alterations in the spinal cord—the phenomenon of central sensitization—that recruit the subliminal components of the receptive fields to a level where they become suprathreshold, and these changes alter the way in which peripheral input is handled by the spinal cord and, therefore, by the higher centres to which the information is ultimately transferred [57].

How do C afferent fibres produce long lasting changes in the dorsal horn? The most satisfactory explanation at present is that these afferents have at least three different actions on dorsal horn neurones:

1. They produce a fast transmitter-mediated excitatory input to those cells with which the C fibres make a direct monosynaptic contact [17,18]. In this way they transfer information relating to the location, onset, duration and intensity of high intensity peripheral stimuli.
2. As a result of the release of neuromodulators (co-released from the same terminal as the fast transmitters) they produce a slow excitatory potential [20,64], giving the afferents the capacity to produce progressive response increments when stimulated repeatedly [31] (wind-up). Thus the identical stimulus evokes successively larger and larger responses as a result of summation of the slow potentials [20].
3. Brief C fibre inputs can produce prolonged alterations in receptive field properties which outlast the periods of both the stimulus and the depolarization, and therefore are not directly linked to a sustained synaptic input [11,57].

The fast excitatory transmitter is likely to be an amino acid such as glutamate which, by acting on quisqualate/kainate or other similar receptors, will produce a short duration inward current, generating a fast monosynaptic excitatory postsynaptic potential lasting approximately 10 ms [17,19]. Simultaneous release of peptides such as substance P or calcitonin gene related peptide [63], which are contained within the same afferent terminal [4], produces further inward currents [32], but with a longer latency and a longer duration as a result of acting on calcium and sodium channels and by decreasing outward potassium current [33,34,45]. Slow potentials produced by small calibre afferents last for tens of seconds and provide the opportunity for considerable temporal summation [20]. Such temporal summation has been shown in human volunteers to be important in the build up of pain that occurs when noxious stimuli are repeated at low frequencies [35].

How can these postsynaptic actions of small calibre afferents which last from milliseconds to seconds produce changes that last for hours? The key to this is a change in intracellular calcium or other second messengers produced during the course of the slow potential. The depolarization may itself increase calcium entry into the cell by opening voltage-dependent calcium channels [27,48] or by decreasing magnesium blockade of NMDA receptors [30]. Alternatively, the changes in second messengers may be independent of depolarization and instead be produced by a receptor-mediated increase in calcium, cyclic AMP, cyclic GMP, IP3, etc. Second messenger systems can, by acting through protein kinases, modify excitability for prolonged periods by phosphorylating ion channels or membrane-bound receptors. Alternatively, they may produce even longer lasting changes by altering gene expression [16,53].

Such a series of events shows how a noxious stimulus, by activating C fibre afferents, can change the excitability of dorsal horn neurones and alter their receptive field properties. Alterations in sensory processing in the dorsal horn will ultimately be reflected as altered perception of peripheral stimuli, including feeling pain in response to innocuous ones. What we feel then is
not necessarily an accurate indication of the nature of the stimulus. The alteration in the excitability of dorsal horn neurones also alters the activity generated in preganglionic sympathetic moto-neurones. Sympathetic reflexes will be exaggerated and prolonged in much the same way as flexion reflexes. This has important peripheral consequences, because of the interactions between the terminals of postganglionic sympathetic efferents and the terminals of primary sensory neurones [23]. Sympathetic activity has the capacity to drive injured afferents, which develop an increased sensitivity to alpha-adrenergic stimulation. In this way a positive feed forward circuit is established in which afferent input initially generates central sensitization, which increases sympathetic outflow, which further increases afferent input, etc. [52].

CONCLUSIONS

Three important predictions related to the treatment of pain can be made on the basis of recent information on the pathogenesis of clinical pain. The first of these is that the adequate management of such pain will require techniques that are aimed at the changes that can occur in the central nervous system, instead of only interrupting the flow of sensory signals. In other words, the aim should not be to produce total analgesia, which blocks physiological as well as pathological pain, but to depress or reverse afferent-induced excitability changes in central neurones. The opioids are a good example of drugs which at appropriate doses can do precisely this. In order to design drugs or techniques that are able to reverse this modification of the central nervous system, it is clearly vital that we understand precisely what these changes are at cellular level.

The second prediction is in many respects a corollary of the first, and it is simply that the most effective way of treating clinical pain is to design management procedures that prevent the occurrence of plasticity in the nervous system. There is experimental evidence that the dose of morphine required to prevent C fibre induced excitability changes from occurring in the spinal cord is an order of magnitude lower than that required to suppress these changes once they occur [62]. Recent clinical trials have confirmed this by showing that postoperative pain is decreased if the patient has either a local anaesthetic block, such as an extradural, or is given morphine before the surgical intervention [29].

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Any surgical procedure that generates a barrage in the small calibre afferents will, in a lightly anaesthetized patient, produce changes in the central nervous system that will subsequently lead to the amplification and prolongation of postoperative pain. Ideally, treatment of pain should begin before it is required. Using the same rationale, it may also be possible therapeutically to decrease some of the chronic problems that follow deafferentation (i.e. phantom limb pain) by modifying the afferent signals that may contribute to maladaptive plasticity.

The third prediction is that treatment of established pain will be most effective when attempts at returning a disordered nervous system to normal are directed not only at trying to break the afferent limb that sets up the changes in the nervous system, but also at acting on the sympathetic disturbances that perpetuate the disorder. Strategies for treatment must recognize and aim to eliminate both those factors that are responsible for initiating the vicious circle of maladaptive plasticity and those which perpetuate it.

The treatment of pain should not simply be the application of techniques that suppress sensation. We need to understand the natural history of the different pain states in order to interrupt their development. This understanding will only arise from an intensive analysis of somatosensation at a basic science level. The questions that need to be asked, though, should be directed by clinical observation. Clinicians dealing with pain need, in turn, to recognize that the nervous system reacts dynamically both to the situations that produce the pain in their patients and to their clinical interventions, some of which may exacerbate rather than reduce pain.

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