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 and can be modulated at many levels. Peripheral sensitization causes increased afferent input to the spinal cord. Numerous receptors and ion channels are involved. Pain can induce physiological and anatomical changes within the nervous system which 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

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
- define common pain terminology (Box 1).

Pain is a complex experience, initiated by sensory information conveyed from an unpleasant stimulus, greatly modified by affective (i.e. emotional), cultural and cognitive perspectives. 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

There is neither a direct nor simple 'pain-specific' conduit within the nervous system. Instead, 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 external noxious energy 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 (Box 1).

Transduction

While there is no hard-wired pain circuitry, there are physiologically specialized peripheral sensory neurons that respond to noxious stimuli, namely **nociceptors**. These are free, unencapsulated peripheral nerve endings found in most tissues of the 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) Aδ are associated with a briefer 'sharp' pain. They are myelinated and respond to mechanical and thermal stimuli. Approximately 15% of C-fibres are 'silent' nociceptors; these do not respond to noxious stimuli but only become active after tissue injury or inflammation when they

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]

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 sensitizations.[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.

Sources:

[a]International Association for the Study of Pain (IASP).

[b]British Pain Society (BPS).

Box 1

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may respond spontaneously or become sensitized to other sensory 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 Aδ fibres terminate in lamina I (marginal zone) and lamina II (substantia gelatinosa). However, some Aδ fibres also terminate in lamina 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 lamina 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 (Aβ fibres) are inhibitory. This may account for the pain-relieving effects of transcutaneous electrical nerve stimulation (TENS) 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 crosses locally and ascends contralaterally. Lamina 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.

The spinomesencephalic tract terminates primarily in the periaqueductal gray (PAG), activating descending pain networks which are involved in the autonomic and somatomotor aspects of defence reaction.

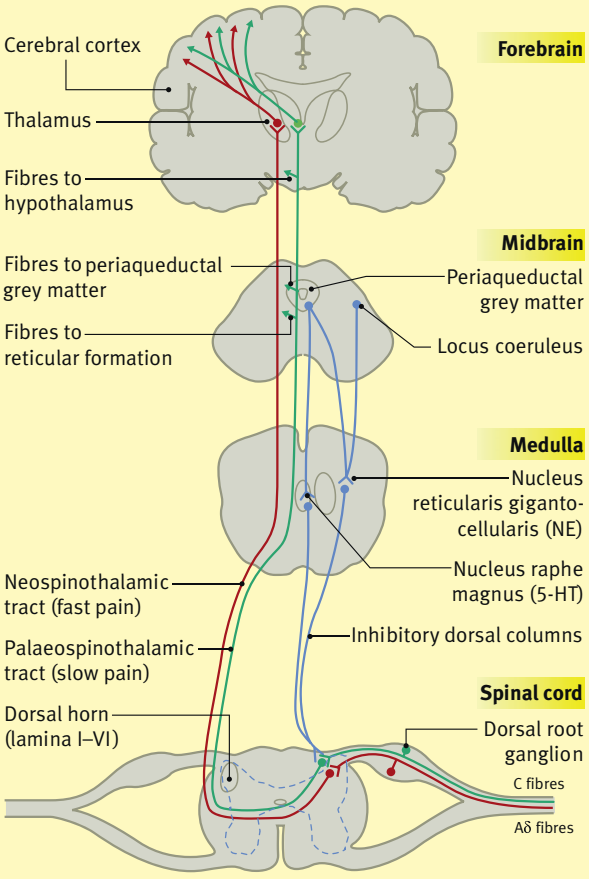
The spinoparabrachial-amygdala system originates from lamina I neurons that express NK1 receptors. It is involved in the emotional or affective components of pain.

Perception

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

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

Peripheral sensitization

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

An inflammatory soup, including endothelin, prostaglandin E2, leukotrienes, bradykinin, cytokines, serotonin and adrenaline is released following tissue injury 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 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 V_1 – $TRPV_1$) 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

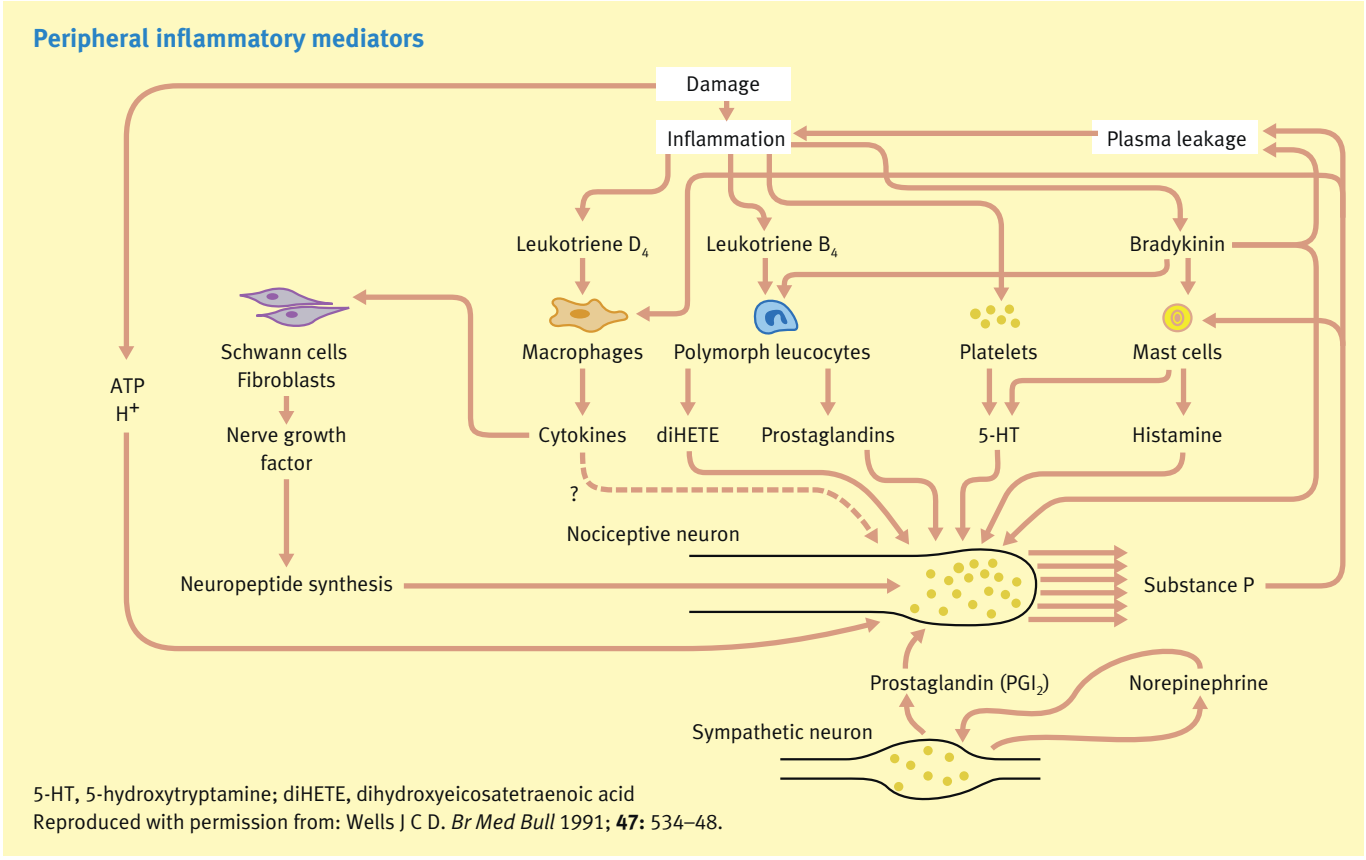


Figure 2

inflammatory mediators. In addition, signalling cascades are initiated which result in acute modulation of the protein structure of ion channels, altering their function and enhancing their responsiveness. Alterations in gene expression and protein synthesis result in increased peptide and receptor expression resulting in more persistent alterations in sensitivity.

Neurotrophic factors have an important role in the growth and survival of neurons. 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.

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 in post-synaptic dorsal horn neurons. 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-delta fibres and C-fibres in the superficial dorsal horn and long outlasts the initiating stimulus.

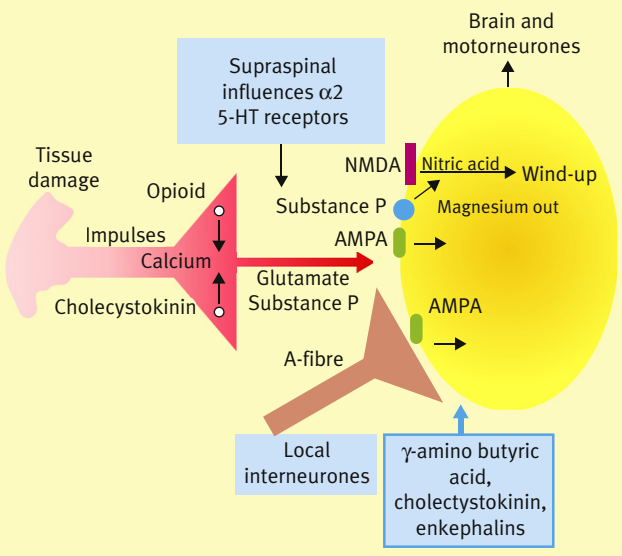
Secondary hyperalgesia is hyperalgesia in undamaged tissue adjacent to the area of actual tissue damage. It is thought to be due to an increased receptive field and reduced threshold of wide dynamic neurons in the dorsal horn.

The excitatory neurotransmitter glutamate has a key role in the activation of both alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (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. There is great interest in protein kinases as potential targets for new analgesic treatments.

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 periaquaductal 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

Interactions between different excitatory and inhibitory systems in the spinal cord



From Besson J. The neurobiology of pain. *Lancet* 1999; **353:** 1610–15.
AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate; 5-HT, 5-hydroxytryptamine; NMDA, N-methyl-D-aspartate.

Figure 3

has been implicated in the development of chronic pain states. Serotonin, noradrenaline and endogenous opioids are important transmitters in 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 system. There are many causes, including traumatic, infective, ischaemic, neoplastic and chemically 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 Aβ afferents to sprout into the superficial pain transmitting areas of the dorsal horn and this process underlies the development of allodynia and hyperalgesia.

Visceral pain

Visceral nociceptors are fewer, more widely distributed and not as well organized as somatic nociceptors. Visceral pain is often diffused 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:

- non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol and capsaicin to reduce the transduction of pain
- local anaesthetics to reversibly block the transmission of pain
- opioids, which act at spinal and supraspinal areas to modify afferent transmission and facilitate descending control pathways
- tricyclic antidepressants and selective noradrenaline reuptake inhibitors (SNRIs), which maintain monoamine levels in the descending pathways
- anticonvulsants, which act to dampen synaptic transmission globally, by interfering with sodium or calcium voltage-gated channel function, thereby reducing excitability in sensitized neurons.

However, 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 be successful. ◆

FURTHER READING

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