Pain and pain syndromes

ABSTRACT

The two main categories of pain, nociceptive and neuropathic, are caused by tissue damage and nerve damage respectively. Psychogenic pain is also described in the literature but it is becoming a pejorative term as the concept of central control of pain is now gaining momentum. There is considerable overlap in brain areas that deal with pain and where mood disorders develop. Some neurotransmitters, e.g. serotonin and noradrenaline, are involved in receiving and processing signals and regulate mood as well. It is no coincidence that many drugs used to treat mood disorders are effective when used for pain relief. This article highlights this interplay of neurotransmission and affective/pain symptomatology.

The International Association for the Study of Pain defines pain as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage' (Merskey and Bogduk, 1994). Acute pain is short lasting, has an identifiable aetiology and a pathology resulting from tissue damage. It is usually relieved by treatment of the underlying condition. By contrast chronic pain (an arbitrary definition would be 3 months or more) may last years. Its pathology is often not identified and in many cases the pain does not respond to treatment.

Types of pain

There are four different types of pain, as outlined in *Table 1*.

Somatic pain

Somatic pain, a type of nociceptive pain, is well localized. It is also known as tissue pain or musculoskeletal pain and may be intermittent, constant, superficial or deep. Described as aching, gnawing, throbbing or cramping, it includes fibromyalgia, tension headaches, pelvic pain, chronic back pain and arthritis (Dunne and Dunne, 2012).

Table 1. Types of pain

Somatic pain	Well localized
	Known as tissue pain
	May be intermittent, constant, superficial or deep
	Described as gnawing, aching, throbbing or cramping
Visceral pain	Arises from internal organs
	Includes fibromyalgia, tension headaches, pelvic pain, chronic back pain, arthritis, irritable bowel syndrome, endometriosis
	Described as a generalized aching
	May be associated with autonomic symptoms
Neuropathic pain	Caused by injury to the somatosensory nervous system
	Affects 6–8% of the population
	Associated with diabetes, post-herpetic neuralgia and phantom limb pain
	Described as shooting, burning, or squeezing
	Associated with paraesthesiae, numbness, hyperalgesia or allodynia
Referred pain	Experienced at a different location from the source, e.g. pain in the left arm from cardiac ischaemia

Visceral pain

Visceral pain arises from internal organs, which are highly sensitive to distension, ischaemia and inflammation. Not every organ has nociceptors, e.g. the lung cannot transmit pain messages but pleural membranes can, which is why pleural injections are often painful. Common causes of visceral pain include irritable bowel syndrome and endometriosis. Visceral pain is usually described as a generalized aching and may be associated with autonomic symptoms.

Neuropathic pain

Neuropathic pain is caused by injury or disease affecting muscles, joints and fascia. It affects 6–8% of the population. Poorly-controlled diabetes, post-herpetic neuralgia and phantom limb pain are examples. Neuropathic pain is described as shooting, burning or squeezing, and is often unrelenting and severe. Paraesthesiae (tingling), and numbness or hypersensitivity (hyperalgesia or allodynia) are often present.

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Table 2. Types of neurons	
Multipolar neurons	The most common
	A cell body gives rise to a single long axon and many shorter branching dendrites
Unipolar neurons	A single primary extension functions as both axon and dendrite
Bipolar neurons	Found usually in sensory organs
	Dendrites carry signals to the cell body: axons convey those signals to brain and spinal cord
Pseudo-unipolar neurons	A variant of bipolar neurons
	Sense pressure, touch and pain
	No true dendrites

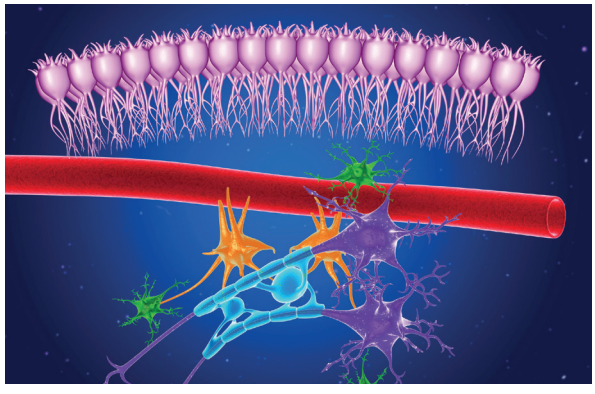

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Figure 1. Brain nervous tissue, showing ependymal cells (pink), a capillary (red), astrocytes (green), microglia (orange) and two nerve cells (purple) with myelin sheaths (light blue) on their axons.

Anatomy

The 100 billion neurons in the brain share a number of common features. Neurons (unlike other cells) are polarized: one neuron can receive contacts from up to 10 000 other cells, and vice versa – any one neuron can contact up to 10 000 postsynaptic cells. Neurons vary in size from 4–100 microns wide. Four groups have been identified (*Table 2*):

1. Multipolar neurons are the most common, where a cell body gives rise to a single long axon and many shorter branching dendrites
2. Unipolar neurons have a single primary extension that functions as both axon and dendrite
3. Bipolar neurons are usually found in sensory organs such as the eye and nose
4. Pseudo-unipolar neurons, a variant of bipolar neurons, sense pressure, touch and pain and have no true dendrites (*Figure 1*).

The CNS is made up of grey and white matter. Grey matter comprises neuronal cell bodies, dendrites, axon terminals, unmyelinated axons, glial cells (astroglia and oligodendrocytes) and capillaries. White matter consists of axons connecting different parts of grey matter. Grey matter and white matter make up 40% and 60% respectively of the brain matter. White matter is mainly composed of myelinated axons (which transmit signals to the grey matter) and has very few neuronal cell bodies.

Pathways

Whether for touch, pain, heat or proprioception the pathway is from the spinal cord to the brain. The cell body of the first order neuron is always located in a dorsal root ganglion. This pseudo-unipolar neuron is T-shaped: one branch extends to the periphery while the other enters and forms part of the spinal cord (Bear et al, 2007).

The lemniscal pathway (lemniscus: Greek for ribbon or band) subserves touch and proprioception. The first axon ascends the dorsal column of the spinal cord. It remains on the same side (ipsilateral) until it connects with the second order neuron in the medulla. The second order axon crosses the midline immediately, travels up the medial lemniscus to the ventral posterolateral nucleus of the thalamus, and connects with the third order neuron.

Before a sensory signal is relayed to the CNS it must be transduced (changed) into an electrical signal in a nerve fibre. Ion channels open in the membrane in response to specific sensory information and signals are transmitted onwards.

Nociceptive pain occurs in five phases: transduction, conduction, transmission, modulation and perception. Transduction (change) begins when peripheral terminals of nociceptive C fibres and A-delta (Aδ) fibres are depolarized. Tissue damage and inflammation may occur following trauma, surgery, inflammation, infection and ischaemia. Mechanical stimuli might include pressure, swelling, abscess, incision or tumour growth; thermal damage would result from burns or scalds; and chemical damage from harmful substances.

A prolonged and sometimes reversible increase in the excitability of neurons in nociceptive pathways is known as central sensitization. It manifests as pain hypersensitivity, allodynia, hyperalgesia and aftersensations. Such changes are seen in patients with fibromyalgia, osteoarthritis and neuropathic pain (Woolf, 2011).

Nociceptors

Pain and temperature information is conducted over small diameter fibres (type Aδ and type C). The cell bodies are in the posterior root ganglia from where fibres ascend or descend the dorsolateral tract (Lissauer's tract) before finally synapsing in Rexed laminae III and IV. This partly explains why the major cause of chronic back pain is secondary inflammation induced by pressure on the dorsal root ganglion caused by lumbar disc herniation.

Pain sensation is sometimes described as 'fast' or 'slow'. Fast pain, called sharp or first pain, is usually conducted over large diameter Aδ fibres. These ultimately reach the ventral posterolateral thalamic nucleus on the contralateral side. Slow pain or second pain, felt as burning pain, is conducted over smaller diameter C fibres. On entering the cord fibres ascend the lateral spinothalamic tract and send collaterals to

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the reticular formation. Fibres from the reticular formation connect to the thalamus, hypothalamus and other areas associated with the emotional component of pain.

The free nerve endings of neurons allow them to transduce, conduct and transmit information (Woolf and Ma, 2007). Tissue insult and inflammation reduce the threshold for nociceptor firing. However, nociceptor activity per se does not lead to the perception of pain because peripheral information has to reach higher centres.

Damaged tissue produces inflammatory (allogenic) substances which stimulate nociceptors directly and reduce the activation threshold, a process called primary sensitization (Reddi et al, 2013). Temporal summation occurs when one presynaptic neuron releases neurotransmitter repeatedly over a period of time (Bessou and Perl, 1969).

Pain sensation

The nodes of Ranvier (1–2 µm gaps within myelinated axons) speed up action potentials. Impulses in the Aδ fibres travel at 20–30 m/sec because they are myelinated and contain such nodes. Aβ fibres are larger and contain more myelin, so transmission of impulses is even faster (35–75 m/sec). Touch, pressure and proprioception are mediated by Aβ fibres. Dull, diffuse aching pain is transmitted by thin and unmyelinated C fibres with a rate of transmission of 0.5–2 m/sec. The Aα fibre mechanoreceptors which are the fastest (80–180 m/sec) also subserve proprioception (*Table 3*).

In the dorsal horn Aδ fibres release glutamate at the secondary neuron and the fibres then decussate. Aδ fibres do not have relay neurons, unlike C fibres. Lissauer's tract comprises myelinated Aδ and unmyelinated C fibres. In the spinal cord axons penetrate the grey matter and synapse on second-order neurons in either the substantia gelatinosa of Rolando or the nucleus proprius.

Even when a limb is amputated nearly all patients develop the illusion that it is still present. Thus, central mechanisms for processing somatic sensory information are still intact despite the absence of peripheral stimuli. This may result from:

1. Abnormal discharges in the remaining cut ends of nerves which grow into neuromas
2. Overactive spinal neurons
3. Abnormal flow of signals through the somatosensory cortex
4. Rapid firing of neurons in the thalamus.

Because of the widespread nature of central pain processing, ablation of the spinothalamic tract, portions of the thalamus or even the primary sensory cortex may not totally relieve the pain (Purves et al, 2001).

Pain transmission

The dorsal and ventral horns of the spinal cord contain ten different layers of grey matter, known as Rexed laminae (named after the Swedish neuroscientist Bror Rexed). Laminae I to VI arranged in the dorsal horn contain the sensory neurons while the ventral horn, comprising the motor neurons, contains laminae VII to IX. Lamina X surrounds the central canal. Laminae III, IV and V are collectively known as the nucleus proprius.

The medial lemniscal system with its large, myelinated nerve fibres transmits signals at velocities of 30–110 m/sec, whereas the anterolateral system, with smaller myelinated fibres, transmits at a few m/sec to 40 m/sec.

Transduction begins when peripheral terminals of nociceptive fibres are depolarized. Nociceptive pain pathways arise mainly from Rexed laminae I, II and V and include the spinothalamic, spinoreticular and spinomesencephalic tracts, dorsal columns and the propriospinal system. Most of these axons ascend in the opposite anterior spinothalamic tract and a smaller number ascend ipsilaterally. Neurons from layers I, II and V project to the lateral thalamus and fibres then project to the somatosensory cortex. Neurons from laminae VI project to the medial thalamus and ultimately reach the reticular formation of the brainstem, periaqueductal grey matter and hypothalamus. As would be expected, such fibres are likely involved in the motivational–affective aspect of pain. The limbic system determines responses to pain affected by attention, mood, and motivation. Pain is modulated by excitatory or inhibitory transmission in the spinal cord. Inhibitory neurotransmitters include endogenous opioids (enkephalins and endorphins), serotonin, noradrenaline, gamma-aminobutyric acid, acetylcholine and oxytocin.

Nerve endings also contain transient receptor potentials, some 28 ion channels in all, located on the plasma membrane. Transient receptor potential channels are similar to voltage-gated K+ channels or nucleotide-gated channels. Transient receptor potential channels convert

Table 3. Types of sensory nerve fibres

Aδ fibres	Conduct quickly at 20–30 m/sec
	Myelinated, large diameter although smaller than Aβ fibres
	Contain nodes of Ranvier
	Acute sharp pain (first pain) and temperature
Aβ fibres	Larger and faster (35–75 m/sec)
	Contain more myelin
	Subserve touch, pressure and proprioception
	From skin receptors (Pacinian, Meissner, Merkel, Ruffini)
C fibres	Thin, unmyelinated, smallest diameter
	Dull, diffuse pain (second pain), itch, tickle
	Transmission is slowest (0.5–2 m/sec)
Aα fibres	Fastest speed (80–180 m/sec)
	Largest diameter
	Subserve proprioception (e.g. muscle spindles, Golgi tendon organ)

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noxious stimuli into receptor potentials, which in turn initiate action potentials in nociceptors. No nociceptors are found inside the CNS (Nilius and Owsianik, 2011).

Joint capsules and ligaments contain high-threshold mechanoreceptors, polymodal nociceptors and 'silent' nociceptors. Many of the fibres innervating endings in joint capsules contain neuropeptides such as substance P and calcitonin gene-related peptide, the release of which may play a role in the development of inflammatory arthritis.

Visceral organs contain mechanical pressure, temperature and chemical receptors. Visceral pain is detected by nociceptors in the internal organs. Sensory nerves in the internal organs are not as widespread as they are in muscles or skin, thus visceral pain is different and feels dull and hard to localize. Visceral pain, unlike somatic pain, may be felt further away from its actual origin. Many visceral nociceptors are silent. In the skin and deep tissues silent or 'sleep' nociceptors are normally unresponsive to noxious mechanical stimulation and become responsive following inflammation and/or tissue injury. One explanation for this 'awakening' phenomenon is that continuous stimulation reduces the threshold of nociceptors. The activation of silent nociceptors may contribute to hyperalgesia, central sensitization and allodynia.

Some algogenic substances from damaged cells activate the transient receptor potential channels which in turn initiate action potentials (Dubin and Patapoutian, 2010). These substances include globulin and protein kinases, arachidonic acid (metabolized into prostaglandin) and cytokines. Prostaglandins block the potassium efflux released from nociceptors which results in additional depolarization, making nociceptors even more sensitive. Aspirin is an effective analgesic because it blocks the conversion of arachidonic acid to prostaglandin. Substance P in neurons and histamine in mast cells have a dual role in inflammation and pain. When injury causes activation of sensory nerve endings either directly or through the release of histamine from the adjacent mast cells, a chain of events ensues. As well as contributing to local vasodilatation, substance P induces histamine release from mast cells, which produces flare and further activates other sensory nerve endings. Histamine is generally associated with itching although it is involved in pain sensation for example, as seen with insect stings.

Histamine is released from mast cells or mastocytes, and mast cell responses cause hypersensitivity and allergic reactions. They are found in skin, near blood vessels and lymphatic vessels, within nerves, in the respiratory system, digestive and urinary tracts. Histamine, interleukins, proteoglycans (e.g. heparin), and various enzymes are present in coarse granules (storage sacs) in the mast cell cytoplasm. When activated, mast cells release the contents of the granules (degranulation) into the surrounding tissues. The result is increased permeability of blood vessels (i.e. inflammation and swelling), contraction of smooth muscles (e.g. bronchial muscle), and increased mucus production.

Nerve growth factor binds to tyrosine kinase receptors on the surfaces of nociceptors leading to their activation. Minute subcutaneous injections of nerve growth factor elicit pain. Substance P and calcitonin gene-related peptide are also released by injury. Substance P is composed of 11 amino acids and is a member of the tachykinin neuropeptide family. It acts as a neurotransmitter and neuromodulator. The vasodilation caused by substance P and calcitonin gene-related peptide leads to the spread of oedema around the initial damage. Calcitonin gene-related peptide, a 37-amino acid neuropeptide, may have an important role in causing migraine.

Tissue damage may also cause an increase in extracellular potassium ions and there is a good correlation between pain intensity and local potassium ion concentration. Serotonin, acetylcholine, low pH (acidic) solution and ATP are also released. Subcutaneous injections of minute qualities of these products excite nociceptors. In terms of muscle spasm and lactic acid, the greater the rate of tissue metabolism, the more rapidly the pain appears. Minute subcutaneous injections of lactic acid excite nociceptors. Perception of a single stimulus requires several transduction mechanisms (Lumpkin and Caterina, 2007). Von Korff et al (1993) found that the presence of up to five different pain complaints (abdominal pain, headache, back pain, chest pain and facial pain) is associated with increased symptoms of depression. Increasing pain severity at onset was associated with more pain-related functional limitations, worse self-rated health, higher unemployment rate, more frequent use of opioid analgesics, and more frequent pain-related doctor visits.

Pain syndromes

Fibromyalgia, a musculoskeletal disorder, affects mainly women between 25 and 50 years of age. Often there is no obvious explanation for the symptoms. Atypical sensory processing in the CNS and dysfunction of skeletal muscle nociception play a role. The concept of 'central pain sensitization' or 'central sensitivity syndrome' considers fibromyalgia to be a disturbance of nociceptive processing which causes a heightened experience of pain described as pain amplification (Dunne and Dunne, 2012). Many patients have increased sensitivity to sensory stimuli not previously painful (allodynia). Allodynia occurs in part through the action of glutamate on the N-methyl-D-aspartate (NMDA) receptor, resulting in increased intracellular calcium levels and kinase activation. It is the consequence of spontaneous nerve activity, enlarged receptive fields and exaggerated stimulus responses transmitted by primary afferent fibres. An important phenomenon is 'windup', increased excitability of spinal neurons evoked by stimulation of afferent C fibres, following a painful stimulus. Subsequent stimuli of the same intensity are perceived as more intense and although this occurs normally in most people it is particularly evident in patients with fibromyalgia. These phenomena are an expression of neuroplasticity (the inherent ability of the brain to reorganize itself by forming new neural connections) and are mainly mediated by NMDA receptors in the dorsal horn (Bellato et al, 2012).

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Normally, descending pain inhibition pathways in the brainstem decrease the strength of incoming nociceptive impulses. In neuropathic pain the function of the descending pathways may be impaired, further amplifying pain.

The commonest psychiatric condition associated with pain is depression. Anxiety will heighten the anticipation of pain, say a visit to the dentist, but is not directly causative. A trial carried out by the authors of a random sample of 55 consecutive patients attending an outpatient psychiatric unit, where they were assessed for concurrent pain, revealed the commonest diagnosis to be depression (H Getachew, F Cullenbrooke, F Dunne, unpublished observational data, 2018). In many cases pain preceded the depression but in others depression was the primary diagnosis. Physicians are now more aware of the association and it is the authors' contention that all depressed patients should be evaluated for pain symptoms and vice versa (Dunne, 2011).

Microglia may play a part in the mechanisms underlying pain hypersensitivity – understanding the role of microglia may lead to new strategies for the diagnosis and management of neuropathic pain (Salter, 2004).

Conclusions

Nociceptive pain is generated by noxious stimuli, inflammatory pain by tissue injury, and neuropathic pain is caused by a lesion of the nervous system. An enhanced capacity to produce or maintain central sensitization is the primary defect in some pain syndromes (Woolf, 2011). Central sensitization produces hypersensitivity in non-inflamed tissue and increases pain sensitivity long after the initiating cause has disappeared (Latremoliere and Woolf, 2009).

Pain is the net effect of a series of interactions in the ascending and descending nervous system involving biological, psychological and physiological processes which affect the cortex and limbic system. Viewing pain in this way allows a greater recognition of all components which encompass the experience. This holistic approach to pain management will have a more beneficial effect than concentrating on one aspect of the pain spectrum. The association between depression and pain becomes stronger as the severity of either condition increases. Likewise, as depression symptoms increase in severity, pain complaints are reported more often (Bair et al, 2003). The most likely explanation is that depression and pain share biological pathways, and neurotransmitters and symptoms follow the same descending pathways in the CNS. In recent years studies have shown overlaps between pain and depression-induced neuroplasticity and neurobiological changes. Sheng et al (2017) have emphasized that sensory pathways of pain share the same brain regions involved in mood management involving the limbic system. **BJHM**

Conflict of interest: none.

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KEY POINTS

- Nociceptive and neuropathic pain are caused by tissue damage and nerve damage respectively.
- Whether for touch, pain, heat or proprioception the pathway is from the spinal cord to the brain.
- When a somatosensory neuron is stimulated naturally or artificially, the sensation perceived is specific to the information provided by that neuron.
- Pain sensation is often described as 'fast' or 'slow' – fast pain is usually conducted over Aδ fibres, while slow pain is conducted over smaller diameter type C fibres.
- Nociceptive pain occurs in five phases: transduction, conduction, transmission, modulation and perception.
- Nociceptors can trigger a prolonged but reversible increase in the excitability and synaptic efficacy of neurons in central pathways, known as central sensitization.
- Algogenic substances (e.g. histamine, bradykinin, substance P) cause sensory nociceptive pain while neuropathic pain is produced by damage to the peripheral or central nervous system.

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