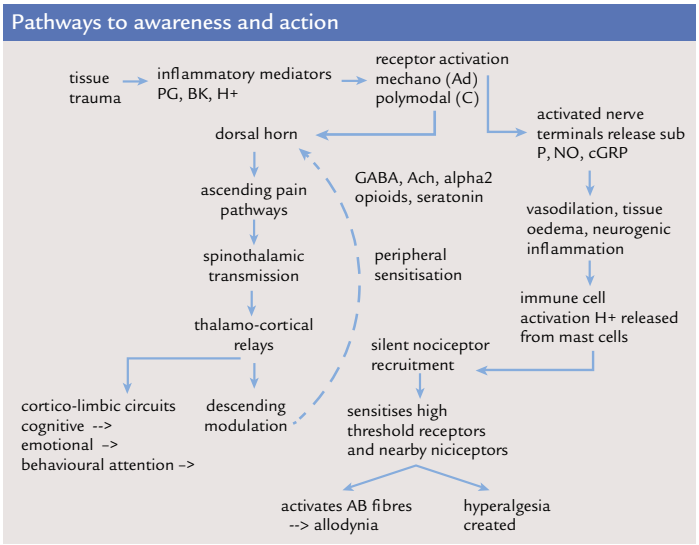

Figure 1. *Initial insult leading to awareness and action. Under normal conditions, a noxious insult causes the release of inflammatory mediators at the tissue level. These mediators include prostaglandins (PG), bradykinin (BK) and histamine (H+). However, there are numerous mediators identified. These mediators activate mechano-receptors and polymodal receptors on Aδ and C fibres respectively. These fibres send an impulse via the opening and closing of sodium channels to the dorsal horn of the spinal cord. From the dorsal horn, ascending pain pathways transmit the impulse to the thalamus; and from here, thalamocortical relays alert the corticolimbic circuits to the painful stimulus, thus creating cognitive, emotional and behavioural conscious awareness of the event. Additionally, from the thalamocortical relays, there is activation of descending pathways to modulate the severity of the incoming message, thus allowing the subject to adapt and manage the pain. This descending modulation is mediated by a variety of neurotransmitters, including γ-amino-butyric-acid (GABA) and acetylcholine (ACh) and serotonin. Drugs that can aid in this descending modulation include opioids and alpha-2 adrenoceptor agonists.*

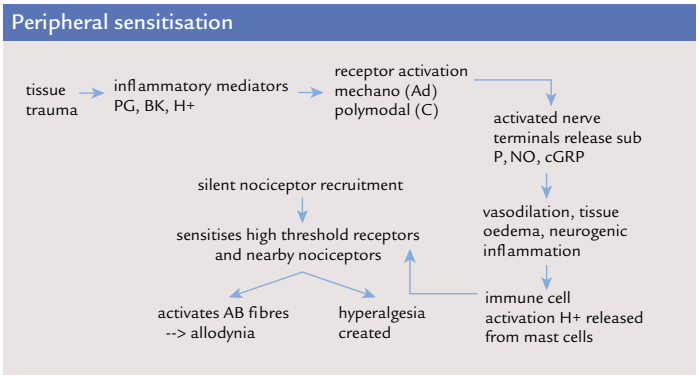

Figure 2. *The development of peripheral sensitisation. Concurrently, the activated nerve terminals release substance P (sub P), nitric oxide (NO) and calcitonin gene-related peptide (cGRP) at the tissue level. Here in the traumatised tissues, these cause vasodilation, tissue oedema and neurogenic inflammation. This causes immune cell activation and the release of histamine from mast cells. This immune component of the pathway allows the recruitment of previously silent nociceptors.*

Once these become activated, there is sensitisation of high-threshold receptors and nearby nociceptors. This results in the activation of Aß fibres. Once these high-threshold receptors are recruited and sensitised, there is a zone of hyperalgesia around the original insult; and once the Aß fibres are activated, the observed response to stimuli becomes allodynia. This is the process that leads to peripheral sensitisation.

Figure 3. *The development of central sensitisation and neuroplasticity. In order to create central sensitisation (or central plasticity), once the pain impulse reaches the dorsal horn of the spine, there is a burst of nociceptor signals causing release of glutamate and substance P. This causes activation of voltage-gated sodium channels and calcium channels and leads to increased hyperexcitability of the neurons involved. There are reduced thresholds of N-methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and increased channel open time of these receptors; which allows more signals to be transmitted with higher frequency and intensity. There is greater transcription of proteins that increase neuron excitability and a centrally sensitised state is created. It is the transcription of new proteins and genetic information that causes the pain pathways in the central nervous system to change and become sensitised, thus the term central sensitisation, or central plasticity. This means that a patient is able to perceive more pain with less stimulation. Thus, it can be seen that an acute insult can create central sensitisation and that neuronal plasticity is not preserved for chronic pain conditions alone.*