Pain—from periphery to brain

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Abstract

Pain is not simply due to the activation of peripheral nociceptors but to multiple factors. Part of the article is a review of scientific work on such factors at the different levels of the peripheral and central nervous system, with particular reference to possible new therapy strategies. A second part describes some aspects of clinical assessment of persistent pain conditions, such as differential diagnostics between musculoskeletal nociceptive and neurogenic pain, between referred pain from a musculoskeletal focus and projected neurogenic pain, and between psychogenic pain and pain with a somatic cause.

Introduction

Over the past 10 years there has been a growing awareness that pain is due not simply to the activation of peripheral nociceptors but to multiple factors, and is therefore susceptible to variable treatments. Depending on the etiology, pain may be classified into several categories, such as nociceptive, neurogenic and chronic pain syndromes. Musculoskeletal and visceral pain states, both nociceptive, are characterized by hyperalgesia (tenderness). However, despite belonging to a similar category, the pain is triggered by different mechanisms. In contrast to cutaneous and musculoskeletal nociceptors, visceral nociceptors are quiescent and relatively insensitive to mechanical stimuli unless the tissue is inflamed when phenotypic changes occur. Injury or disease of the nervous system causes neurogenic pain which is often severe and intractable and may not respond even to powerful opiates. Peripheral nerve damage may lead to the appearance of ectopic impulse discharge in both large- and small-diameter primary afferent neurons. The ensuing hyperexcitability results in, not only spontaneous ectopic discharge, but also hypersensitivity to a broad range of stimuli. Noradrenaline released by sympathetic efferent activity causes sustained and sympathetically maintained pain. Recent studies suggest that there is a third pain syndrome, distinct from the neurogenic and nociceptive, where pain is related to a sickness response that occurs with exposure to chemical compounds and infectious agents. This type of illness has now been studied at the level of interactions between the immune system (inclusive of cytokines) and circuits activated by a subset of subdiaphragmatic vagal afferents. Central changes produce systemic heightened pain sensitivity (hyperalgesia or ‘hurting all over’), with other central components such as fever, malaise, anorexia and activation of the endocrine pathways.

Despite a wealth of experimental literature about the effects of gender on pain perception, its importance to analgesic response has only recently been evaluated. In animal studies, females are seen to exhibit increased sensitivity to noxious stimuli, and pain responsiveness can be influenced by sex steroid hormones. Males obtain greater morphine-induced antinociception than females and their responses are also modulated by sex steroid hormones. Finally, there is evidence that in humans kappa-opioid analgesics are significantly more effective in females. It should be noted that, although females report greater sensitivity and lower tolerance to strong electrical stimulation than males, this may be partly attributable to the additional factors of anxiety and hypervigilance (i.e. increased attention to external stimulation and a preoccupation with sensations of pain) seen in females.

Primary afferent nociceptor terminal

Recent excitement in the field of pain research prominently devolves from discoveries of the molecular and cellular mechanisms that underlie transducer function in primary afferent nociceptors. The most common class of primary afferent nociceptors (polymodal nociceptors) is activated by noxious stimuli of
thermal, mechanical or chemical origin. Thermal nociceptive transduction could involve both a nonselective cation channel that is activated by heat-induced elevation of the intracellular calcium level and a vanilloid (capsaicin) receptor (VR-1), which is also activated by heat at noxious levels. Specific voltage-gated channels also have key roles in inflammatory pain. Modulation of tetrodotoxin-resistant sodium channels (SNS or PN3) in particular play significant roles in the primary afferent nociceptor sensitization induced by inflammatory mediators. Prostaglandin E2 was able to bring about an increase in the peak current through tetrodotoxin-resistant sodium channels and cause a hyperpolarizing shift in its activation curve as well as in the steady-state inactivation curve. This observation is important in the understanding of acute and chronic inflammatory states, since the sensitization of primary afferent nociceptors by prostaglandin E2 and other hyperalgesic inflammatory mediators is believed to be a major contributor to them. Many inflammatory mediators (e.g. prostaglandin—prostacyclin, serotonin and adenosine) act through the cAMP second messenger system. Ligand-gated ion channels also have important roles in peripheral pain mechanisms. A vanilloid-(capsaicin)-gated ion channel, activated by noxious heat as well as vanilloids, modulated by a low pH and specifically expressed in primary afferent nociceptors, has been cloned, an achievement with some considerable clinical significance, as capsaicin, an excitotoxin, is effective in ameliorating certain chronic pain states.

Although multiple growth factors contribute to the function and survival of AD- (small-diameter, myelinated) and C- (unmyelinated) fibre nociceptors, the role of the nerve growth factor (NGF) has formed the main focus for most studies. NGF levels have been found to be upregulated during inflammation. Administration of NGF produces hyperalgesia (overall tenderness) in rats, and in humans, a prolonged muscular pain. The low affinity NGF (P75) receptor may also contribute to NGF’s effects on pain and hyperalgesia, and mice with deleted P75 exhibit loss of heat injury-induced hyperalgesia. Conversely, in some patients with congenital insensitivity to pain, mutation of the high affinity (TrkA) receptor has been reported.

NGF is an inviting target for the design of pain therapies: a TrkA-IgG fusion molecule and anti-NGF antisera, which acts as an NGF antagonist, was found to decrease experimental inflammatory pain. There is evidence from some nerve injury pain models that this treatment may modify neuropathic pain, and it has been suggested that tyrosine kinase inhibitors might therefore serve as novel analgesic drugs to reduce the effects produced by NGF activation of TrkA.

**Pain processing in the spinal cord**

C-fos immuno-histochemistry, complementing electro-physiological techniques, provides a straightforward anatomical method of identifying those populations of cells in the dorsal horn of the spinal cord responding to noxious stimuli. Recent studies characterizing the internalization of specific receptors (i.e. the substance P receptor) following noxious stimulation, offer both anatomical and functional correlates of ‘first’ synapse transmission. Further, based on the model of 6-adrenergic receptor desensitization, studies evaluating substance P’s role in the transmission of nociceptive information at the ‘first’ synapse level confirm and expand the work with antibody-labelled microprobes.

It is demonstrated that the action of substance P, released following noxious stimulation, is more widespread and intense in the spinal cord when pain is chronic and inflammatory than in acute pain. In rats, substance P conjugated with the ribosome-inactivating protein saponin, intrathecally administered becomes internalized, and selectively both destroys substance P receptor-containing neurons and attenuates behavioural responses to noxious stimuli, suggesting a feasible target for new therapies.

**Pain modulation in the cord: enhancement**

Long-term potentiation (LTP) was characterized initially in the hippocampus. It has been shown to have early, intermediate and late (protein synthesis) components, to be Ca\(^{2+}\) and NMDA receptor-dependent, and to be affected by growth factors. An LTP-like phenomenon which can enhance rostral transmission of the nociceptive signal has been found to occur in nociceptive neurons at the level of the ‘first’ synapse. It is quite distinct from central sensitization, a hetero-synaptic facilitation of dorsal horn neurons that underlies tactile allodynia (pain response to normally non-painful stimuli) and sensory hyperalgesia. A second distinct phenomenon related to plasticity occurs in response to C-fibre injury where sprouts on non-nociceptive myelinated afferent axons extend into regions of the dorsal horn that are normally exclusive to nociceptive primary afferent terminals. This sprouting possibly creates a novel linkage of non-nociceptive afferents to ‘second order’ nociceptive neurons in the dorsal horn and may explain how it is possible for a non-noxious stimulus (Aβ-fibre-mediated) to evoke pain after nerve injury.
Pain modulation in the cord: inhibition

Rostral transmission of nociceptive messages can be attenuated by circuits that inhibit transmitter release at the level of ‘first’ synapse in the dorsal horn. Clinical use of this mechanism is mainly by infusing the different agonists for neurotransmitter receptors (e.g., opioids) into the spine. Several research groups have begun the definition of cortical and subcortical sites involved in responses to acute noxious stimulation in chronic pain states and pain modulation using functional magnetic resonance imaging (fMRI), positron emission tomography (PET) scanning with radio-labelled water and receptor ligands, and neuro-electric source imaging. One specific cortical area recently implicated in pain perception is the anterior cingulate cortex which ‘lights up’ with pain (both experimental and clinical), while a separate part of it has been found to be associated with attention tasks. Activity in this cortical site may be due to input from a pain-specific thalamic nucleus or to interaction of pain- and temperature-specific pathways to the insular cortex.

Another discovery from these imaging studies is that reversible plastic changes occur at the ‘brain’ level, which means that the altered cortical somatotopy seen in patients with phantom limb pain can revert to normal when the pain is alleviated.

Clinical pain control: placebo or ‘the real thing’

An extensive and growing body of evidence now exists for the ability of a variety of empirical, traditional and folk remedies to relieve pain. Critics have suggested that there is no basis for the analgesic effects of some of these therapies beyond a placebo response. Placebo analgesia perhaps operates through changing patients’ attentional focus, mood or expectations, though it is possible that these effects may be mediated by endogenous opioid peptides acting in circuits at both brainstem and spinal levels, since placebo analgesia in humans has been significantly reduced by the administration of the opioid antagonist naloxone. Additionally, a spinal cord circuit (from cord to brainstem) termed diffuse noxious inhibitory control appears to be involved in the effects of counter-irritation methods such as acupuncture.

Clinical implications

Clinical pain assessment can be done in many ways; a model in three steps has been found useful. The diagnostic steps are: (1) diagnostics of the pain condition (aiming at a ICD-10 code) including aetiology of pain; (2) type of pain: nociceptive, neurogenic, psychogenic, and idiopathic (unknown origin); and (3) consequences in functioning (according to e.g. WHO-ICHF) of the pain condition: impairments of body function, activity limitations, participation restrictions, and whether environmental factors facilitate or hinder functioning and quality of life. The mainly corresponding steps for treatment and/or rehabilitation are: (1) etiological treatments; (2) symptomatic treatments; and (3) rehabilitation.

Clinical pain assessment is usually not associated with difficulties but takes some time and requires thorough examination. A common problem is to differentiate between musculoskeletal (nociceptive) and neurogenic pain. This is often important since these types of pain have different treatment strategies and also usually different contents of rehabilitation programmes. The criteria of (nociceptive) musculoskeletal pain can be described as: (1) the pain may exist during rest but a typical feature is that pain intensity increases during loading or movement; and (2) local signs of pathology (e.g. inflammation or dislocation) are found in the musculoskeletal system. The characteristic features of neurogenic pain are: (1) radiation of pain follows a distribution that corresponds to the damaged neuronal structure, i.e. extends along a neuroanatomically correlated area, e.g. a dermatome of a nerve root or innervation field of a peripheral nerve (projected area); (2) sensory deficits with neuroanatomical correlation; and sometimes (3) motor deficits hypertrophy. Since different kinds of nerve fibres are found in spinal and other peripheral nerves, other nerve fibres than nociceptive C-fibres are usually damaged too, by a nerve lesion. That is the reason why it is often rewarding to perform an examination of the distribution of the different cutaneous sensory modalities (and also sometimes motor functions/atrophies).

A recurrent clinical problem is the differential diagnosis between referred pain generated from a (nociceptive) musculoskeletal focus and projected neurogenic pain. This can be in the form of, for example, pain in the low back extending to a lower extremity or in the cervical spine combined with brachialgia. Features of brachialgia due to referred pain from a primary musculoskeletal focus can be (compared with neurogenic pain): (1) usually the pain localization is not as constant as in neurogenic pain (in principle, the more intensive the pain is in its focus, the larger extension and intensity of the referred pain); (2) referred pain is seldom reported to be in a particular finger (sometimes ‘all fingers’, sometimes only ‘hand’ in the same patient); (3) no clear permanent sensory deficit is demonstrable (temporary
small sensory alterations can be found in exceptional cases). When central sensitization is present, the differential diagnostics between neurogenic projected and referred pain may be more complicated.

Psychogenic pain is caused by psychiatric disease and is considered to be less frequent than the other types of pain. A criterion of this kind of pain is that there is no somatic cause of pain and that the pre-existence of psychiatric disease can be established according to acceptable criteria. Chronic pain is held to be a cause of depression, but in psychogenic pain the debut of depression ought to come first and then leads to pain symptoms in addition to the various symptoms of depression.

References

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