The neurobiology of chronic pain states

Anthony H 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 and is important in the switch from acute to chronic 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 sensitization; neuropathy

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

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

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 leading to comorbidities such as depression and sleep problems. 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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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.

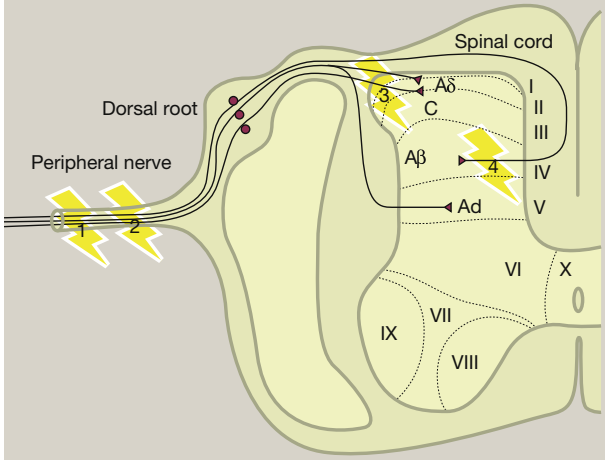
Other factors such as nerve growth factor and cytokines are also important at the peripheral level, and resultant changes in the phenotype of the sensory neurons can alter their responsiveness. This can lead to ongoing peripheral sensitization and activation, which causes a persistent drive into the 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. Cyclo-oxygenase-2, is induced at the site of tissue damage so that this site becomes the source of alogenic prostanoids. Non-steroidal anti-inflammatory drugs (NSAIDs) may be useful in this circumstance. The triptans (drugs that act on the inhibitory 5-HT1B/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.[5]

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.[4] Expression of sets of sodium channels on the peripheral neurons shows plasticity after nerve injury. In particular NaV 1.7 and 1.8 appear to take part in

A series of changes at peripheral and central spinal sites alters the relation between the applied stimulus and the output of the spinal cord



1) Peripheral sensitization in inflammation. 2) Changes in sodium ion channel function and distribution after nerve injury. 3) Alterations in calcium channel activity and levels, which increase transmitter release into the spinal cord. 4) Spinal hyperexcitability occurs as a result of these different processes.

Figure 1

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.[4,6] 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.[5] 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 α2δ-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 α2δ-subunit in neuropathic pain pathology. The α2δ-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 co-released 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 allodynia and hyperalgesia may ensue. The human counterpart

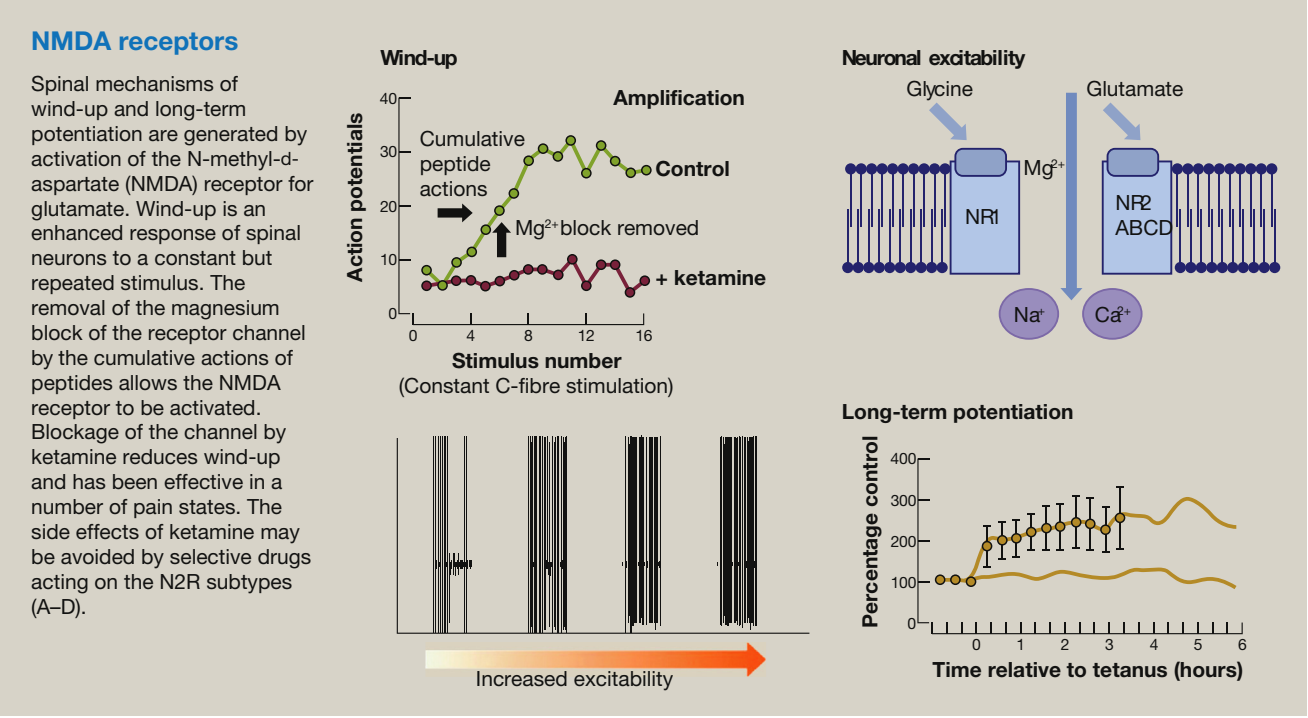


Figure 2

of wind-up is temporal summation, and this has been observed and modulated in some cases in many clinical pain syndromes, including neuropathy, ischaemic pain, fibromyalgia and whiplash.

Activation of intracellular second messenger cascades may then lead to altered gene expression, protein synthesis and therefore long-term plastic changes. Long-term potentiation (LTP) of dorsal horn neurons, caused by repetitive afferent stimulation, may be of importance in maintaining exaggerated neuronal responses for long periods after increased peripheral drive has subsided. Many preclinical studies have reported the activation of a number of early-onset genes and changes in intracellular signalling after persistent noxious stimuli, and these changes may act to switch sensory spinal neurons to a higher level of responsivity.[1,2,8,9]

Potentially, there are several ways in which the effect of released glutamate can be antagonized through NMDA receptor blockade but the ubiquitous nature of the receptor makes it hard to achieve therapeutic effects at the target site in the absence of adverse side effects. Antagonists at multiple sites on the NMDA receptor complex, including ketamine, have been shown to be effective in a number of animal models and in humans but the low therapeutic index means that side effects are common and the drugs cannot be easily used. Hopes for better agents lie in the subtypes of NMDA receptors.[8,9]

Processing of pain at higher centres

Pain is not just a sensation; there are also affective and emotional aspects of the stimulus that have major impact on the suffering experienced. Anxiety, sleep disorders and depression are common comorbidities in chronic pain patients. Certain spinal neurons project to thalamus and cortex and generate the sensory aspects of pain and the location and intensity, while others project in parallel to limbic areas.[2,10] Many of the midbrain areas involved in fear, anxiety, mood and autonomic responses are therefore contacted by pathways activated by painful stimuli. Feedback from higher centres can project onto descending pathways from the brain to the dorsal horn of the spinal cord, where modulation of nociceptive information occurs. Study of these facilitatory and inhibitory pathways has not only improved our understanding of the mechanisms of drugs used to treat pain, such as the antidepressants, but also our knowledge of events underlying the persistence of pain states.

Descending facilitations in pain

Most of the work in this area originally concentrated on the often tonically active inhibitory pathways, but more recently there has been growing interest in facilitatory pathways.[10–12] Pains from peripheral nerve injury, inflammation and cancer, arise from peripheral and then central spinal processes, but the brain determines the level of pain perceived. Increases in pain sensitivity that follow injury can be regulated by superficially located projection neurons of the dorsal horn of the spinal cord that respond to substance P. These project through the parabrachial area (an area activated in humans in hyperalgesic states) to the amygdala and hypothalamus, systems involved in the affective aspects of pain.[10] The pathways then relay to neurons in the brainstem rostroventral medulla (RVM), which appears to be the source of 5-HT in the spinal cord. The final arm is a descending serotonergic facilitatory pathway, terminating on excitatory 5-HT3 receptors in the spinal cord. In animal models of neuropathic and bone cancer pain states there are enhanced descending facilitatory controls of mechanical evoked responses of spinal neurons, mediated through the activation of spinal 5-HT3 receptors. These

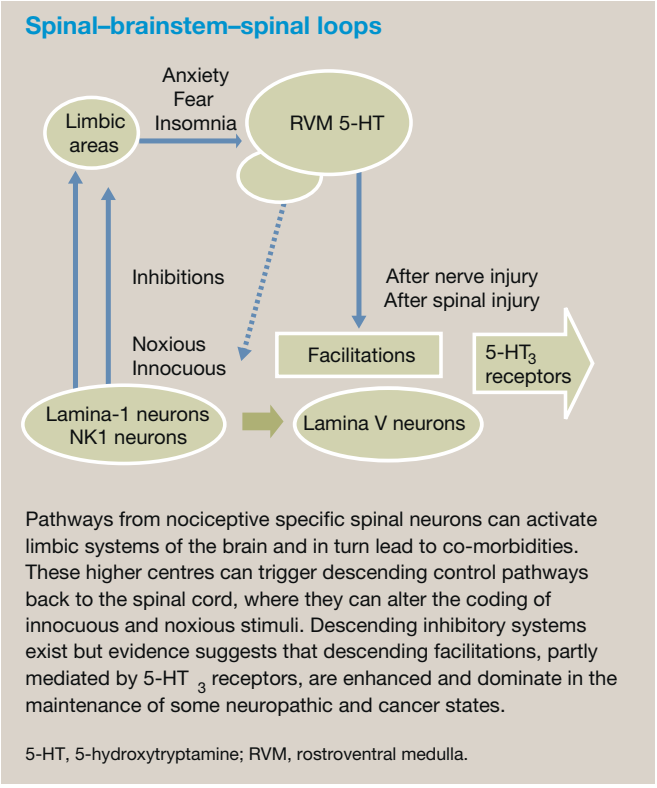


Figure 3

excitatory influences are likely to contribute to the later maintenance stages of pain from nerve and tissue injury and also regulate pregabalin actions at spinal levels.[10,11] Noradrenergic alpha-2 adrenoceptor inhibitions can act to balance descending excitations but these appear to be reduced after nerve injury.[10] Pain versus pain, conditioned pain modulation is a measure of descending inhibition and is lost in many pain states. It is also a predictor of persistent pain.[12] Thus the brain switches descending controls with a loss of inhibition and a gain of facilitation and this can be used to predict therapies in patients with neuropathy.[5]

Finally, these descending inhibitions and facilitations act alongside peripheral changes caused by tissue and nerve damage, and are independent of wind-up and LTP, thus adding another hierarchy of pain amplification (Figure 3).

These peripheral, spinal and supraspinal systems act in parallel and allow 'bottom-up' and 'top-down' modulation. Peripheral sensitization is accompanied by signs of inflammation, localized to anatomical areas related to the peripheral tissue damage that then drives central hypersensitivity. In nerve damage there appears to be a number of central compensatory changes for the sensory loss that lead to hyperexcitability. Of course, there are mixed pain states. Examples would be cancer pain and low back pain, where in some cases elements of tissue and nerve damage occur together. But even in the absence of a clear peripheral process, the spinal and supraspinal mechanisms can possibly still become active. Thus in fibromyalgia, it is conceivable that abnormal brain processing could potentially drive diffuse descending facilitations of spinal circuits and result in a diffuse pain state in the absence of peripheral pathology.[10]

Sensory phenotypes are starting to be used as a reflection of underlying mechanisms in patients and as potential predictors of therapy.[13]

The challenge produced by these multiple pain amplification processes in the different types of chronic pain may best be met by polypharmacy and combinations of non-pharmacological therapies and attention to the comorbidities that are part of the neurobiology of chronic pain. ◆

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