An introduction to pain pathways and mechanisms

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. It discusses pain receptors, transmission of pain signals to the spinal cord and pain pathways within the spinal cord. It looks at how pain can be modulated at different levels along the pathway, and the sites of action of analgesic drugs, and also discusses different types of pain including visceral and neuropathic pain.

Nociceptors

Nociceptors are the specialized sensory receptors responsible for the detection of noxious (unpleasant) stimuli. They are the free nerve endings of primary afferent Aδ and C neurones (*Table 1*). Distributed throughout the body (skin, viscera, muscles, joints, meninges) they can be stimulated by mechanical, thermal or chemical stimuli. The noxious stimulus is transduced into an electrical impulse, which is then conducted to the CNS. An electrical potential exists across the neuronal cell membrane. This electrical gradient is maintained by active transport of potassium ions into the cell and sodium ions out of the cell. Sodium and potassium ions also move passively down concentration gradients. A negative membrane potential of -70 mV is maintained in the resting state. In response to a stimulus there is a change in the cell membrane ion permeability. If the stimulus is below a threshold level then the changes remain localized. Above the threshold level the membrane becomes depolarized. Sodium channels open and sodium enters into the cell, increasing depolarization and causing the membrane potential to increase to +40 mV. Depolarization spreads along the nerve and an action potential is propagated.

Inflammatory mediators (e.g. 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 sensitization.

Primary afferent fibres

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

Aβ fibres

These are highly myelinated and of large diameter, therefore allowing rapid signal conduction. They have a low activation threshold, which means that a lower stimulus intensity is required to cause depolarization relative to depolarization of Aδ and C fibres. They respond to light touch and transmit non-noxious stimuli.

Aδ fibres

These fibres are lightly myelinated and of smaller diameter, and hence conduct more slowly than Aβ fibres. They respond to mechanical and thermal stimuli. They transmit the impulses which represent rapid, sharp pain and are responsible for the initial reflex response to acute pain.

C fibres

C fibres are unmyelinated and are also the smallest type of primary afferent fibre, so have the slowest conduction. C fibres are polymodal, activated by chemical, mechanical and thermal stimuli. C fibre activation leads to the sensation of slow, burning pain.

Dorsal horn of the spinal cord

Aδ and C fibres synapse with secondary afferent neurones in the dorsal horn of the spinal cord. Primary afferent terminals release a number of excitatory neurotransmitters including glutamate and substance P.

Complex modulation of the pain pathway occurs in the dorsal horn. There are interactions between afferent neurones, interneurones and descending modulatory pathways (see below). The balance between excitatory transmission and inhibitory signalling from descending pathways and interneurones determines activity of the secondary afferent neurones and hence of pain signalling to higher centres. Glycine and gamma-aminobutyric acid (GABA) are important neurotransmitters acting at inhibitory interneurones.

Ascending tracts in the spinal cord

There are two main pathways (*Figure 1*) that carry nociceptive signals to higher centres in the brain.

Table 1. Characteristics of primary afferent fibres

	Aβ fibres	Aδ fibres	C fibres
Diameter	Large (5–12 μm)	Small (1–5 μm)	Smallest (<1 μm)
Myelination	Highly	Thinly	Unmyelinated
Conduction velocity	30–70 m/s	3–30 m/s	<2 m/s
Receptor activation thresholds	Low	High and low	High
Sensation on stimulation	Light touch, non-noxious	Rapid, sharp, localized pain	Slow, diffuse, dull pain

adapted from Carpenter and Reddi (2012)

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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. The spinothalamic tract transmits signals that are important for pain localization.

In addition to relaying information from the spinal cord to the somatosensory cortex, the thalamus plays an important role in integrating information. Projections to areas such as the periaqueductal grey matter are important for activating descending modulation. Lesions of the thalamus can lead to intractable spontaneous pain.

The spinoreticular tract

Fibres decussate in the spinal cord and ascend the contralateral cord to reach the brainstem reticular formation. This is an area responsible for arousal and wakefulness. There are further diffuse projections to the CNS, including the anterior cingulate cortex, the insular and prefrontal cortex, all areas involved in the affective and motivational aspects of pain. Projections to the periaqueductal grey and rostroventromedial medulla are important for the fight or flight response and stress-induced analgesia (Macintyre et al, 2010).

Pain processing in the brain

The somatosensory cortex is important for the localization of pain. However, imaging techniques such as functional magnetic resonance imaging 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 the range of areas important in pain perception (*Figure 2*).

The experience of pain is complex and subjective. Cognitive factors such as catastrophising and distraction can modulate pain perception. Catastrophising (exaggerated negative responses) can enhance pain perception through altered anticipation, attention and emotional responses. Distraction is effective in modulating the sensory and affective components of pain. Connections exist between cortical areas and the brainstem, and distraction of subjects during a painful experience results in increased activity in the periaqueductal grey matter, correlating with a reduction in pain rating (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 Aβ fibres with tactile, non-noxious stimuli inhibitory interneurones in the dorsal horn are activated leading to inhibition of pain signals transmitted via C fibres (*Figure 3*). Transcutaneous electrical nerve stimulation

Figure 1. Ascending pain pathways.

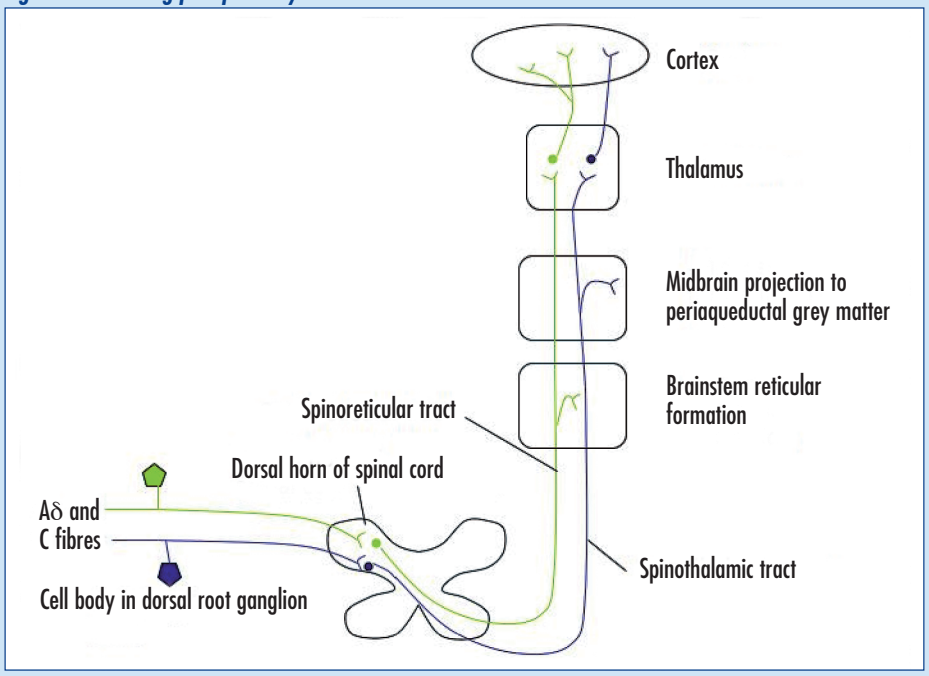
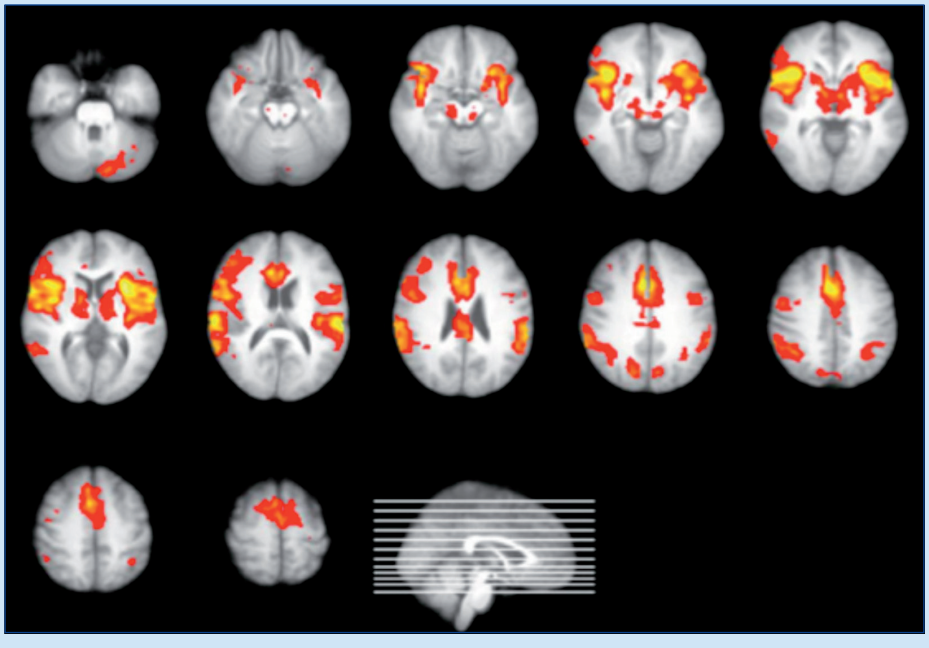


Figure 2. Functional magnetic resonance imaging demonstrating the multiple brain regions activated in response to painful stimulation.



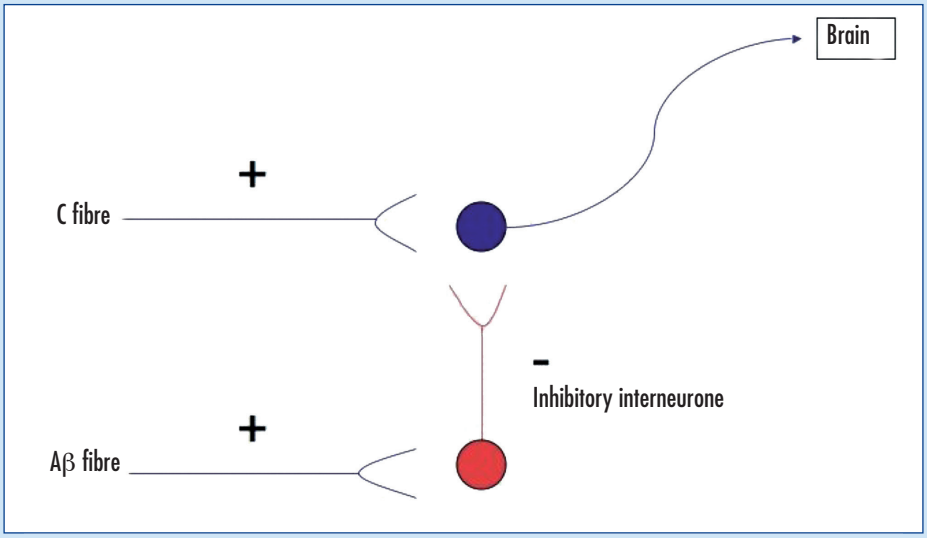


Figure 3. Gate control theory of pain. Stimulation of Aβ fibres activates inhibitory interneurones in the dorsal horn.

(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 in the midbrain is an important area of the brain for descending inhibitory modulation. The periaqueductal grey receives afferents from the thalamus, cortex and collaterals from the spinothalamic tract. It contains 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, using 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.

Visceral pain

Visceral pain is pain arising from the internal organs. The viscera are largely innervated by C fibres. Visceral sensory afferents travel with autonomic nerves. Visceral pain is typically diffuse and poorly localized, 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 as a result of 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 the source of the pain. It is caused by the convergence of different afferents onto the same dorsal horn neurones in the spinal cord. For example shoulder pain can be felt as a result of 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 caused by 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) (*Table 2*). 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 3*).

Non-steroidal anti-inflammatory drugs

Prostaglandins activate and sensitize nociceptors (see above). Prostaglandin production is catalysed by the enzyme cyclooxygenase (COX), which 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 non-steroidal anti-inflammatory drugs (e.g. ibuprofen) reduces prostaglandin production and therefore reduces the activation and sensitization of nociceptors and hence inflammatory pain.

Table 2. Useful definitions

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 caused by 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

From International Association for the Study of Pain (2011)

Important side effects of non-steroidal anti-inflammatory drugs include impaired platelet function and bleeding, gastric ulceration, renal impairment and bronchospasm in sensitive asthmatics. COX-II inhibitors (e.g. 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 periaqueductal grey matter by enhancing descending inhibition. Common side effects of opioids include respiratory depression, constipation, nausea and sedation.

Local anaesthetics

Local anaesthetics (e.g. bupivacaine and lidocaine) bind reversibly to sodium channels in the neurone and prevent sodium influx during depolarization. This means that threshold potential is not reached and action potential propagation is prevented. Local anaesthetics act on motor and autonomic fibres, in addition to sensory fibres, and so also cause motor weakness and autonomic changes. High plasma concentrations of local anaesthetic can cause serious CNS and cardiovascular toxicity.

Antidepressants

Antidepressants including tricyclics (e.g. amitriptyline) and serotonin-noradrenaline reuptake inhibitors (e.g. 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.

Tricyclic antidepressants can cause anticholinergic side effects such as dry mouth, blurred vision and urinary retention. In order to allow tolerance to develop the dose should be titrated slowly upwards. Cardiac conduction abnormalities and dysrhythmias can also occur and tricyclic antidepressants should be used with caution in patients who have pre-existing heart disease. CNS effects include sedation.

Anticonvulsants

Anticonvulsants such as gabapentin and pregabalin are also used to treat neuropathic pain. They bind to the α2-δ subunit of voltage-gated calcium channels, which inhibits 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, minimizing unwanted side effects. For example, by using a combination of non-steroidal anti-inflammatory drug and opioid for postoperative pain, the amount of opioid required is less and opioid-related side effects are reduced.

Conclusions

Pain is both a sensory and emotional experience, and patients' past experiences, fears and anxieties play an important role in how pain is perceived. 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. **BJHM**

Figure 2 *is reproduced from Tracey (2008) by kind permission of Oxford University Press.*
Conflict of interest: none.

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Table 3. Sites of analgesic drug action

Site of action	Drug
Peripheral	Non-steroidal anti-inflammatory drug
	Local anaesthetics
	Opioids
CNS	Opioids
	Antidepressants
	Anticonvulsants
	Paracetamol
	Local anaesthetics

KEY POINTS

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