

An introduction to pain pathways and mechanisms

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Introduction

Pain is a vital function of the nervous system in providing the body with a warning of potential or actual injury. It is both a sensory and emotional experience, affected by psychological factors such as past experiences, beliefs about pain, fear or anxiety.

This article provides an overview of the physiological mechanisms of pain and the important pain pathways. We will discuss pain receptors, transmission of pain signals to the spinal cord and pain pathways within the spinal cord. We will look at how pain can be modulated at different levels along the pathway, and the sites of action of analgesic drugs. We will also discuss different types of pain including visceral and neuropathic pain.

Nociceptors

Nociceptors are the specialised sensory receptors responsible for the detection of noxious (unpleasant) stimuli, transforming the stimuli into electrical signals, which are then conducted to the central nervous system. They are the free nerve endings of primary afferent A δ and C fibres. Distributed throughout the body (skin, viscera, muscles, joints, meninges) they can be stimulated by mechanical, thermal or chemical stimuli.

Inflammatory mediators (eg bradykinin, serotonin, prostaglandins, cytokines, and H⁺) are released from damaged tissue and can stimulate nociceptors directly. They can also act to reduce the activation threshold of nociceptors so that the stimulation required to cause activation is less. This process is called primary sensitisation.

Primary afferent fibres

In addition to the A δ and C fibres that carry noxious sensory information, there are primary afferent A β fibres that carry non-noxious stimuli. Each of these fibre types possesses different characteristics that allow the transmission of particular types of sensory information (Table 1).

- *A β fibres* are highly myelinated and of large diameter, therefore allowing rapid signal conduction. They have a low activation threshold and usually respond to light touch and transmit non-noxious stimuli.
- *A δ fibres* are lightly myelinated and smaller diameter, and hence conduct more slowly than A β fibres. They respond to mechanical

and thermal stimuli. They carry rapid, sharp pain and are responsible for the initial reflex response to acute pain.

- *C fibres* are unmyelinated and are also the smallest type of primary afferent fibre. Hence they demonstrate the slowest conduction. C fibres are polymodal, responding to chemical, mechanical and thermal stimuli. C fibre activation leads to slow, burning pain.

	Aβ fibres	Aδ fibres	C fibres
Diameter	Large	Small 2-5 μ m	Smallest <2 μ m
Myelination	Highly	Thinly	Unmyelinated
Conduction velocity	> 40 ms ⁻¹	5-15ms ⁻¹	< 2ms ⁻¹
Receptor activation thresholds	Low	High and low	High
Sensation on stimulation	Light touch, non-noxious	Rapid, sharp, localised pain	Slow, diffuse, dull pain

Table 1 Characteristics of primary afferent fibres

Dorsal horn of the spinal cord

A δ and C fibres synapse with secondary afferent neurones in the dorsal horn of the spinal cord. The dorsal horn can be divided histologically into ten layers called Rexed laminae. A δ and C fibres transmit information to nociceptive-specific neurones in Rexed laminae I and II, in addition to projections to other laminae. Primary afferent terminals release a number of excitatory neurotransmitters including glutamate and substance P.

Complex interactions occur in the dorsal horn between afferent neurones, interneurones and descending modulatory pathways (see below). These interactions determine activity of the secondary afferent neurones. Glycine and gamma-aminobutyric acid (GABA) are important neurotransmitters acting at inhibitory interneurones.

Ascending tracts in the spinal cord

There are two main pathways that carry nociceptive signals to higher centres in the brain.

- The *spinothalamic tract*: secondary afferent neurones decussate within a few segments of the level of entry into the spinal cord and ascend in the contralateral spinothalamic tract to nuclei within the thalamus. Third order neurones then ascend to terminate in the somatosensory cortex. There are also projections to the periaqueductal grey matter (PAG). The spinothalamic tract transmits signals that are important for pain localisation.
- The *spinoreticular tract*: fibres also decussate and ascend the contralateral cord to reach the brainstem reticular formation, before projecting to the thalamus and hypothalamus. There are many further

projections to the cortex. This pathway is involved in the emotional aspects of pain.

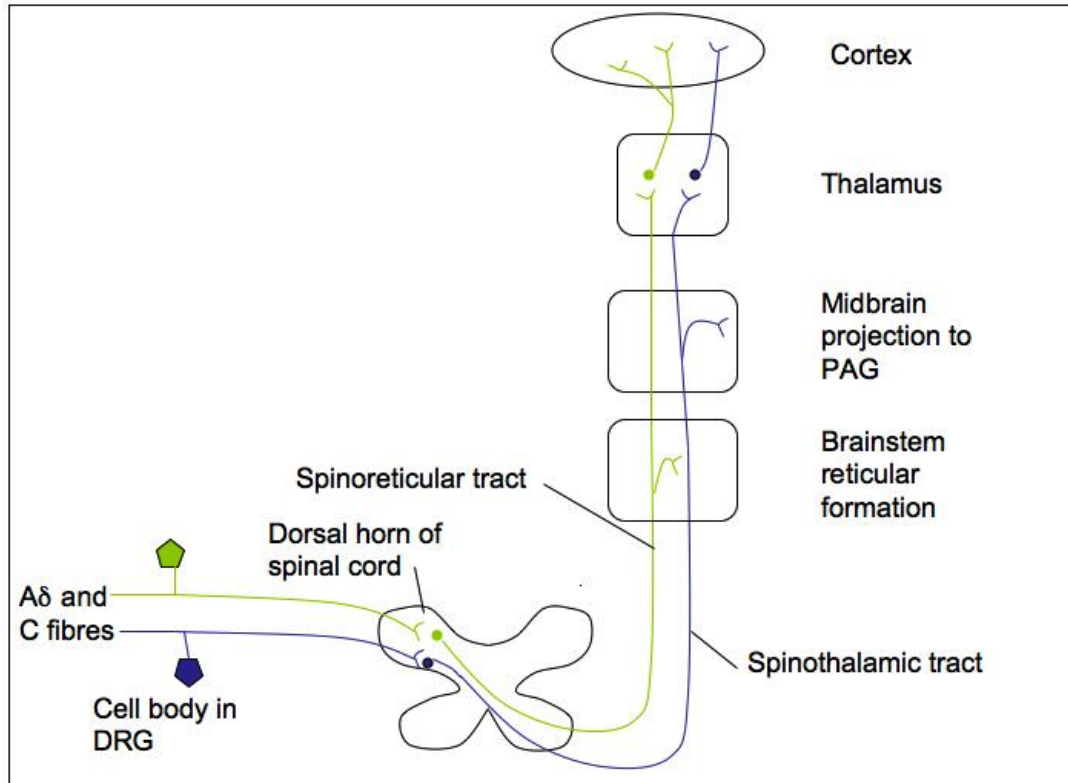
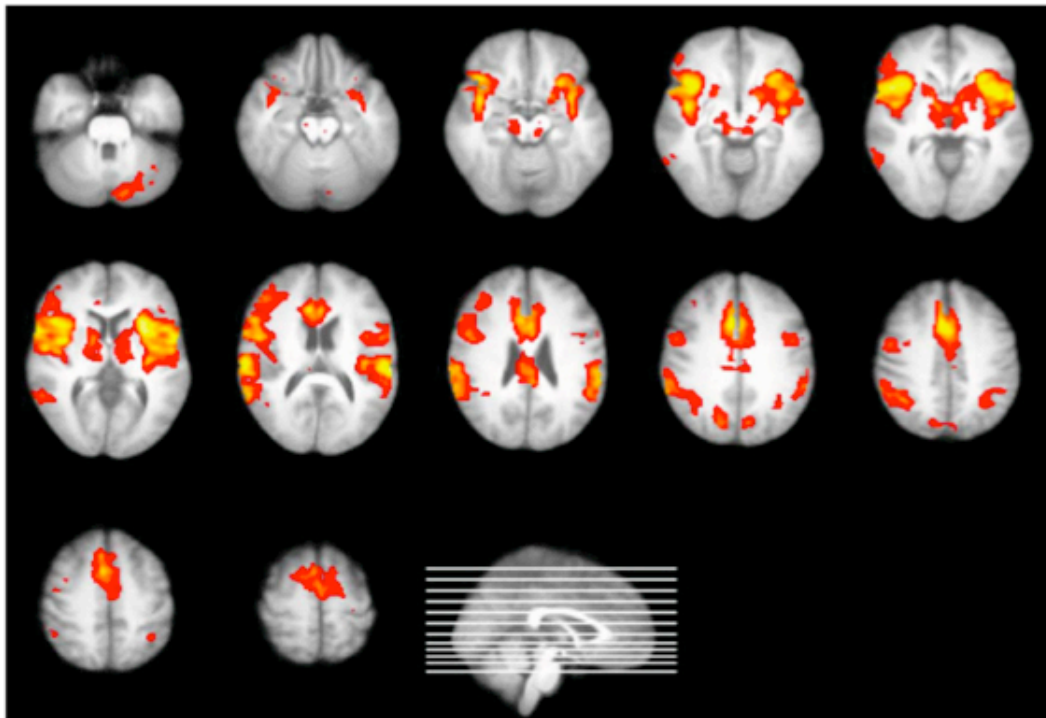


Figure 1 Ascending pain pathways. DRG dorsal root ganglion, PAG periaqueductal grey matter

Pain processing in the brain

The experience of pain is complex and subjective, and is affected by factors such as cognition (eg distraction or catastrophising), mood, beliefs and genetics. The somatosensory cortex is important for the localisation of pain. However, imaging techniques such as functional magnetic resonance imaging (fMRI) have demonstrated that a large brain network is activated during the acute pain experience. This is often called the 'pain matrix'. The commonest areas activated include the primary and secondary somatosensory cortex (S1 and S2), insular, anterior cingulate cortex and prefrontal cortex, and the thalamus, demonstrating that these areas are all important in pain perception (Figure 2).

Figure 2 Functional magnetic resonance imaging (fMRI) demonstrating the multiple brain regions activated in response to painful stimulation. Reproduced with permission, Tracey 2008



Inhibition of pain transmission

There are mechanisms that act to inhibit pain transmission at the spinal cord level and via descending inhibition from higher centres.

Gate control theory of pain

The gate control theory of pain was proposed by Melzack and Wall in 1965 to describe a process of inhibitory pain modulation at the spinal cord level. It helps to explain why when we bang our head, it feels better when we rub it. By activating $A\beta$ fibres with tactile, non-noxious stimuli inhibitory interneurons in the dorsal horn are activated leading to inhibition of pain signals transmitted via C fibres (Figure 3). Transcutaneous electrical nerve stimulation (TENS) is based on the gate control theory. Stimulation of large diameter afferent nerve fibres by cutaneous electrodes activates inhibitory processes in the dorsal horn and inhibits pain transmission by C fibres.

Descending inhibition

The periaqueductal grey (PAG) in the midbrain and the rostral ventromedial medulla (RVM) are two important areas of the brain involved in descending inhibitory modulation. Both these centres contain high concentrations of opioid receptors and endogenous opioids, which helps explain why opioids are analgesic. Descending pathways project to the dorsal horn and inhibit pain transmission. These pathways are monoaminergic, utilising noradrenaline and serotonin as neurotransmitters. Acupuncture is used for both acute and chronic pain. The mode of action is not well understood, but may be through activation of descending inhibitory pathways and release of endogenous opioids.

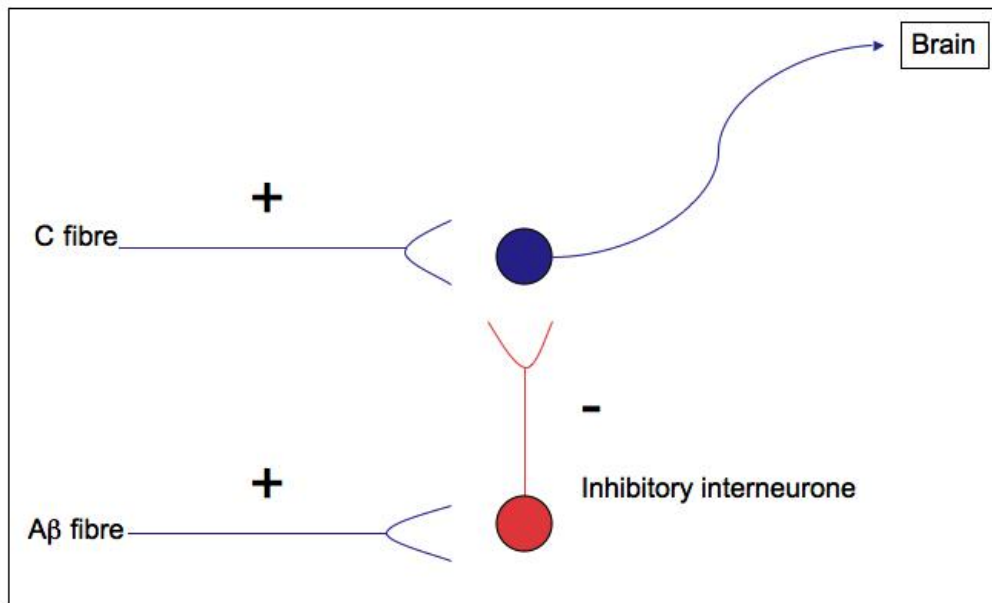


Figure 3 Gate control theory of pain
Stimulation of A β fibres activates inhibitory interneurons in the dorsal horn

Visceral pain

Visceral pain is pain arising from the internal organs. The viscera are largely innervated by C fibres. Visceral pain is typically diffuse and poorly localised, often described as deep, dull or dragging. It can be associated with autonomic changes such as nausea, vomiting, and changes in heart rate or blood pressure. It can also evoke strong emotional responses.

In contrast to somatic pain, which is felt due to stimuli such as burning or crushing, visceral pain is triggered by smooth muscle distension or contraction, stretching of the capsule surrounding an organ, ischaemia and necrosis, or irritation by chemicals produced during inflammatory processes. Referred pain is pain experienced at a site distant from source of the pain. It is due to the convergence of different afferents on to the same dorsal horn neurones in the spinal cord. For example shoulder pain can be felt due to diaphragmatic irritation that occurs following laparoscopic surgery that can stretch the diaphragm.

Neuropathic pain

Neuropathic pain is caused by damage to nerves in the central or peripheral nervous system. Damage can be due a number of mechanisms including trauma or surgery, diabetes mellitus, chemotherapy, radiotherapy, ischaemia, infection or malignancy.

Neuropathic pain has some different characteristics to nociceptive pain. Pain is more likely to be spontaneous and is described as burning or 'like an electric shock'. Pain may be experienced in response to a stimulus that does not usually cause pain (allodynia), or there may be a heightened response to a stimulus that is usually painful (hyperalgesia). Neuropathic pain can be difficult to treat and non-traditional analgesic drugs such as antidepressants and anticonvulsants are useful.

Analgesic drugs

Analgesic drugs with different modes of action target pain at different points along the pain pathway (Table 2).

Non-steroidal anti-inflammatory drugs

Prostaglandins activate and sensitise nociceptors (see *Nociceptors*, above). Prostaglandin production is catalysed by the enzyme cyclo-oxygenase (COX). Cyclo-oxygenase exists in two forms. COX-I is the *constitutive* form and is found in many tissues. It has important functions including gastric mucosal protection and platelet function. COX-II is described as the *inducible* form and is found at sites of inflammation. Inhibition of COX by NSAIDs (eg ibuprofen) reduces prostaglandin production and therefore reduces the activation and sensitisation of nociceptors and hence inflammatory pain. Important side effects of NSAIDs include impaired platelet function and bleeding, gastric ulceration, renal impairment and bronchospasm in sensitive asthmatics. COX-II inhibitors (eg parecoxib) target the inducible form of the enzyme and have a lower risk of gastrointestinal bleeding.

Paracetamol

Paracetamol acts centrally and inhibits brain cyclo-oxygenase, although the precise mechanism of action is not fully understood.

Opioids

Opioid receptors are found peripherally and throughout the CNS. The analgesic effects are mediated via μ receptors. Opioids reduce pain transmission at the dorsal horn by inhibiting excitatory neurotransmitter release. They act centrally in the PAG by enhancing descending inhibition. Common side effects of opioids include respiratory depression, constipation, nausea and sedation.

Local anaesthetics

Local anaesthetics (eg bupivacaine and lidocaine) produce local analgesia by reversibly inhibiting action potential propagation in sensory fibres. They also act on motor and autonomic fibres and so can cause motor weakness and autonomic changes. High plasma concentrations of local anaesthetic can cause serious CNS and cardiovascular toxicity.

Antidepressants

Antidepressants including tricyclics (eg amitriptyline) and serotonin-noradrenaline reuptake inhibitors (eg duloxetine) are used to treat neuropathic pain. They increase the concentration of serotonin and noradrenaline in the

CNS, facilitating the descending inhibitory serotonergic and noradrenergic pathways.

Anticonvulsants

Anticonvulsants such as gabapentin are also used for neuropathic pain. They inhibit the release of excitatory neurotransmitters and therefore pain transmission.

Multimodal analgesia

Multimodal analgesia describes using a combination of drugs with different modes of action. In this way it may be possible to use lower doses of drugs, minimising unwanted side effects. For example, by using a combination of NSAID and opioid for postoperative pain, the amount of opioid required is less and opioid related side effects are reduced.

Site of action	Drug
Peripheral	NSAIDS Local anaesthetics Opioids
Central nervous system	Opioids Antidepressants Anticonvulsants Paracetamol Local anaesthetics

Table 2 Sites of analgesic drug action. NSAID Non-steroidal anti-inflammatory drug

Term	Definition
Pain	An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage
Nociceptor	A high-threshold sensory receptor of the peripheral somatosensory nervous system that is capable of transducing and encoding noxious stimuli
Hyperalgesia	Increased pain from a stimulus that normally provokes pain
Neuropathic pain	Pain caused by a lesion or disease of the somatosensory nervous system
Allodynia	Pain due to a stimulus that does not normally provoke pain
Sensitization	Increased responsiveness of nociceptive neurons to their normal input, and/or recruitment of a response to normally subthreshold inputs

Table 3 Useful definitions (Source: International Association for the Study of Pain)

Conclusion

Pain is both a sensory and emotional experience, and patients past experiences, fears and anxieties can play an important role. Pain transmission is a result of complex peripheral and central processes. These processes can be modulated at different levels and pain perception is a result of the balance between facilitatory and inhibitory interactions.

Current areas of interest in pain research include investigating the effect of mood on pain processing in the brain and looking for novel drugs to block channels involved in pain transmission.

Key points

- 1 The pain experienced by patients is a result of the interaction between sensory and emotional experiences.
- 2 A δ fibres transmit rapid, sharp, localised pain.
- 3 C fibres transmit slow, diffuse, dull pain.
- 4 Pain transmission can be modulated at a number of levels, including the dorsal horn of the spinal cord and via descending inhibitory pathways.
- 5 The spinothalamic and spinoreticular tracts are important ascending pain pathways.
- 6 Neuropathic pain can be spontaneous and is often described as burning or 'like an electric shock'.

Conflict of interest: none

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