

The anatomy and physiology of pain

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Abstract

Pain is an unpleasant experience that results from both physical and psychological responses to injury. A complex set of pathways transmits pain messages from the periphery to the central nervous system, where control occurs from higher centres. Primary afferent pain fibres synapse with second-order neurons in the dorsal horn of the spinal cord. Ascending spinothalamic and spinoreticular tracts convey pain up to the brain, where pain signals are processed by the thalamus and sent to the cortex. Descending tracts, via the midbrain periaqueductal grey and nucleus raphe magnus, have a role in pain modulation. When nerves are damaged, neuropathic pain results and various mechanisms have been proposed for how this takes place. These mechanisms involve both peripheral and central sensitization.

Keywords Central sensitization; gate-control theory; neuropathic pain; nociception; pain pathways; peripheral sensitization; somatic pain; visceral pain

What is pain?

In 1996 the International Association for the Study of Pain (IASP) defined pain as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage'. This statement requires further explanation as it encompasses some important concepts. Pain is a **subjective experience**, which cannot be easily measured. It requires **consciousness**. Describing pain as an **'experience' separates pain from 'nociception'**. **Nociception is the neural process involving the transduction and transmission of a noxious stimulus to the brain via a pain pathway**. Pain is the result of a complex interplay between signalling systems, modulation from higher centres and the unique perception of the individual.

We learn about pain when we experience injury in early life. Scientists recognize that stimuli that cause pain are likely to be **damaging to (or likely to damage) tissue**. However, many people report pain **in the absence of tissue damage or any likely pathological cause**; usually this happens for **psychological** reasons. Patients misunderstand the relationship between tissue damage and pain, but sometimes healthcare professionals get it wrong too. If someone says they are in pain, regardless of whether a damaging stimulus can be identified, or not, what they are experiencing should be accepted as pain.

If a person experiences pain as a result of a particular activity, they usually stop doing that activity, because they identify pain as a **warning sign that harm is occurring**. However, if the pain continues, the person can do less and less. At this point pain is

not **providing the person with a useful signal since the likelihood of injury occurring with the activity has ceased**. In fact lack of activity may now be becoming physically and psychologically bad for the patient. The continuing pain is distressing for the patient and the dissociation between pain and tissue damage is confusing.

The IASP definition avoids tying pain to the stimulus. In this article, although we will look at nociceptive pathways, it is important to recognize that the whole experience of pain is far more than **physical stimuli triggering neural signals**.

Pain pathways

Pain receptors and primary afferents

Nociceptors are receptors in tissues which are activated specifically by painful stimuli. This 'noxious' information is transduced by the receptors into an electrical signal and transmitted from the periphery to the central nervous system along axons. There are two types of nociceptors:

- high-threshold mechanoreceptors (HTM), which respond to mechanical deformation
- polymodal nociceptors (PMN), which respond to a variety of tissue-damaging inputs:
 - hydrogen ions (protons)
 - 5-hydroxytryptamine (5-HT)
 - cytokines
 - bradykinin
 - histamine
 - prostaglandins
 - leucotrienes.

These inflammatory mediators bathe the nociceptors, activating and sensitizing them. Prostaglandins and bradykinin sensitize nociceptors to activation by low-intensity stimuli. Histamine and 5-HT cause pain when directly applied to nerve endings. Hydrogen ions and 5-HT act directly on ion channels on the cell membrane, but most of the others bind to membrane receptors and activate second-messenger systems via G proteins.

Nociceptors are therefore the free nerve endings of **nerve fibres**. **There are two main fibre types: Aδ and C fibres**. A comparison of the properties of these pain fibres is shown in [Table 1](#). These primary afferent nerve fibres have cell bodies in either the dorsal root ganglia or trigeminal ganglion and terminate in the dorsal horn of the spinal cord. Although all pain fibres terminate in the **dorsal horn**, their route to this end-point varies. Most enter the dorsal horn in the ventro-lateral bundle of the dorsal root ([Figure 1](#)). They travel just lateral to the larger-diameter myelinated Aβ fibres, which respond to non-painful stimuli such as vibration and light touch. However, 30% of the C fibres enter the spinal cord via the ventral root. Once they have entered the spinal cord the nerve roots may bifurcate into **ascending and descending branches**, which can enter the dorsal horn one or two segments higher or lower than the segment of origin.

The spinal cord and the gate-control theory

The dorsal horn of the spinal cord is the site where the primary afferent fibres synapse with second-order neurons. It is also where complex interactions occur between excitatory and inhibitory interneurons and where descending inhibitory tracts from higher centres exert their effect ([Figure 2](#)).

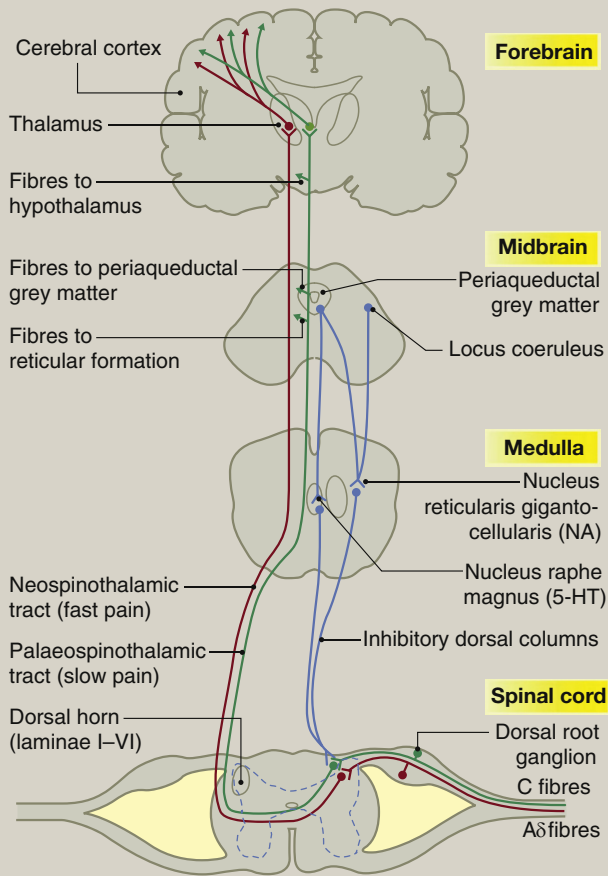
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Characteristics of primary afferent fibres

Fibre type	A δ (finely myelinated)	C (unmyelinated)
Fibre diameter	2–5 μm	<2 μm
Conduction velocity	5–15 m/second	0.5–2 m/second
Distribution	Body surface, muscles, joints	Most tissues
Pain sensation	Rapid, pricking, well localized	Slow, diffuse, dull, aching
Position of synapse within dorsal horn of spinal cord	Laminae I and V	Lamina II (substantia gelatinosa)

Table 1

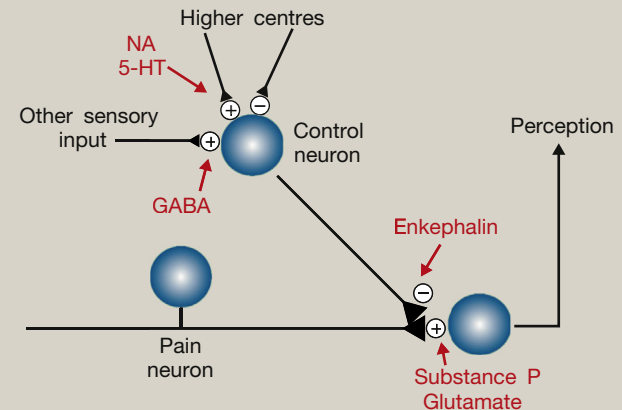
Spinal and supraspinal pathways of pain



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

Figure 1

Excitatory and inhibitory interactions at the spinal cord level



NA, noradrenaline; 5-HT, 5-hydroxytryptamine; GABA, γ -aminobutyric acid.

Figure 2

The dorsal horn is divided into laminae (called Rexed laminae). There are numerous connections between the laminae. Lamina II is also known as the **substantia gelatinosa** and this extends from the trigeminal nucleus in the medulla, to the filum terminale at the caudal end of the spinal cord. C fibres terminate in lamina II and A δ fibres terminate in laminae I and V. A β fibres (light touch and vibration) enter the cord medial to the dorsal horn and pass without synapse to the dorsal columns. They give off collateral branches to the dorsal horn which terminate in several laminae (III–V). They also synapse directly with terminals of unmyelinated C fibres in lamina II. Laminae II and V are important areas for the modulation and localization of pain.

There are three types of second-order neurons in the dorsal horn:

- **nociceptive specific (NS)**
 - respond selectively to high-threshold noxious stimuli
 - found in laminae II and III
- **wide dynamic range (WDR)**
 - respond to a range of sensory stimuli
 - found in laminae V and VI
- **low-threshold (LR)**
 - respond solely to innocuous stimuli.

At the spinal cord level the passage of pain information from periphery to central areas is controlled by a number mechanisms that modulate the pain signals:

- inhibitory control by higher centres
- activity in A β collaterals
- segmental (spinal) modulation by a variety of mechanisms including endogenous opioid and cannabinoid systems, inhibitory amino acids, for example γ -aminobutyric acid (GABA), galanin, cholecystokinin and nitric oxide (Table 2).

The first two of the above mechanisms act to 'close the gate' on the onward transmission of C fibre activity. Melzack and Wall initially proposed the gate-control theory in 1965. They proposed that lamina II inhibitory interneurons can be activated directly or indirectly (via excitatory interneurons) by stimulation of non-

Chemicals involved in the transmission of pain

Class	Chemical	Comments
Amines	Noradrenaline 5-HT	Involved with descending modulation of pain
Endogenous opioid peptides	Enkephalins β -Endorphin	Produced in cell body and transported to nerve terminal. Widespread in CNS, but especially in sites associated with pain. Bind to opioid receptors with inhibitory effect
Non-opioid peptides	Substance P Galanin Cholecystokinin and others	Widespread especially in DRG of C fibres. Associated with inflammation. Widespread. Involved with antinociception. Occur in DRG, dorsal horn and spinal tracts. May be involved with visceral pain. Become depleted in nerve injury
Excitatory amino acids	Glutamate	Act on NMDA and non-NMDA receptors. Involved in development, memory and neuronal plasticity
Inhibitory amino acids	GABA Glycine	Regulate behaviour associated with non-noxious stimuli
Others	Cannabinoids Nitric oxide	CB1 receptors in SC and on primary afferent neurons: involved in antinociception. In sensory neurons and dorsal horn. Involved in peripheral and central sensitization. Linked with NMDA activity

CNS, central nervous system; DRG, dorsal root ganglia; NA, noradrenaline; NMDA, N-methyl-D-aspartate; 5-HT, 5-hydroxytryptamine; GABA, γ -aminobutyric acid.

Table 2

noxious large sensory afferents from the skin ($A\beta$ fibres) that would then suppress transmission in small unmyelinated (C fibre) afferents and therefore block the pain. Thus rubbing a painful area relieves the pain. This is the working mechanism behind transcutaneous electrical nerve stimulation (TENS) in pain control.

Ascending tracts

Second-order neurons ascend to higher centres via the contralateral **spinothalamic** and **spinoreticular** tracts, which

are located in the anterolateral white matter of the spinal cord (Figure 1). The properties of these tracts are highlighted in Table 3.

The brain

The thalamus is the key area for processing somatosensory information. Axons travelling in the lateral and medial spinothalamic tracts terminate in their respective medial and lateral nuclei and from here neurons project to the primary and secondary somatosensory cortices, the insula, the anterior cingulate cortex and the prefrontal cortex. These areas play various roles in

Properties of the spinothalamic and spinoreticular tracts

Spinothalamic tract

More recently evolved
Contains axons of neurones in laminae I and V (where $A\delta$ fibres terminate)

Lateral tract

'Neospinothalamic'
Projects to ventral posterior lateral nucleus of thalamus, then to post-central gyrus

Axons are somatotopically ordered (caudal elements are more lateral)

Sends collateral branches to the periaqueductal grey (PAG) matter in the midbrain

Involved in the sensory-discriminative aspect of pain

Medial tract

'Paleospinothalamic'
Projects via medial thalamus

Involved in autonomic and affective part of pain

Spinoreticular tract

More phylogenetically ancient
Arises from cells deeper in grey matter including lamina V

Projects to thalamus and hypothalamus via nuclei of brainstem reticular formation. Some fibres project diffusely to the whole cerebral cortex

Little somatotopic organization

Involved in perception of diffuse, emotionally disturbing pain

Table 3

the perception of pain and also interact with other areas of the brain, for example the cerebellum and basal ganglia (which are areas more traditionally known to be associated with motor function rather than pain).

Descending tracts

These pathways (Figure 1) have a role in the modulation of pain. Noradrenaline and 5-HT are the key neurotransmitters involved in descending inhibition. Two important areas of the brainstem are involved in reducing pain: the periaqueductal grey (PAG) and the nucleus raphe magnus (NRM).

Periaqueductal grey

This region surrounds the cerebral aqueduct in the midbrain and is important in the control of pain. Electrical stimulation of the PAG produces profound analgesia and injection of morphine here has a far greater analgesic effect than injections anywhere else in the central nervous system. The PAG receives inputs from the thalamus, hypothalamus and cortex and also collaterals from the spinothalamic tract. PAG (anti-nociceptor) neurons excite cells in the NRM that in turn project down to the spinal cord to block pain transmission by dorsal horn cells.

Nucleus raphe magnus

A second descending system of serotonin-containing neurons exists. The cell bodies of these neurons are located in the raphe nuclei of the medulla and, like the noradrenalin-containing neurons, the axons synapse on cells in lamina II. They also synapse on cells in lamina III. Stimulation of the raphe nuclei produces a powerful analgesia and it is thought that the serotonin released by this stimulation activates inhibitory interneurons even more powerfully than noradrenaline and thus blocks pain transmission.

Brainstem neurons may control nociceptive transmission by:

- direct action on dorsal horn cells
- inhibition of excitatory dorsal horn neurons
- excitation of inhibitory neurons.

Visceral pain

This is the pain arising from internal organs. In comparison to somatic pain, visceral pain is poorly localized, because the density of nociceptors on viscera is lower and afferent fibres are less well represented in cortical mapping. Just as with somatic pain, the fibres that transmit pain from visceral nociceptors are A δ and C fibres and travel with autonomic afferents. Visceral pain pathways are shared with somatic pathways in the same ascending tracts of the spinal cord. The result is that pain from an internal organ can be interpreted as arising from converging somatic afferents and therefore visceral pain may be referred to the corresponding somatic tissue. Visceral pain can also be referred to a site far away from the source of stimulation. An example of this is when deep pain from the bladder is referred in a segmental fashion to the superficial S2-4 dermatomes in the perianal region.

Visceral pain also differs from somatic pain in that it is often colicky in nature and is accompanied by nausea and autonomic disturbance. Whereas somatic pain is caused by stimuli such as cutting and crushing, visceral structures do not show a painful response to these, but instead respond to distension as well as to inflammation and ischaemia.

Abnormal pain and how the nervous system responds to injury

Definitions

So far we have considered **nociceptive pain**, that is pain arising from an identifiable lesion causing tissue damage, accompanied by stimulation of nociceptors in somatic or visceral structures.

However, sometimes pain signalling goes wrong. This gives rise to abnormal pain, which is described using a range of terms that can be confusing.

Neuropathic pain: pain or abnormal sensation initiated or caused by a primary lesion or dysfunction of the nervous system. This can be a motor, sensory or autonomic dysfunction. Patients can report spontaneous pain, in the absence of an obvious peripheral stimulus. The pain may be paroxysmal or continuous and is often described as a 'burning', 'tingling', 'shooting', 'stabbing' or 'numb' sensation.

Neuropathic pain is also characterized by evoked pains:

- **Allodynia** – painful response to a normally innocuous stimulus.
- **Hyperalgesia** – pain of abnormal severity following a noxious stimulus.
- **Hyperpathia** – exaggerated and prolonged response to stimulation. May be delayed in onset and after repeated stimulation. Often an explosive onset.
- **Hyperaesthesia** – increased sensitivity to stimulation.
- **Dysaesthesia** – evoked or spontaneous altered sensation. Discomfort rather than pain.

Mechanisms in neuropathic pain

Pain can result from damage to either the peripheral or the central nervous system. Traditionally, abnormal pain from peripheral nerves has been termed 'neuropathic' and pain from damage to central nerves has been called 'central pain'. However, in clinical practice, the symptoms and signs can be the same for both conditions and it is not always easy to tell where the injury is occurring.

The nervous system has the ability to adapt to injury and can change its response to stimulation. The pathways described above are not hard-wired, but instead display the phenomenon of **plasticity**. Several mechanisms to explain how these changes take place have been proposed and some are summarized below.

Peripheral sequelae of nerve injury

When an A δ or C fibre is cut or partially damaged (e.g. in post-herpetic neuralgia), it tries to repair itself. In doing so it does not heal in its original form but instead a neuroma, or swelling, develops around the joined axon. Spontaneous electrical activity can be seen around neuromata, thought to be due to altered distribution, expression and gating properties of sodium channels. Ectopic impulse generation can also be seen at the spinal cord level in dorsal root ganglia.

In addition, peripheral nociceptors become sensitized by injury so that they:

- have a lower threshold for firing
- increase their response to noxious stimuli
- can fire in response to non-noxious stimuli.

Thus damaged nerves become the foci of hyperexcitability and ectopic discharge. Ectopic firing is influenced by physical stimuli (e.g. heat or cold) and the metabolic and chemical environment of the nerve.

Injury also causes changes in the Schwann cells and glia that surround axons. These are non-neuronal cells that provide support and nutrition to nerves. Injury causes phenotypic shifts leading to changes in growth factor, breakdown of the myelin sheaths surrounding nerves and a resultant change in axonal function. Furthermore, uninjured axons can spread into areas of injury and, particularly if this involves central neurons, the result is the spread of pain to uninjured areas and development of 'mirror' pain.

The role of the sympathetic nervous system

The sympathetic nervous system can play a role in some painful conditions, such as complex regional pain syndrome. It is responsible for both causing and maintaining the pain. Injury (usually to a limb) can cause abnormal processing of information in the spinal cord, which in turn leads to abnormal sympathetic outflow to the injured extremity. The result is neuropathic pain, which is often resistant to treatment and the following changes in the limb:

- abnormal regulation of vasculature
- oedema
- discolouration
- changes in sweating
- temperature changes
- trophic changes in skin
- reduced motor activity in the affected part.

Primary afferents from nociceptors can be influenced by sympathetic neurons. The sympathetic postganglionic neurotransmitter noradrenaline can exert its effect anywhere along the pathway from the free nerve endings to the dorsal root ganglion. In response to injury, nociceptor neurons can show increased expression of α -adrenoceptors, making them more responsive to the chemical influence of noradrenaline. In addition, sympathetic terminals sprout into the dorsal root ganglia (DRG) after nerve injury and may come into contact with sensory neurons here. Alteration of the blood supply to afferent nerve terminals may also contribute to their sensitivity to the effects of sympathetic stimulation.

Central sensitization

Changes occur in the dorsal horn of the spinal cord after nerve injury. Repetitive C fibre activation by noxious stimuli leads to a

prolonged dorsal horn response. This phenomenon has been termed 'wind-up'.

Within the dorsal horn there is a reduction in local inhibition by the neurotransmitters GABA and glycine and evidence of excitotoxic death of inhibitory interneurons. At the same time there is a strengthening of excitatory synaptic connections. Incoming axons develop ectopic activity and output to the spinothalamic tract neurons is increased. This process involves neurochemical changes mediated via *N*-methyl-D-aspartate (NMDA), neurokinins, and nitric oxide. The result of all of these changes is that the sensory threshold for pain signalling is lowered and there is spread of the receptive field.

In addition it has been shown that structural rewiring occurs in the dorsal horn of the spinal cord in response to injury. C fibre terminations in the substantia gelatinosa (lamina II) degenerate and A β (fine touch) fibres, which are usually located in laminae III and IV, sprout into lamina II. This may explain allodynia, where light touch is perceived as painful. These changes seem to be triggered by loss of nerve growth factor.

Finally, there are changes at a supraspinal level. Following injury there is evidence of cortical remapping and reorganization in both the primary somatosensory and motor cortices and in the subcortical areas. This is well recognized following limb amputation where lack of afferent input from the amputated limb leads to less occupation of the corresponding area of the somatosensory cortex. As a result the neighbouring cortical area (representing a different anatomical site) expands. The clinical manifestation of these changes is that the patient not only develops phantom limb pain very soon after amputation, but also that the phantom limb can sometimes be mapped out by touching a very different site of their body (e.g. pain in phantom hand felt by touching side of face). Reduction in the intensity of the phantom limb pain by effective treatment can be shown to reverse the cortical changes.

Summary

This article gives a broad overview of the anatomy and physiology of pain. It explains pain as a complex experience involving both physical and psychological adaptations. The normal pain pathways are described in some detail in a systematic fashion from nociceptor to central nervous system and back to periphery. It concludes with an explanation of some of the mechanisms involved with pain transmission. ◆