

The neurobiology of chronic pain states

Anthony Dickenson

Abstract

Plasticity enables alterations in transmission in nociceptive systems. It is this plasticity in the nervous system that can alter the linear relation between noxious stimuli and the perception of pain. In this way, a number of CNS mechanisms can alter neuronal activity, leading to abnormal ongoing and stimulus-evoked pains due to peripheral and central changes. Peripheral nerves can become sensitized, spinal cord neurons can be rendered hyperexcitable and ascending projections to higher centres can further trigger changes in descending controls from the midbrain and brainstem. Together, these changes, all of which appear to involve reversible physiological and pharmacological plasticity, can alter the relationship between an applied stimulus and the perceived response and so lead to persistent pain states.

Keywords Chronic pain; inflammation; N-methyl-D-aspartate; neuropathy; sensitization

Royal College of Anaesthetists CPD Matrix: 1A01, 1D00

Different types of pain

Although many pains arise from damage to tissue such as trauma, surgery and arthritis, chronic neuropathic pains can arise from a disease or lesion to both the peripheral and central nervous systems.

Characteristic symptoms experienced with chronic or persistent pain, resulting from these various causes, include expanded receptive fields, increased amplitude of response to a given stimulus (hyperalgesia), pain elicited by normally innocuous stimuli (allodynia) and spontaneous pain in the absence of external stimuli.¹

Sensory deficits can also exist in neuropathic pain. In addition, as pain persists, the affective and emotional responses along with the sensory aspects of the stimulus can alter. Although the sensory and psychological aspects of pain are separable, their neural pathways are interlinked. Furthermore, at both peripheral and central sites, mechanisms can amplify and prolong the painful stimulus so severe pain in the presence of relatively minor peripheral pathology can result.² Thus responses of spinal and supraspinal neurons are heightened after nerve or tissue injury leading to increased spontaneous activity and hyperexcitability of these neurons (Figure 1). This article considers these signalling systems and the changes therein in the context of chronic pain.

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Learning objectives

After reading this article, you should be able to:

- list the receptor and neurotransmitter changes after tissue injury
- outline the role N-methyl-D-aspartate (NMDA) receptor plays in sensitization
- understand descending modulatory pathways

Peripheral changes after tissue damage

Many changes in the periphery have been implicated in the development of the chronic stages of inflammatory pain where sustained activation and/or sensitization occurs due to chemical mediators released into the damaged tissue. The transmission of acute pain involves activation of sensory receptors on peripheral C-fibres, the nociceptors.³ These receptors include those that are able to transduce thermal and mechanical stimuli in the noxious ranges and also many families of chemical receptors that respond to algogens that are released into damaged tissue. In the acute stage, nociceptors respond to thermal and mechanical stimuli; however, when tissue damage and inflammation occurs, the actions of prostanoids, bradykinin, ATP, serotonin (5-HT), etc. on their excitatory receptors play a major role in sensitization and activation of C-fibres.

Other factors such as nerve growth factor and cytokines are also important at the peripheral level, and resultant changes in the phenotype of the sensory neurons can alter their responsiveness. This can lead to ongoing peripheral sensitization and activation, which causes a persistent drive into the spinal cord, so inducing central hyperexcitability. The actions of these mediators cause sensitization, as they reduce the threshold of the sensory nerves. This is the basis for the tenderness following injury to tissue.³ Prostanoids reduce the threshold for activation of sodium channels, and these mediators can similarly reduce the threshold of noxious heat receptors into the physiological body temperature range. Cyclooxygenase-2, is induced at the site of tissue damage so that this site becomes the source of algogenic prostanoids. Non-steroidal anti-inflammatory drugs (NSAIDs) may be useful in this circumstance. The triptans (drugs that act on the inhibitory 5-HT_{1B/D} receptors) are exclusively for headache and not for pains in other areas of the body. It is not clear at present whether the genesis of headache is at peripheral levels or due to central changes that in turn alter peripheral processes.³

Peripheral changes after nerve damage

In states of nerve injury there may be sensory loss as a result of the nerve lesion and also ongoing and stimulus-evoked pains. After nerve injury, many peripheral nerves display ectopic discharge, which may lead to an increased barrage of nociceptive signalling onto dorsal horn transmission neurones without a peripheral stimulus: stimulus-independent pain.⁴

Changes in the sodium channel populations on peripheral nerves and their subsequent aberrant activity have been of great interest in the development of pain states.⁵ Expression of sets of sodium channels on the peripheral neurons shows plasticity after

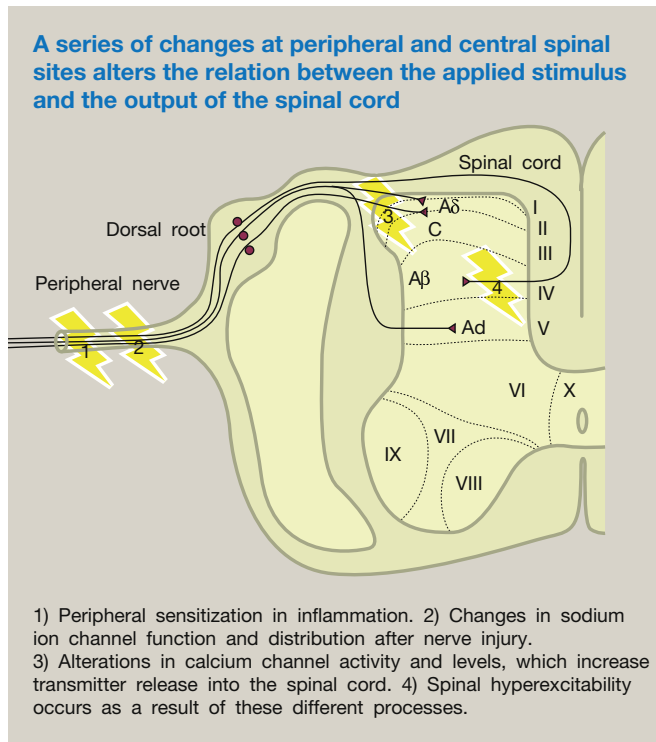


Figure 1

nerve injury. In particular NaV 1.7 and 1.8 appear to take part in the development of hyperexcitability and increased nociceptive transmission and the latter has been implicated in some familial pain disorders so validating these are key future targets.^{5,6} Abnormal sodium channel function is the pharmacological basis for the use of drugs such as carbamazepine, lamotrigine and local anaesthetics in patients with neuropathic pain. After nerve injury, demyelination and abnormal trafficking of sodium channels occur along the membrane of injured nerves and may also occur in their uninjured neighbours.⁴ This contributes to the development of central sensitization and amplification of peripheral events, possibly leading to allodynia and hyperalgesia seen in patients.

Calcium channels and the release of transmitters

Voltage-gated calcium channels (VGCC) permit neurotransmitter release from the central presynaptic terminals of peripheral fibres arriving at the dorsal horn of the spinal cord, and so are crucial for activation of spinal post-synaptic neurons, which promote propagation of the sensory signal to the higher centres of the CNS. As with sodium channels, there are a large number of calcium channels that play a role in neuronal excitability.⁷ Gabapentin and pregabalin have shown benefit in patients with neuropathic pain. Their target is the $\alpha 2\delta$ -accessory subunit of calcium channels, a subunit that appears to regulate the function of these channels.⁷ These drugs have been shown to be effective in reducing neuronal responses in a model of neuropathic pain but the lack of effect in normal animals highlights a clear state dependency of this agent's action and implicates a role for trafficking of the $\alpha 2\delta$ -subunit in neuropathic pain pathology. The $\alpha 2\delta$ -subunit has been shown to up-regulate after nerve injury

and this correlates not only with the development of behavioural and neuronal hypersensitivity in these animals but also with gabapentin's behavioural efficacy.⁷ However, these spinal calcium channels can be controlled by higher centres of the brain (discussed below).

Spinal transmission and its amplification

The release of transmitter into the spinal cord allows spinal neurons to be activated through post-synaptic receptors, which in turn activate local motor reflexes and parallel ascending projections to the brain to produce the sensory-discriminative and affective components of pain. Despite suggestions that nerve injury leads to anatomical reorganization and even neuronal death in spinal cord circuits, most studies do not support the idea that chronic pain involves permanent changes.

The major transmitters in peripheral sensory fibres are glutamate and a number of peptides, including substance P and calcitonin-gene-related peptides.⁸ Several receptors for glutamate have been identified in the brain and spinal cord, including N-methyl-D-aspartate (NMDA), α -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA), kainate and metabotropic glutamate receptors. All have a prominent localization in the superficial dorsal horn where incoming sensory fibres terminate. The parallel neuroanatomical distribution of these receptors in the spinal cord provides further support for functional interactions between NMDA and non-NMDA receptors in modulating nociceptive transmission (Figure 2). As in many areas of the CNS, the actions of glutamate on its receptors allow for both acute and persistent activity, and this latter function at spinal levels has major implications for chronic pain.^{8,9} The excitatory amino acids are found in most sensory fibres, including both large- and small-diameter fibres where, in the latter case, they are co-localized with peptides such as substance P. The coexistence of these two transmitters suggests that they are released together in response to a noxious stimulus. The NMDA receptor is an ion channel receptor that allows calcium and sodium to enter neurons, but the channel is blocked by physiological levels of magnesium ions at the resting membrane potential. The removal of the magnesium-ion block is mediated by peptides, which are coreleased with glutamate. After a brief acute stimulus, pain transmission from C-fibres is largely mediated by the action of glutamate on AMPA receptors.^{8,9} However, when the stimulus is sustained or its intensity is increased the action of substance P and probably other peptides removes the magnesium-ion block and the NMDA receptor is activated. Substance P therefore plays an important role in recruiting NMDA receptors and contributes to the cascade of events leading to the enhancement and prolongation of the neuronal response.⁹

Under conditions where the stimulus is maintained, NMDA receptors have been implicated in the spinal events underlying 'wind-up' whereby the responses of dorsal horn neurons are significantly increased after repetitive C-fibre stimulation despite the input remaining constant. This increased response of dorsal horn neurons is probably one basis for central hyperexcitability when afferent inputs continue to maintain the enhanced neuronal activity. Thus, when spinal neurones shift to a more excitable state the brain will receive greater and longer duration inputs for a given stimulus, receptive fields become greater and

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