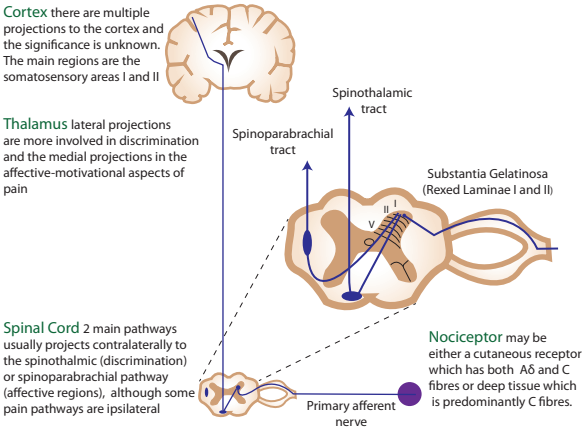
PAIN

Definition of Pain "an unpleasent sensory and emotional experience associated with actual or potential tissue damage, or describes in terms of such damage"

Ascending Pain Pathways

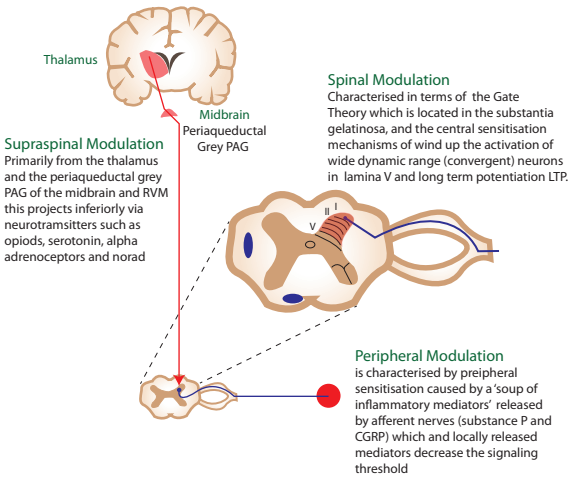


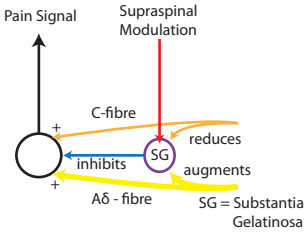
Basic pain pathways Physiological pain occurs when a noxious stimulus activates peripheral nociceptors and is recognised as a potentially harmful stimulus. The pathophysiological processes which include inflammation and nerve damage following injury or ischaemia, result in an altered response and are therefore termed pathophysiological pain. Nociceptors are widespread in the skin, muscle, connective tissues, blood vessels and viscera. They respond to mechanical, thermal, and chemical stimuli. The main molecular events that control the excitability of of a primary neuron include the opening and closing of voltage gated sodium or potassium channels. Primary afferent nociceptors are pseudounipolar, with the cell body located in the dorsal root ganglion. The two main cutaneous neuron types associated with noxious stimulation are the Aδ fibres which are small myelinated fibres responsible for localisation and sharp focussed pain responses more so in the cutaneous setting and the C fibres which are slow unmyelinated fibres associate with dull diffuse pain and are found in higher relative numbers on the viscera. In addition to having a preponderance of C fibres, the primary afferent fibres in the deep tissues may elict repsonses such as sweating, increased blood presure and increased respiratory rate.

Peripheral sensitisation is an excitatory modulation of the pain response in peripheral tissues. Part of the inflammatory response is the release of intracellular contents from damaged cells such as macrophages, lymphocytes and mast cells. Nociceptive stimulation also results in a neurogenic inflammatory response with the release of substance P, deurokinin A and calcitonin gene related peptide (CGRP) from the peripheral terminals of nociceptor afferent fibres. The result is a reduction in the threshold for firing of the afferent nerve and the so called peripheral sensitisation. Clinically this results in increased sensitivity to both noxious and non-noxious pain (eg pressing a swollen inflammed tissue causes more pain).

Central sensitisation beyond the primary area of hyperalgesia there is a secondary area of hyperalgesia where the threshold is not decreased. This region is explained by central sensitisation mechanisms caused in the dorsal horn of the spinal cord which cause an excitatory modulation of the pain response. These mechanisms include wind-up which is mediated by NMDA receptors and refers to a phenomenon when repeated stimulus 'winds-up' the neurons and may lead to a sustained response. There is also a widening of receptor fields and this may be witnessed by the convergent (wide dynamic response WDR) neurons in lamina V now sending pain signals to non noxious stimuli. The final mechanism disussed here is long term potentiation, which relates to the increased efficacy of pathways that are repeatedly activated, potentiating responses in the long term and implicated in chronic pain syndromes. The concept of central sensitisation is fundamental to practice of pre-emptive analgesia which seeks to prevent these secondary responses. Preventive analgesia is the persistence of analgesic treatment efficacy beyond its expected duration. In clinical practice, preventive analgesia appears to be the most relevant and holds the most hope for minimising chronic pain after surgery or trauma, possibly because it decreases central sensitisation and 'windup'.

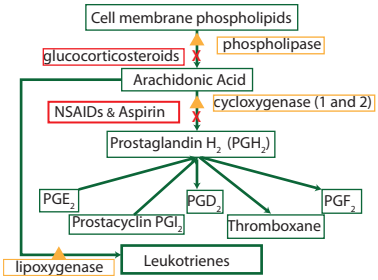
Descending Pain Pathways





Gate theory and central modulation was proposed as an explanation for modulation of the pain response. It is believed to occur in the substantia gelatinosa. In this theory the information which arrives from the primary afferent nerve is modulated by an inhibitory signal produced by an additional neuron. Essentially the Aδ fibres are believed to augment this response and therefore reduce pain signalling. The C Fibres are believed to reduce inhibition and therefore increase the pain signalling. It is possible to take this concept further as some texts do and intergrate the supraspinal modulation as well, which would also influence the inhibitory neuron through mediators such as opiods, alpha adrenoceptors, serotonin and noradrenaline.

Eicosanoids arachidonate metabolites, including prostaglandins, prostacyclin, thromboxane A2, leukotrienes, lipoxins, and hepoxylins—are not stored but are produced by most cells when a variety of physical, chemical, and hormonal stimuli activate acyl hydrolases that make arachidonate available. Prostaglandins (PGs), leukotrienes (LTs), and related compounds are called eicosanoids, from the Greek eikosi ("twenty"). Precursor essential fatty acids contain 20 carbons and three, four, or five double bonds. The production of protaglandins and leukotrienes occurs in a stepwise process which has several therapeutic targets and is shown adjacent. Eicosanoids and PAF lipids contribute to inflammation, smooth muscle tone, hemostasis, thrombosis, parturition, and gastrointestinal (GI) secretion. PGE_2 Hyperalgesia, vasodilation, production gastric mucus, gastric acid, fever. PGI_2 Hyperalgesia, vasodilation, inhibit platelet aggregation, gastric mucus, renin release, natiuresis. TXA_2 Platelet aggregation, vasocontriction. PGF_2 Bronchoconstriction, unterine contraction. PGD_2 Vasodilation, bronchoconstriction. Several classes of drugs, most notably aspirin, the traditional nonsteroidal anti-inflammatory agents (NSAIDs), and the specific inhibitors of cyclooxygenase-2 (COX-2), such as the coxibs, owe their principal therapeutic effects to blockade of eicosanoid formation.



Classification scheme for analgesics

Opioid Analgesics

Opiates	Semi synthetic	Synthetic	Endogenous
Morphine	Oxycodone	Phenylpiperidines	Endorphins
Codiene	Partial agonist	Pethidine	Endomorphins
	Buprenorhine	Fentanyl	Enkephalins
	Antagonist	Alfentanil	Dysnorphins
	Naloxone	Remifentanil	
	Naltrexone	Complex Analgesic	
		Tramadol	

Non Opioid Analgesics

Paracetamol	NSAIDS	Other
	Non selective	NMDA antagonists - Ketamine
	COX -2 selective	Alpha2 Agonists - Clonidine
		Antidepressants - Amitryptaline
		Anticonvulsants
		Gases and Vapours
		Substance P depletors
		Hormones / Steroids

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