

(Taken from "Mechanisms of Inflammatory Pain" by Dr. A. Rice, St.Mary's Hospital, London and from "Neurophysiology of pain" by Professor Dickenson, University College, London.)

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".

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 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 (1990) 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.

Professor Dickenson, a professor of Pharmacology who is an expert in mechanisms of pain, discussed how this type of event might occur in the central nervous system.

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 resulting in hyperexcitability, expanded receptive fields and receptive fields and neurochemical changes in the nerve. This is an example of the plasticity mentioned earlier.

There are numerous different neurotransmitters, some excitatory, some inhibitory.

TISSUE INJURY

Kinins

Hydrogen

Potassium

Prostaglandins

NOCICEPTOR

PRIMARY AFFERENT NEURONE

neuropeptides

IMMUNE CELLS

cytokines

Neurotrophins*

cannabinoids

opioids

BLOOD VESSELS

NO, kinins

SYMPATHETIC

EFFERENTS

Prostaglandins

*neurotrophins are important in the nervous system and are thought to be important in generating hyperalgesia.

Nerve Growth Factor (NGF) is one such neurotrophin and is a likely target for future

analgesics. A later speaker (Dr. Eastwood) described NGF as like oxygen to a fire.

Immune cells (mast cells) are also involved in hyperalgesia, as they produce NGF, 5-HT and histamine. In conditions such as interstitial cystitis, NGF is found. 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.

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).

The various changes suggest a similar picture to a reversion to the neonatal system mentioned earlier.

PERIPHERAL ACTIVATION

CENTRAL HYPERSENSITIVITY

HYPERALGESIA; ALLODYNIA

GENE INDUCTION

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.

Sodium channels are involved in the excitation of neurones. These are the target for drugs such as anticonvulsants and local anaesthetics.

The calcium channel is involved with the release of neurotransmitter. Gabapentin is a relatively novel anticonvulsant drug which only reacts with abnormal calcium channels.

It has been found to be useful to combat neuropathic pain and recently to have some effect on muscle spasms.

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.

