

Anatomy, physiology and pharmacology of pain

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Abstract

Pain is a complex perceptual experience. The transmission of pain involves both peripheral and central processes that can be modulated at many levels. Peripheral sensitization causes increased afferent input to the spinal cord. Numerous receptors and ion channels are involved. Physiological and anatomical changes within the nervous system are implicated in the development of neuropathic and visceral pain states. The complexity of pain transmission means there are many pharmacological targets and multimodal therapy is required to optimize pain control.

Keywords Allodynia; hyperalgesia; neuropathic; nociceptors; pain; sensitization

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Pain is a complex experience, initiated by sensory information conveyed from a noxious stimulus, greatly modified by affective (i.e. emotional), cultural and cognitive perspectives. Pain definitions are given in [Box 1](#). While the physical processes that relay a stimulus to become the 'feeling of pain' can be described, the nature of pain as a sensation and its overall significance to the individual is unique.

Pain pathways

The experience of pain is the final product of a complex information-processing network. Following delivery of a noxious stimulus, a series of electrical and chemical events occur. The first stage is **Transduction**, where an external noxious stimulus is converted into electrophysiological activity. In the second stage, **Transmission**, this coded information is relayed via the spinal cord to the brainstem and thalamus. Finally, connections between the thalamus and higher cortical centres control **Perception** and integrate the affective response to pain.

Transduction

Nociceptors are physiologically specialized peripheral sensory neurons that respond to noxious stimuli. These are free, unencapsulated peripheral nerve endings found in most tissues of the

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Learning objectives

After reading this article you should be able to:

- draw the neural pathway(s) by which pain is perceived
- outline the concepts of peripheral and central sensitization in chronic pain
- list pharmacological agents used to modulate pain

body including skin, deep somatic tissue (e.g. muscles and joints) and the viscera.

C polymodal nociceptors are the most numerous type and respond to a wide range of mechanical, thermal and chemical noxious stimuli. They are slowly conducting (<3 m/second) and associated with prolonged 'burning' pain. The more rapidly conducting (5–30 m/second) A δ nociceptors are associated with a more brief 'sharp' pain. They are myelinated and respond to mechanical and thermal stimuli.

Transmission

The central processes of primary afferent neurons enter the spinal cord via the dorsal roots where they synapse with second order neurons in the dorsal horn. In addition descending axons from the brainstem synapse in the dorsal horn and modulate nociceptive transmission.

The spinal grey matter contains the nerve cell bodies of spinal neurons and the white matter contains axons that ascend to or descend from the brain. In 1952 Rexed subdivided the grey matter into 10 laminae, Laminae I–VI correspond to the dorsal horn. C and A δ fibres terminate in laminae I (marginal zone) and laminae II (substantia gelatinosa). However, some A δ fibres also terminate in laminae V. Excitatory or inhibitory interneurons which regulate flow of nociceptive information are located in laminae V and VI. Cells which respond to innocuous stimuli such as light touch but not noxious stimuli are located in laminae III and IV; these are known as low threshold (LT) neurons.

In addition to nociceptive and LT neurons, wide dynamic range cells are present in laminae V. They receive input from a diverse range of neurons and have a large receptive field. Both innocuous and noxious stimuli are excitatory. However, in the surrounding region, non-noxious stimuli (A β fibres) are inhibitory. This may account for the pain-relieving effects of transcutaneous electrical nerve stimulation (TES) and the analgesia achieved by rubbing the affected area. Nociceptive input to the dorsal horn is relayed to the higher centres in the brain via several ascending pathways ([Figure 1](#)).

The spinothalamic tract (STT) is considered the major pain pathway and originates from neurons in laminae I and V–VII. The majority of axons cross locally and ascend contralaterally. Laminae I cells project to the posterior part of the ventromedial nucleus of the thalamus and mediate the autonomic and unpleasant emotional perception of pain. Neurons in the deeper laminae project to the ventral posterolateral nucleus of the thalamus and carry the discriminative aspects of pain.

Perception

Anatomical and physiological data show that several nociceptive related nuclei in the thalamus project to a number of cortical

Definitions

Pain

- An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage^a
- Pain is an emotion experienced in the brain; it is not like touch, taste, sight, smell or hearing. Pain can be perceived as a warning of potential damage, but can also be present when no actual harm is being done to the body^b

Neuropathic pain

- Pain caused by a lesion or disease of the somatosensory system^a

Allodynia

- Pain due to a stimulus that does not normally provoke pain^a

Hyperalgesia

- An increased response to a stimulus that is normally painful. The result of peripheral and central sensitization^a
- The perception of a painful stimulus as more painful than normal^b

Dysaesthesia

- Unpleasant abnormal sensations, whether spontaneous or evoked

Hyperpathia

- A painful syndrome characterized by an abnormally painful reaction to a stimulus, especially a repetitive stimulus, as well as a reduced threshold

^a Source: International Association for the Study of Pain (IASP).

^b Source: British Pain Society (BPS).

Box 1

areas. Recent studies using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have shown changes in blood oxygenation in those areas subserving nociceptive function. Multiple cortical areas have been identified including the primary and secondary somatosensory cortices, the anterior cingulate cortex (ACC) and the insular cortex (IC).

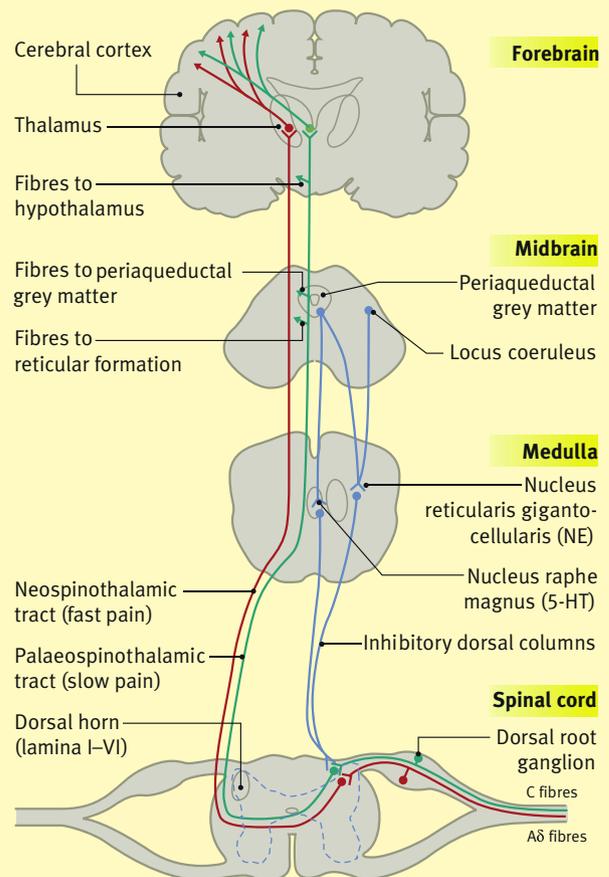
This widely distributed cerebral activity reflects the complex nature of pain involving discriminative, affective, autonomic and motor components.

Peripheral sensitization

Following tissue injury, there is a cascade of events involving primary sensory afferents, sympathetic efferents, white blood cells and platelets that induces peripheral sensitization (Figure 2).

An inflammatory soup, including endothelin, prostaglandin E₂, leukotrienes, bradykinin, cytokines, serotonin and adrenaline is released and causes increased excitability. Mast cells, macrophages and neutrophils release a number of pro-inflammatory substances. There is an increase in the efficacy of transducing

Spinal and supraspinal pathways of pain



Ascending nociceptive fast (red) and slow (green) pathways. Descending inhibitory tracts (blue). 5-HT, 5-hydroxytryptamine; NE, norepinephrine.

Figure 1

ion channels, a reduction in the firing threshold of voltage-gated channels and an exaggerated response following activation of these channels.

Voltage-gated sodium channels and the capsaicin receptor (transient receptor potential channel V₁ – TRPV₁) are intimately involved in activation and sensitization of peripheral nociceptors.

Cyclic adenosine monophosphate (cAMP) and protein kinases play an important role in the sensitizing action of many of the inflammatory mediators. In addition, signalling cascades are initiated which result in acute modulation of the protein structure of ion channels, enhancing their responsiveness. Alterations in gene expression and protein synthesis result in more persistent alterations in sensitivity.

Nerve growth factor (NGF) is increased in inflammatory states and induces hyperalgesia in experimental models. It alters the expression of a number of mediators involved in peripheral sensitization.

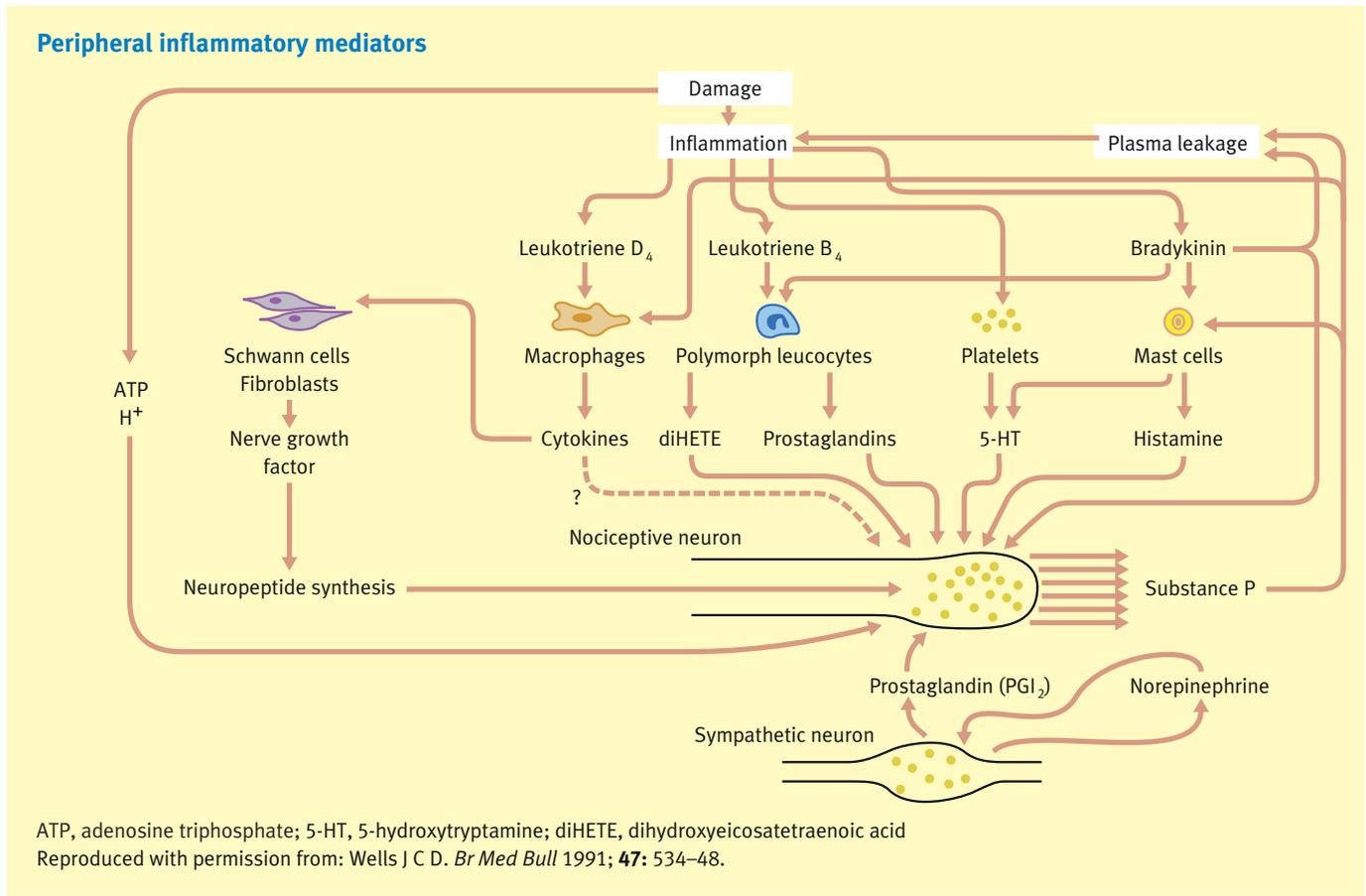


Figure 2

Central sensitization

The term central sensitization is used to describe the phenomena of wind-up, long-term potentiation and secondary hyperalgesia.

Wind-up occurs in response to repeated noxious stimuli from peripheral nociceptors. It refers to a process involving wide dynamic range neurons in the deeper levels of the dorsal horn. It is produced by repeated low-frequency activation of C-fibres causing a progressive increase in electrophysiological response. The N-methyl-D-aspartate (NMDA) receptor is closely involved in this sensitization process.

Long-term potentiation at individual synapses, thought to be important in learning and memory, may also be the mechanism of hyperalgesia and central sensitization. It has been shown to follow high-frequency stimulation of both A- δ fibres and C-fibres in the superficial dorsal horn and long outlasts the initiating stimulus.

Secondary hyperalgesia occurs in undamaged tissue adjacent to the area of actual tissue damage. It is thought to be due to an increased receptive field and reduced threshold of wide dynamic neurons in the dorsal horn.

The excitatory neurotransmitter glutamate has a key role in the activation of both α -amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptors and NMDA receptors in the dorsal horn, which generate excitatory post-synaptic potentials (Figure 3). Persistent excitatory transmission increases the intracellular calcium concentration activating second messenger kinases.

Descending pain mechanisms

The brainstem plays a crucial role in the modulation of pain processing at the spinal cord level. Pathways originating in the cortex and thalamus are relayed via the rostroventromedial (RVM) medulla and adjacent areas to the dorsal horn of the spinal cord. These areas of the brainstem also receive afferent input from the superficial dorsal horn and from the periaqueductal grey (PAG), nucleus tractus solitarius (NTS) and parabrachial nucleus, thus forming spinobulbospinal loops. The balance between the descending facilitatory and inhibitory pathways is subject to change following injury and an imbalance has been implicated in the development of chronic pain states. Serotonin, noradrenaline and endogenous opioids are important transmitters in the descending system and this is the basis for the use of antidepressants and opioids in the treatment of chronic pain.

Neuropathic pain

Neuropathic pain occurs as a consequence of injury or disease affecting the somatosensory nervous system. There are many causes, including trauma, infection, ischaemia, neoplasia and chemical/drug induced. Work in animal models suggests that the peripheral and central sensitization processes described already are involved in the development and maintenance of neuropathic pain. Furthermore, nerve injury induces A β afferents to sprout into the superficial pain transmitting areas of the dorsal horn and this process underlies the development of allodynia and hyperalgesia.

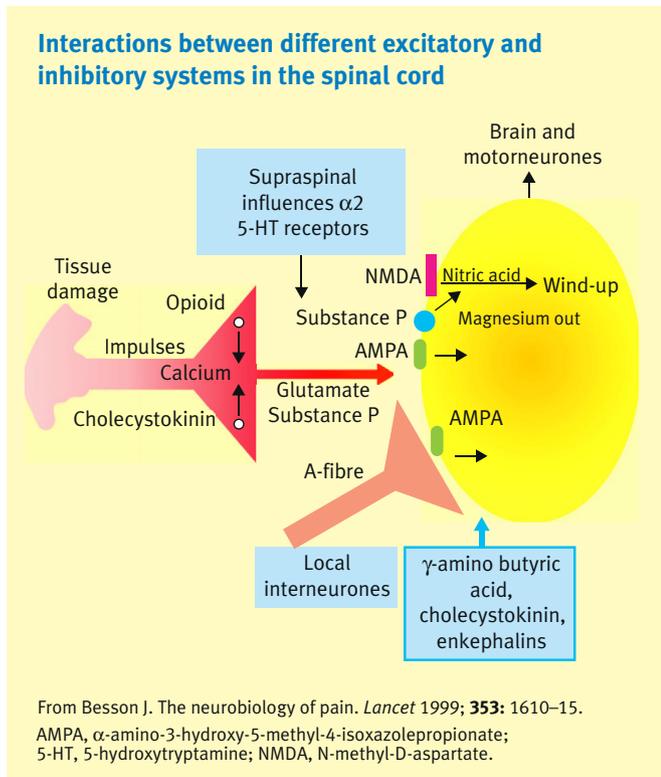


Figure 3

Visceral pain

Visceral nociceptors are fewer, more widely distributed and not as well organized as somatic nociceptors. Visceral pain is often diffuse and poorly localized. Visceral afferent fibres respond in a graded fashion to intensity of stimulation, rather than to individual stimulating modalities. They also exhibit spatial summation, so that if a large area is stimulated, the pain threshold is lowered. This does not occur in cutaneous nociception. Referred pain is often perceived in superficial body structures, due to convergence of afferent information via segmental spinal nerves.

Pharmacology

As the transmission of pain involves many different receptors within the peripheral and central nervous system, multimodal analgesia is best employed to optimize pain control and limit side effects. Common drugs used in pain management include the following.

Anti-inflammatories: non-steroidal anti-inflammatory drugs (NSAIDs) reduce the synthesis of prostaglandins, potent sensitizers of primary afferent nociceptors, by inhibiting cyclooxygenase which is a key enzyme in the inflammatory cascade. The risk of gastrointestinal and other side effects with NSAIDs often prevent their use, particularly in the elderly.

Opioids: opioids are agonists at the mu receptor; they are discussed in further detail on pages 505–509 of this issue.

Antidepressants: are the mainstay of pharmacological management of neuropathic pain. Tricyclic antidepressants, such as

amitriptyline, nortriptyline and imipramine, prevent reuptake of endogenous serotonin and noradrenaline within the central nervous system, increasing the activity of the descending inhibitory pain pathways. Anti-cholinergic side effects predominate, with dry mouth and drowsiness. There is also evidence for the use of duloxetine, a serotonin and noradrenaline reuptake inhibitor (SNRI) in painful diabetic neuropathy.

Anticonvulsants: this group of drugs act either by the blockade of sodium or voltage-gated calcium channels in nerve fibres, reducing excitability of neurons. These drugs may be effective in the management of chronic pain, although frequently cause adverse effects including ataxia, sedation and nausea. Examples include carbamazepine, lamotrigine, gabapentin and pregabalin.

Topical preparations

- lidocaine 5% plaster – is indicated for post-herpetic neuralgia, and is also used for localized neuropathic pain (e.g. scar pain).
- capsaicin – is derived from the chilli pepper. It binds to the VR1 nociceptors causing initial excitation (burning and sensitivity), then a period of reduced sensitivity and often prolonged desensitization.

NMDA antagonists: ketamine, binds to activated N-methyl-D-aspartate (NMDA) receptors within the central nervous system, preventing activation by excitatory amino acids such as glutamate. This is thought to reduce the effects of ‘wind-up’ and subsequent development of chronic pain. It also has actions as an opioid agonist, and causes inhibition of serotonin and noradrenaline reuptake.

Less commonly used agents include the following.

Antiarrhythmics: by blocking sodium channels, and therefore preventing nerve conduction, antiarrhythmics have been used in the management of neuropathic pain. Lidocaine has been used as an intravenous infusion in the hospital setting.

Cannabinoids: these have been used for a number of years for a variety of conditions. The most active naturally occurring compound is δ -9-tetrahydrocannabinol and synthetic versions including nabilone have been developed which are agonists at the CB₁ receptor. Whilst the most common effects are psychotropic, analgesia can be induced but the drugs are often poorly tolerated.

In addition to the physiological remedies outlined above, the personal impact of pain (i.e. on mood, anxiety, physical and social functioning) should always be considered and addressed, if pain management is to result in an improvement in quality of life for the patient.¹ ◆

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FURTHER READING

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