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NEUROSCIENCE

Pain mechanisms

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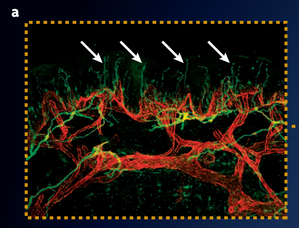
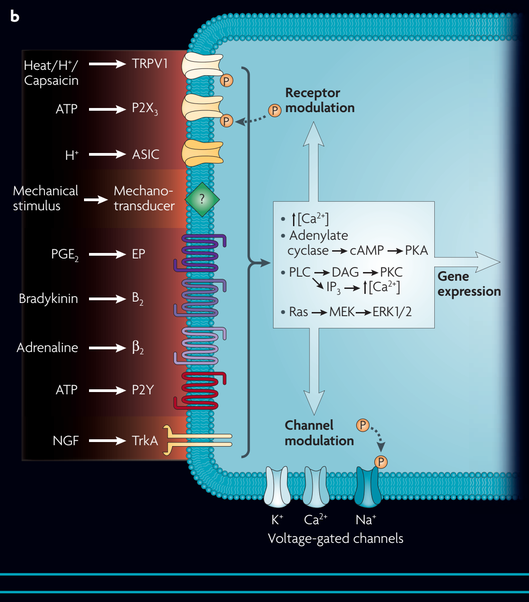
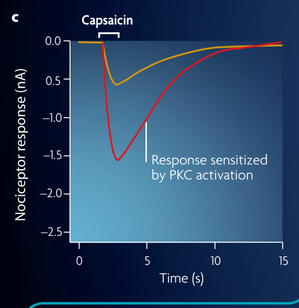
Pain is an unpleasant sensation resulting from the intricate interplay between sensory and cognitive mechanisms. Chronic pain, resulting from disease or injury, affects nearly every fifth person in the Western world, constituting an enormous burden for the individual and society. Sensitization of pain signalling systems is a key feature of chronic pain and results in normally non-painful stimuli eliciting pain. Such sensory changes can occur not just at the sites of injury, but in surrounding normal tissues. This and other observations suggest that sensitization occurs within the CNS as well as within nociceptor terminals. Here we consider the consequences of a noxious stimulus applied to our unfortunate builder's hand, from sensory transduction to pain perception. We describe the structural and functional elements present at different levels of the nociceptive system, as well as some of the changes occurring in chronic pain states. Although our poster highlights a flow of information from the periphery to the CNS, it should be noted that higher brain centres exert both inhibitory and facilitatory controls on lower ones. The challenge for the next decade will be to effectively translate this knowledge into the development of novel analgesic agents for better pain relief.

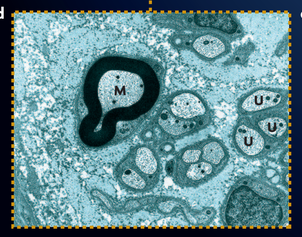
Peripheral nociceptor terminals

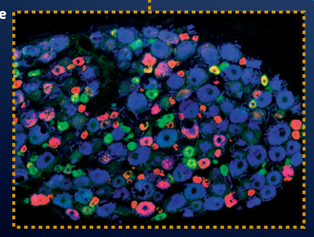
Nociceptors are essential for the appreciation of pain. These primary sensory neurons have cell bodies in the dorsal root or trigeminal ganglia, and possess naked peripheral endings that terminate in the skin, mostly in the epidermis (arrows, **a**). Ion channels in the plasma membrane of nociceptors have a key role in the transduction of stimuli such as heat or pain-producing chemicals, as illustrated in **b**. The ion channel(s) that responds to noxious mechanical stimuli is still unknown. Inflammation will result in the production of a large number of mediators (for example, prostaglandin, bradykinin and nerve growth factor (NGF)). These mediators bind to G-protein-coupled receptors or, in the case of NGF, tyrosine kinase receptors on the nociceptor terminal, resulting in the activation of multiple second messenger pathways that have an important role in sensitization. Sensitization is achieved by receptor and/or channel modulation and, over a longer period of time, by alterations in gene expression. One example of such sensitization is shown in **c**, where the activation of protein kinase C facilitates the response of sensory neurons to capsaicin.





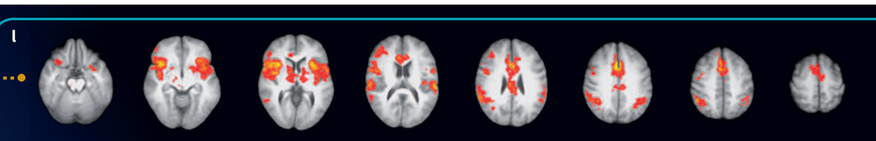






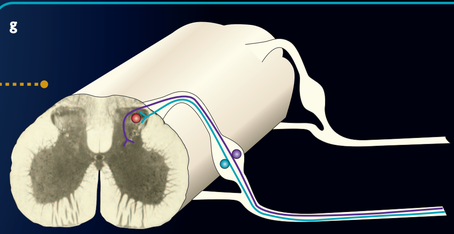
Peripheral nerves and the DRG

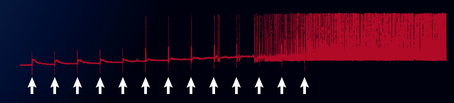
In peripheral nerves, nociceptors have unmyelinated or thinly myelinated axons (**d** is an electron micrograph of a cross-section of a human nerve, showing one large myelinated (M) and multiple unmyelinated (U) fibres). Nociceptors have a lower conduction velocity compared with other peripheral sensory nerve fibres. Within the dorsal root ganglion (DRG; **e**), nociceptive afferents mostly have small diameter cell bodies and can be identified by particular patterns of gene expression. They can be divided into those that express neuropeptides (red in **e**) and those that are non-peptidergic (green in **e**). Large diameter, mostly non-nociceptive afferents are shown in blue. The development of ectopic (spontaneous) activity in primary afferents following nerve injury (**f**) is likely to contribute to the generation of neuropathic pain. In addition, injured axons develop a novel mechanosensitivity and an increased response to catecholamines, changes that are likely to represent alterations in ion channel expression and trafficking within DRG cells.



Brain

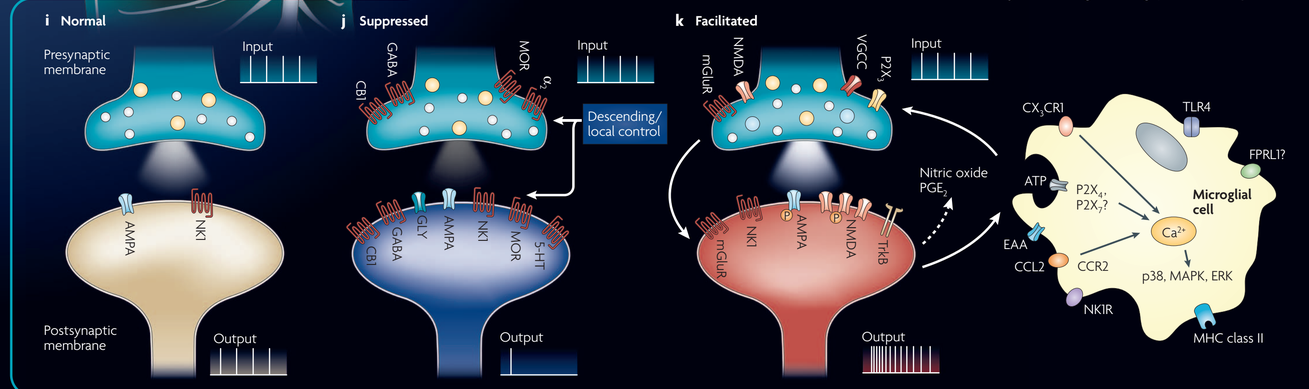
Neuroimaging with functional MRI allows direct evaluation of where pain is represented in the brain. A painful stimulus reliably leads to activation of multiple brain areas, commonly referred to as the pain matrix. Figure **l** shows an example of activation of this matrix in one individual in a series of axial brain sections after the application of noxious heat to one hand. The strength of activation is colour-coded (red, moderate responses; yellow, strong responses). The different areas activated are thought to be associated with different aspects of pain. S1 and S2 (the primary and secondary somatosensory cortices, respectively) may primarily function to discriminate the location and intensity of a painful stimulus, while the anterior cingulate cortex, frontal cortex and anterior insula regions seem to be more involved in cognitive and emotional components. Other areas less commonly activated, including the amygdala and the entorhinal complex, are associated with fear and anxiety. The different brain areas also show strong modulation depending on the context in which the stimulus is given, including the degree of attention/distraction, anxiety, expectation, depression and following analgesic drug treatment.





Spinal cord

Primary afferent nociceptors mostly terminate in the spinal cord (**g**), which has an important role in the integration and modulation of pain-related signals. Second-order neurons receiving input from nociceptors and projecting to the brain are located in both superficial and deep laminae of the dorsal horn. These cells often have convergent inputs from different sensory fibre types and even different tissues. Spinal nociceptive processing exhibits activity-dependent plasticity (**i–k**), as repetitive activity can induce long-lasting facilitation in output systems (**h**). Such enhanced responses, generically referred to as central sensitization, add to the abnormal pain sensitivity seen in many chronic pain states. Multiple processes seem to contribute to these states, including the enhancement of presynaptic transmitter release and, crucially, recruitment of postsynaptic NMDA receptors (**k**). Non-neuronal cells, particularly microglia, release factors that may contribute to central sensitization. Both pre- and postsynaptic elements are strongly gated by descending facilitatory and inhibitory influences from the brain. The inhibitory influences (**j**) use neurotransmitters that are mimicked by some analgesic drugs, such as morphine.



Definitions

Nociception — The detection of stimuli that are capable of producing tissue injury.
Pain — An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (as defined by the International Association for the Study of Pain).
Inflammatory pain — Pain as a consequence of inflammation (for example, rheumatoid arthritis).
Neuropathic pain — Pain as a consequence of injury to the nervous system. This can include the PNS (for example, postherpetic neuralgia) or CNS (for example, spinal cord injury).
Sensitization — Plastic changes in the PNS or CNS (adaptive or pathological) that lead to enhanced responses and/or lower thresholds.
Hyperalgesia — Increased pain perception in response to the same stimulus following tissue injury.
Allodynia — The perception of a stimulus as painful when previously the same stimulus was reported to be non-painful.

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Confocal image of nociceptor terminals (**a**) courtesy of Donald A. Simone, University of Minnesota, USA. Nociceptor response (**b**) courtesy of Vittorio Vellani and Peter McNaughton, University of Cambridge, UK. Electron micrograph of a nerve (**d**) courtesy of Susan Hall, King's College London, UK. Trace recording (**h**) courtesy of Stephen Thompson, University of Plymouth, UK. fMRI images (**l**) courtesy of Irene Tracey, Oxford University, UK.

Weblinks for more information
International Association for the Study of Pain: http://www.iasp-pain.org
The American Pain Society: http://www.ampainsoc.org
The Pain Society: http://www.britishpainsociety.org
The London Pain Consortium: http://www.lpc.ac.uk
Pain in Europe survey: http://www.painineurope.com

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