Section 7

An Overview of Neurotransmitters

Numerous neurotransmitters mediate the transmission of the sensations of pain in both the brain and the spinal cord. Neurotransmitters can be categorized into the following groups:

Excitatory neurotransmitters to include:

- Glutamate
- Tachykinins
- Agents that act at the various neurokinin receptors, such as substance P ('P is for pain'), neurokinin A and neurokinin B.
- Calcitonin gene-related peptide
- Vasoactive intestinal polypeptide
- Somatostatin

Inhibitory neurotransmitters to include: Gamma Amino Butyric Acid (GABA). Over forty percent of inhibition in the human central nervous system is GABAergic.

Neurotransmitters involved in descending pain regulation include:

- Noradrenaline (norepinephrine)
- Serotonin.

Further Analysis of the Major Neurotransmitters

Glutamate

The three major glutamate receptors are ‘’NMDA”, "AMPA" and the metabotropic receptor. "The NMDA receptor mediates a host of spinal responses to severe painful stimulation, but there are several catches to understanding how it works. Normally, the receptor is inactive as it is physiologically choked by a magnesium ion sitting in its ion channel. In order for this ion to be removed, adjacent peptide receptors have to be stimulated - the Mg++ then pops off, and an emphatic painful response occurs. Neurophysiologists have known about this phenomenon for ages, gracing it with the label "wind-up" - as the frequency of C-fibre stimulation increases there is a dramatic and long-lasting central response, with some populations of spinal neurones becoming more and more sensitive to stimulation. Consequences of glutamate receptor activation include production of c-fos and spinal production of prostanoids and the ubiquitous Dr NO, nitric oxide. Unfortunately all this knowledge benefits clinicians surprisingly little, as drugs that antagonise the effect of glutamate at the NMDA receptor tend to induce psychosis in humans, but the combination of low dose NMDA antagonists with opioids may be supra-additive with fewer side effects.” [1]

GABA

GABA is found throughout the brain and spinal cord and, it has major pain inhibitory effects. Interneurons in laminae I, II and III are GABA-rich, and mediate gate control in the dorsal horn by synapsing on neurones that contain substance P. [2]

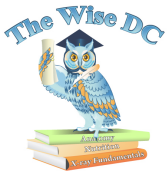
Tachykinins
Neurokinin receptors mediate pain in the spinal cord. Substance P binds to the NK-1 receptor while neurokinins A and B bind respectively to the NK-2 and NK-3 receptors. Collectively these substances are known as 'tachykinins'. The tachykinin receptors are G-protein coupled, and increase intracellular calcium levels, triggering gene transcription." [3]

Analysis Of Pain At The Cellular Level

Arguably, the most significant discovery *ever* in the field of pain has been the gene c-fos. This gene and its cellular product, the protein called *Fos* are crucial to the central nervous system changes that occur when a person feels pain. Central nervous system c-fos expression correlates extremely well with painful stimulation. Fos is one of the **inducible transcription factors** (ITFs) that controls mammalian gene expression.

Since c-fos is a proto-oncogene promote vast intracellular changes including cellular restructuring and proliferation and is thought to be involved in the long-term neurological consequences of noxious stimulation. Genetic research suggests that noxious peripheral stimulation causes Fos to appear in the spinal cord. Brief stimulation for as little as 10 minutes causes ITFs to appear within 30 minutes, peak at one to two hours, and disappear within about eight hours. Prolonged stimulation causes a many-fold increase in ITF expression, and substantially prolongs expression. Nociceptive C-fiber stimulation seems to be the main stimulus for ITF production in the spinal cord(c-fos appears within an hour in laminae I and II, the parasympathetic column, the dorsal grey commissure, as well as in the hindbrain). The reuniens, rhomboid and submedius nuclei all express c-fos, as do a number of areas in the cortex, thalamus, hypothalamus, amygdale and the parabrachial nucleus.

With prolonged stimulation, c-fos disappears from spinal neurons after two to seven days. This disappearance is despite increased neuronal excitability and a marked increase in expression of neurokinin and glutamate receptors, and may be simply because the neuronal changes are fixed, so the ITF is no longer needed. However, chronic lesions of sensory nerves, such as a partial sciatic nerve ligation can induce chronic c-fos expression even in nerves which don't normally express the ITF.
In conclusion, c-fos plays a vital role in cell replication and differentiation. [4]



[1] www.anaesthetist.com/icu/pain
[2] www.anaesthetist.com/icu/pain
[3] www.anaesthetist.com/icu/pain
[4] www.anaesthetist.com/icu/pain