The International Association for the Study of Pain (IASP) definition of pain is:

"An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage."

A pain system involves receptors that pick up the message, neural pathways that transmit it and analytical centres in the brain to process the information.
Pain receptors are generally referred to as "nociceptors".

Reception:

Somatic nociceptors tend to be polymodal, i.e. they can detect damage due to a variety of stimuli including heat, mechanical trauma, chemical irritation etc. These give rise to burning pain or itch via C fibres and sharp pain via A delta nerve fibres.
Visceral nociceptors are somewhat different.

These occur in viscera such as the bladder and gut. They can encode both innocuous and noxious distension of the viscera (innocuous referring to normal distension, noxious to damaging levels of distension).

Some only start firing at noxious levels. This may account for what are known as "visceral hyperalgesia syndromes" such as Irritable Bowel Syndrome and Interstitial Cystitis. (Hyperalgesia= increased response to painful stimuli)

There may also be referred pain from the viscera e.g. post-sterilisation shoulder pain referred from under the diaphragm to the shoulder tip, or bladder distension may cause pain in the skin

of the foot.

In 1996, Dmitrieva and McMahon ([i]) found that

"inflammation sensitises visceral primary afferent neurones."

-in other words, an episode of inflammation, such as a bladder infection, might sensitise the bladder nerves and trigger an increased response to even normal levels of distension, which may persist well after the infection has resolved.

Habler et al ([ii]) found that previously "silent" nerves became active during inflammation. 70% of primary afferents (main sensory nerves) in the bladder cannot be stimulated in the normal physiological situation, but if the bladder is inflamed (e.g. with turpentine in an experimental situation), these neurones start firing.

Investigators have discovered that hypersensitivity to temperature or touch peaks when the numbers of certain immune cells within damaged nerves are highest. This suggests that cytokines, small peptides produced by these cells, are involved in mediating pain. A similar process also occurs in the spinal cord, regardless of the original site of injury.

Current research is focusing on identifying the cells that produce various cytokines within the CNS: neurons, microglia and astrocytes (star-shaped cells). Astrocytes produce proteins which change cell function, and appear to have a key role in pain.

Transmission:

Nerve information from nociceptors reaches the spinal cord dorsal horns; this afferent input terminates in various laminae (layers), depending on the type of nerve fibre involved.

A large number of secondary order intermediate neurons are then activated.

Dorsal horn cells are either nociceptor-specific, responding only to noxious stimuli, or multireceptive (?wide dynamic range', ?convergent'), which may also be activated by innocuous stimuli.

Intermediate neurons transmit the information to neurons that connect to the brain (ascending pathways).

Numerous different neurotransmitters, some excitatory, some inhibitory, are involved.

Note that input into a spinal nerve root (from a specific dermatome) distributes several segments distally after the afferent has entered the dorsal root entry zone.

For example an L5 root may have collaterals extending as far as L1-2.

In the spinal nerve ligation model (nerve is tied tightly) loss of input into the spinal cord might cause upregulation of the excitatory systems (i.e. the system tries to compensate for the reduced or lost signal by becoming more sensitive).

This results in hyperexcitability, expanded receptive fields and neurochemical changes in the nerve.

This is an example of plasticity, the ability of the nervous system to change.

The spinal nerve ligation model results in a variety of effects, which together tend to increase the excitation of the CNS and decrease down-regulation (dampening down messages from the brain) via the GABA neurotransmitter system.

One of the changes observed is an increase in NGF messenger RNA (which codes for the neurotrophin, nerve growth factor).

This is known as gene induction.

German author Zimmermann reported in 2001 ([iii]),

"Repeated or prolonged noxious stimulation and the persistent abnormal input following nerve injury activate a number of intracellular second messenger systems, implying phosphorylation by protein kinases, particularly protein kinase C (PKC).

Intracellular signal cascades result in immediate early gene (IEG) induction, which is considered as the overture of a widespread change in protein synthesis, a general basis for nervous system plasticity.

Although these processes of increasing nervous system excitability may be considered as a strategy to compensate functional deficits following nerve injury, its by-product is widespread nervous system sensitization resulting in pain and hyperalgesia."

Pain Transmission

The pathophysiology of neuropathic pain involves:

- Excitotoxicity: One of the mechanisms now known to be responsible for the central sensitisation is the NMDA receptor output.

This glutamate receptor switches a low level of peripheral input to a high level of neuronal activity.

Once the NMDA receptor is recruited by repeated C fibre (sensory from the periphery) stimulation, there is a massive output for the same (maybe minimal) level of stimulation as before.

When the stimulus is discontinued, there is a slow recovery to normal, baseline levels of NMDA. NMDA receptors are implicated in "wind-up", neurogenic inflammation, neuropathy and spinal ischaemia. Ketamine, at low doses, blocks NMDA receptors.

Ketamine is a dissociative anaesthetic that is occasionally used for pain relief but unfortunately may cause side-effects such as hallucinations, amnesia and motor deficits. Schwartzman and Maleki noted ([iv]):

"The role of the clinician in identifying and eliminating the source of the pain is crucial before the effects of excitotoxicity and central sensitization permanently alter the physiology of the central pain-projecting neurons and make treatment ineffectual."

Glutamate has also been implicated in CNS inflammatory conditions.

In an experimental model of Multiple Sclerosis, glutamate excitotoxicity was investigated ([v]): increased extracellular glutamate is important in damage to oligodendrocytes and axons.

Activated immune cells present in the inflammatory infiltrates in CNS lesions produce cytotoxic factors such as tumor necrosis factor ([vi]), matrix metalloproteinases ([vii]), active oxygen species ([viii])

and autoantibodies (
[ix]
), and may also kill by direct cell-to-cell contact.

During inflammation, glutamate is produced and released into the extracellular space ([x]) by activated leukocytes and microglia.

Increased glutamate levels have been found in the cerebrospinal fluid of patients with CNS inflammatory conditions, such as acute encephalitis, meningitis and MS ([xi] ; [xii]).

   -   Sodium channels: accumulation of sodium channels can occur at the neuroma site, at tips of injured axons, along the length of the axon and at the dorsal root ganglion and results in foci of hyperexcitability and ectopic discharges in the axon and the cell body of the injured neuron, causing episodes of stimulus-independent (spontaneous) pain.
   -   Therefore these sodium channels are the target for drug treatment with agents such as anticonvulsants and local anaesthetics.
   Ectopic discharges: "Injured afferent neurons produce spontaneous activity that is generated away from the normal impulse generation site... this activity, referred to as ectopic discharges, may play a significant role in neuropathic pain" ([xiii]) Data from rat studies suggest that there are two components of ectopic discharge generator mechanisms: sympathetically dependent and sympathetically independent.

   -   Deafferentation: due to partial or complete interruption of peripheral or central afferent neural activity. In 2000, German authors reported on a rat study of L5 spinal nerve injury: "After dorsal rhizotomy neuropathic pain behavior may be related to deafferentation whereas after spinal nerve lesion it may be caused by ectopic activity." ([xiv])

   -   Central sensitisation: "may be manifested as increases in spontaneous and stimulus-evoked neuronal activity within the spinal cord, which, in turn, contribute to the development and maintenance of neurogenic and inflammatory pain syndromes." ([xv])

There may be an increase in spontaneous neural activity of pain transmission pathways (including dorsal horn neurons and pain-related thalamic neurons) resulting in spontaneous pain.

- Sympathetic involvement: Baron noted ([xvi]): "After nerve lesion the sympathetic nervous system might interact with afferent neurons.

Activity in sympathetic fibers can induce further activity in sensitized nociceptors and, therefore, enhance pain and allodynia (sympathetically maintained pain).

This pathologic interaction acts via noradrenaline released from sympathetic terminals and newly expressed receptors on the afferent neuron membrane."

Peripheral sensitisation:

In peripheral sensitisation, tissue damage, and inflammation, along with sympathetic nerve terminals, give rise to a ?sensitising soup' of chemicals such as prostaglandins, histamine, cytokines etc.

These cause a lowered threshold of nociceptors, ectopic nerve discharges, and accumulation of sodium channels.

Central sensitisation:

Soon after a peripheral nerve injury, the dorsal horn is bombarded by a variety of neurotransmitters.

Amongst these, glutamate and aspartate, which are excitatory transmitters, interact with the N-methyl-D-aspartate (NMDA) receptors and neurokinin interacts with the neurokinin type 1 (NK1) receptors.

Hyperalgesia after tissue injury and inflammation may be due to prolonged and excessive activation of spinal cord excitatory amino acid receptors and subsequent intracellular cascades.

Tonic activation of NMDA receptors activates second-messenger systems, resulting in sensitization of ion channel complexes, including that of the NMDA receptor. As a consequence, this leads to calcium entry into the cell.

Calcium acts as a very important secondary messenger, activating nitric oxide synthetase and thus resulting in the synthesis of nitric oxide.

It leads to immediate early gene expression as well as activating phospholipases, which decrease the threshold of the dorsal horn and lead to ectopic discharges.

Luo et al. ([xvii]) investigated the upregulation of dorsal root ganglion $\alpha_2\delta$ calcium channel subunit and its correlation with allodynia in spinal nerve-injured rats.

They hypothesised that "nerve injury may result in altered $_2\delta$ subunit expression in spinal cord and dorsal root ganglia (DRGs) and that
this change may play a role in neuropathic pain processing."

The anticonvulsant drug Gabapentin only reacts with abnormal calcium channels and has been found to be useful to combat neuropathic pain and recently to have some effect on muscle spasms. Luo et al. noted that spinal injection of gabapentin suppresses allodynia by an unknown mechanism.

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These are all features of peripheral sensitisation.

Central sensitisation or ?wind-up' is mediated by a number of neuromodulators, such as adenosine triphosphate (ATP), calcitonin gene-related peptide (CGRP), aspartate glutamate (NMDA), nerve growth factor (NGF), substance P, nitric oxide, neurokinin and eicosanoids (prostaglandins, thromboxanes, leukotrienes).

Thus these substances are appropriate targets to prevent central sensitization.
Immune cells (mast cells) are also involved in hyperalgesia, as they produce NGF, 5-HT and histamine. NGF is found in conditions such as interstitial cystitis. NGF introduced into the bladder experimentally, induces a protein called Fos in the spinal cord.

Fos is a marker of persistent activation such as that seen in central sensitisation.

A new line of research is looking into the role of endocannabinoid receptors, which are present in the body.

These respond to cannabis-related compounds and similar compounds within the body in much the same way as endogenous opioid receptors respond to opiates like morphine and endorphins, which are the body's equivalent substances. Cannabinoids reduce NGF-induced Fos expression.

Processing:

As stated before, pain is a subjective, conscious sensation, so it is obviously essential to look at which parts of the brain are involved.

Recently available imaging techniques such as PET and fMRI (functional MRI) scans have shown that there is no single pain centre but rather several areas that are activated by pain.

The thalamus, limbic system and various cortical areas (inferior parieto-temporal, prefrontal, insular and anterior cingulate) are all involved.

It is likely that NMDA involves the limbic system, which is also responsible for the link between sensation, emotions and the endocrine (hormonal) system.

Laurent et al. ([xix]) looked at PET and fMRI scans of brain function related to central pain. T

hey noted the prior sixteen studies using PET had demonstrated pain-related activations in the thalamus, insula/SII, anterior cingulate and posterior parietal cortices.

They also reported that activity in right pre-frontal and posterior parietal cortices, anterior

cingulate and thalami can be modulated by attention (hypnosis, chronic pain, diversion, selective attention to pain) and therefore "probably subserve attentional processes rather than pain analysis."

The brain not only receives incoming information but also sends descending inhibitory messages to "dampen" the system.

Descending inhibitory control from the thalamus is partly mediated within the brainstem in the periaqueductal grey.

This system inhibits the transmission of phasic (short, sharp) pain more effectively than tonic (persistent) pain. The latter is probably inhibited within the mesolimbic dopamine system.

The main neurotransmitters involved with the descending control include:

- Serotonin (5-HT)
- acetylcholine (Ach)
- noradrenaline (alpha2 receptors)
- gamma-aminobutyric acid (GABA)
- endorphins (opioid receptors)
- glycine
- cholecystokinin (CKK)

Hence agents, which affect these neurotransmitters are targets for pain treatment.In summary, pain is initiated by nociceptors, which detect damage.

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The message is transmitted via numerous neurotransmitters along neurones to the central nervous system (CNS).

In the spinal cord, there may be a "sensitisation" which results in any descending control of pain (from the brain) being over-ridden.

Pain is perceived in the brain and may affect a number of different parts of the brain, which has a bearing on other effects such as emotional, endocrine and immune. Descending control may modulate pain.

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