The anatomy and physiology of pain

Charlotte E Steeds

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 pathophysiological 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-hydoxytryptamine (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).

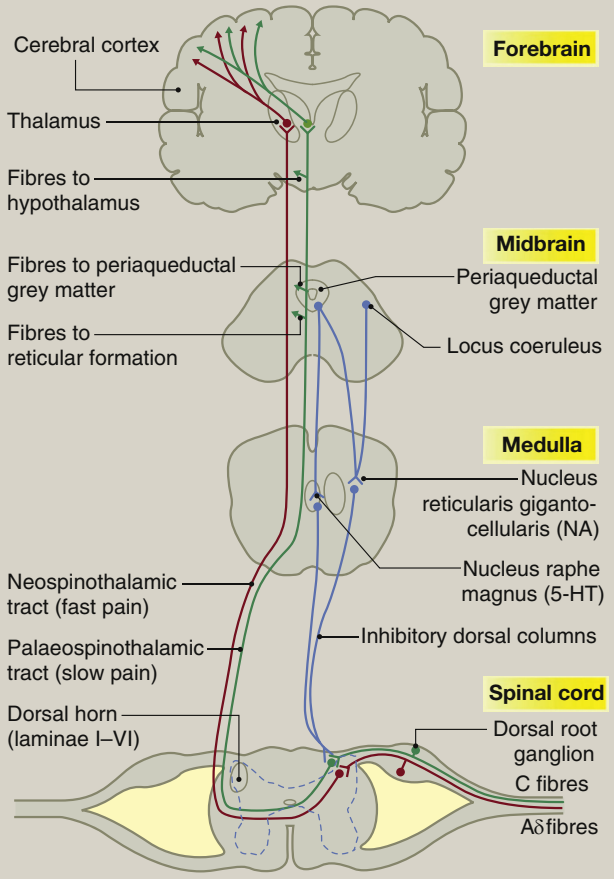
Charlotte E Steeds *BSc MBBS FFARSCI is a Locum Consultant in Anaesthesia and Pain Medicine at University Hospitals Bristol, UK.*

Characteristics of primary afferent fibres

Fibre type	Aδ (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

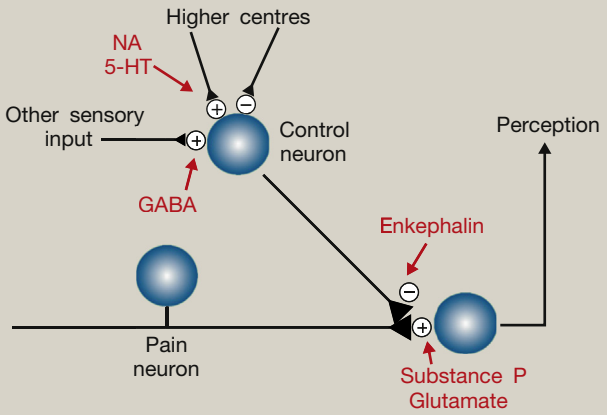
Spinal and supraspinal pathways of pain



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 Aδ fibres terminate in laminae I and V. Aβ 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 Aβ 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-