Pain

Clinical pain is broadly categorised as acute pain and chronic pain. A neurological disease affecting the sensory pathway can produce severe chronic pain— termed neuropathic pain— unrelated to any peripheral tissue injury. The afferent sensory nerves associated with impulses for pain in the peripheral tissue are C and Aδ which have small diameters. These nerves have sensory endings around peripheral tissues and can be activated by several stimulations. The majority of non-myelinated C fibres are associated with polymodal nociceptive endings and can convey a dull, diffuse burning pain, whereas myelinated (Aδ) fibres convey a sensation of sharp, well-localised pain. C and Aδ fibres convey nociceptive information from muscle and viscera as well as from the skin. The cell bodies of spinal nociceptive afferent fibres lie in the dorsal root ganglia.

Molecular mechanism for pain generation

The nociceptive afferent neurons release **glutamate** and **possibly ATP** as the fast neurotransmitters at their central synapses in the dorsal horn. **Glutamate acting on the AMPA** receptor is responsible for **fast synaptic transmission** at the first synapse in the dorsal horn. There is also **a slower NMDA receptor-mediate response**, which is important for the phenomenon of **"wind-up".** The nociceptive afferent neuron containing several neuropeptides, particularly substance P and calcitonin gene-related peptide(CGPR). These are released as mediators at both central and peripheral terminals and play an important role in the pathology of pain. In the periphery substance, substance P and CGRP produce some of the features of neurogenic inflammation.

Neuropathic pain states, characterized by deviations from normal physiological pathways, lead to conditions such as hyperalgesia and allodynia. Hyperalgesia, which is an exaggerated pain response to mild noxious stimuli, involves both peripheral sensitization of nociceptive nerve terminals and central facilitation of transmission at the levels of the **dorsal horn and thalamus**. The peripheral component of hyperalgesia is attributed to mediators such as bradykinin and prostaglandins, which act on nerve terminals, enhancing their responsiveness. Additionally, the expression of certain sodium-channel subtypes, particularly Nav1.7, is increased in sensory neurons in various pathological pain states, enhancing their activity and underlying the sensitization to external stimuli that cause inflammatory pain and hyperalgesia. Individuals with mutated Nav1.7 can not generate pain sensory.

Central facilitation and inhibition

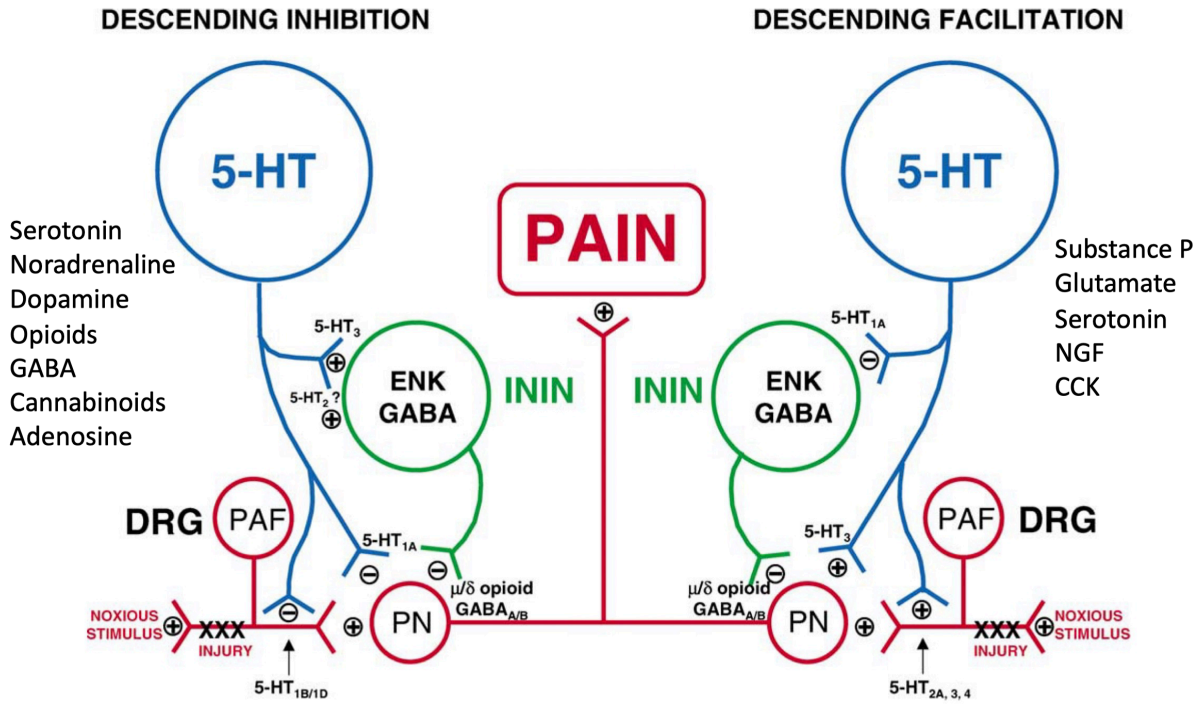
Central mechanisms of neuropathic pain include the facilitation of synaptic transmission within the dorsal horn of the spinal cord. This facilitation is evidenced by the '**wind-up' phenomenon**, where synaptic potentials in dorsal horn neurons steadily increase in amplitude in response to nociceptive inputs. **Mediators such as 5-HT, substance P, CGRP, brain-derived neurotrophic factor (BDNF), and nitric oxide (NO) are integral to this process.** They increase the secretion of peptides on nociceptor afferent neurons, promoting the formation of synaptic contacts. Conversely, the central nervous system employs **descending inhibitory** pathways to control impulse transmission in the dorsal horn. A key component of this system is the periaqueductal grey (PAG) area in the midbrain, which receives inputs from various brain regions, such as the hypothalamus, amygdala, and cortex. These pathways modulate the nociceptive gate in the dorsal horn primarily through n**eurotransmitters like 5-HT and enkephalins.** They inhibit the discharge of spinothalamic project neurons directly or via interneurons, like increasing GABA, or couple with Gi and Go pathways. This descending inhibition is a crucial mechanism for the efficacy of opioid analgesics.

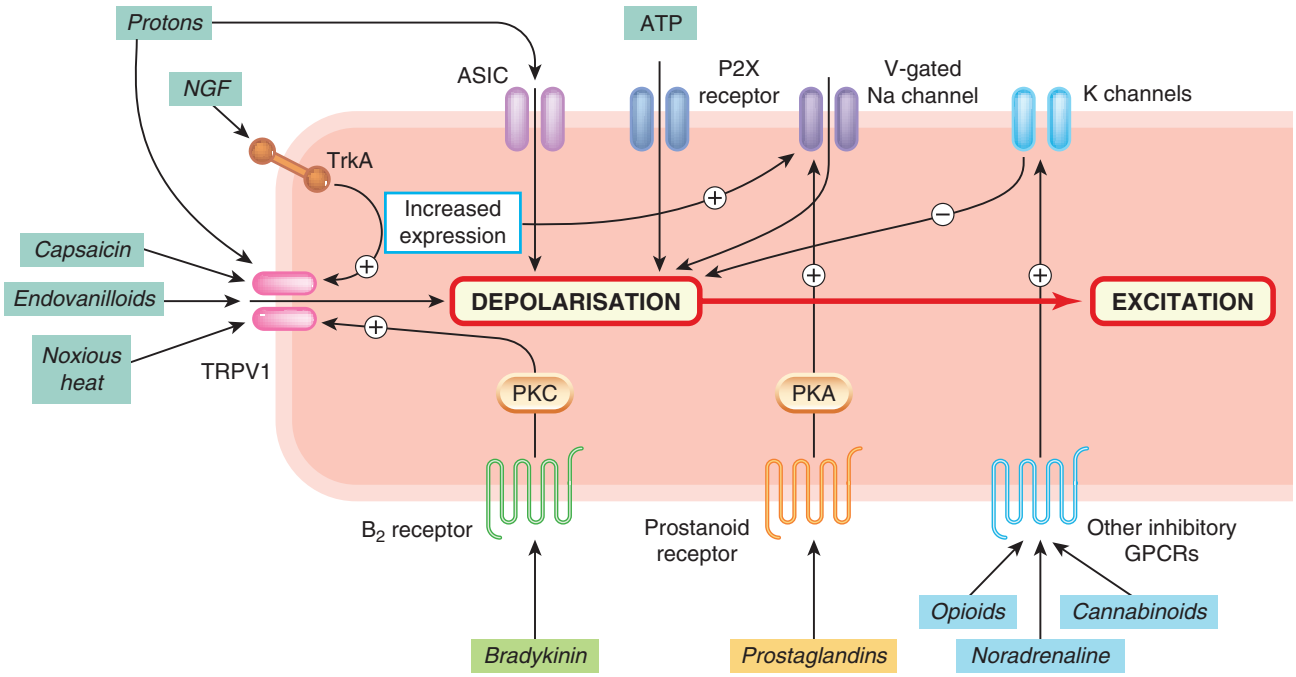
In the central nervous system, 5-HT plays dual roles. It contributes to both the facilitation and inhibition of pain. In descending facilitation, 5-HT acts through specific receptors to enhance the excitatory transmission of pain signals, contributing to conditions like hyperalgesia. Conversely, in descending inhibition, 5-HT helps to suppress pain transmission, demonstrating the neurotransmitter's complex and pivotal role in pain modulation. This dual functionality highlights the potential of targeting 5-HT pathways in developing treatments for neuropathic pain.

CHEMICAL SIGNALLING IN THE NOCICEPTIVE PATHWAY

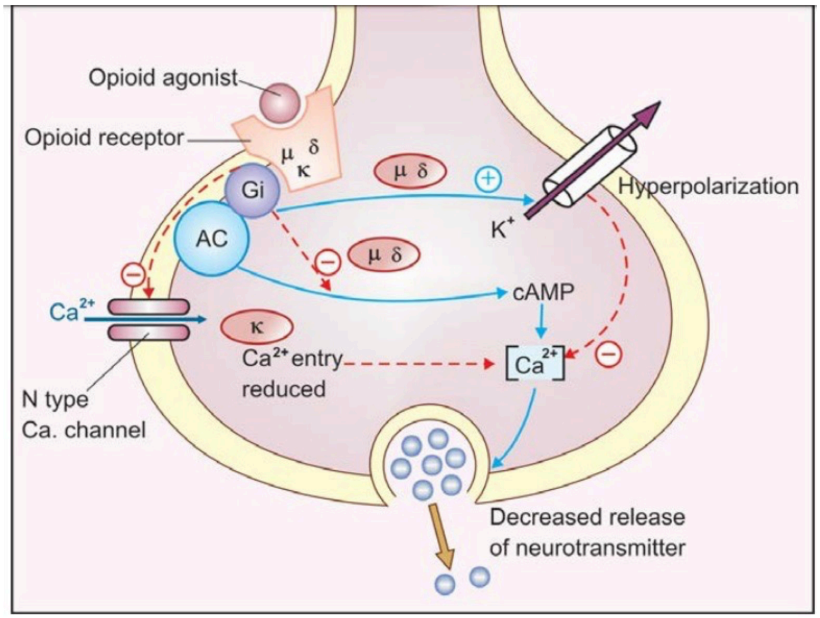
Many chemical substances can stimulate the nociceptive ending. The transient receptor potential (TRP) channel family comprises some 27 or more structurally related ion channels that serve a wide variety of physiological functions Capsaicin, the substance in chilli peppers that gives them they're selectively excites nociceptive nerve terminals, causes intense pain if injected into the skin or applied to sensitive structures such as the cornea. It produces this effect by activating TRPV1. Agonists such as capsaicin open the channel, which is permeable to Na+, Ca 2 + and other cations, causing depolarisation and initiation of action potentials. The large influx of Ca 2 + into peripheral nerve terminals also results in peptide release (mainly substance P and CGRP), causing intense vascular and other physiological responses. TRPV1 responds not only to capsaicin-like agonists but also to other stimuliincluding temperatures over about 42°C (the threshold for pain) and proton concentrations in the micromolar range (pH 5.5 and below), which also cause pain.

Another chemical substance is prostaglandins. Prostaglandins do not themselves cause pain, but they strongly enhance the pain-producing effect of other agents such as 5-HT or bradykinin (which will active B2 receptor and active TPRV1) It is of interest that bradykinin itself causes prostaglandin release and thus has a powerful ‘self-sensitising’ effect on nociceptive afferents. The analgesic effects of NSAIDs result from inhibition of prostaglandin synthesis.





One of the most popular analgesic drugs is **opioid drugs**. Opium contains **morphine** and substances have similar structures to **codeine, heroin** and so on. It has been used for social and medicinal purposes for thousands of years as an agent to produce euphoria, analgesia and sleep, and to prevent diarrhoea. Opioids promote the opening of potassium channels and inhibit voltage-gated calcium channels. These membrane effects decrease neuronal excitability (because the increased K + conductance causes hyperpolarisation of the membrane making the cell less likely to fire action potentials) and reduce transmitter release (due to inhibition of Ca 2+entry). Opioid has four types of receptors. μ Receptors are responsible for most of the analgesic effects of opioids, and for some major unwanted effects. μ, δ, and ORL1 subtypes open the potassium channel and κ subtypes close the Ca channel. At the biochemistry level, all four types of opioid receptors belong to the family of Gi /G o protein-coupled receptors. Opioids thus exert powerful effects on ion channels on neuronal membranes through a direct G protein coupling to the channel. At the biochemical level, all four receptor types inhibit adenylyl cyclase and cause MAP kinase (ERK) activation. Opioid receptors are widely distributed in the brain and spinal cord. Opioids are effective as analgesics when injected in minute doses into several specific brain nuclei (such as the insular cortex, amygdala, hypothalamus, PAG region and RVM) as well as into the dorsal horn of the spinal cord. Evidence suggests that endogenous opioid peptide release both at supraspinal and spinal sites and that at the spinal level, there is also a component of the analgesia that results from



the release of serotonin (5-HT) from descending inhibitory fibres. There is also evidence (Sawynok, 2003) that opioids inhibit the discharge of nociceptive afferent terminals in the periphery, particularly under conditions of inflammation, in which the expression of opioid receptors by sensory neurons is increased. Injection of morphine into the knee joint following surgery to the joint provides effective analgesia, undermining the age-old belief that opioid analgesia is exclusively a central phenomenon.