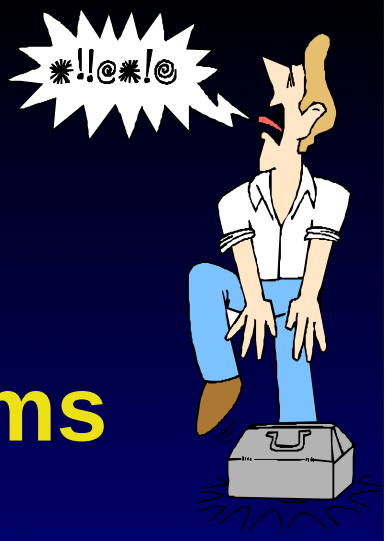
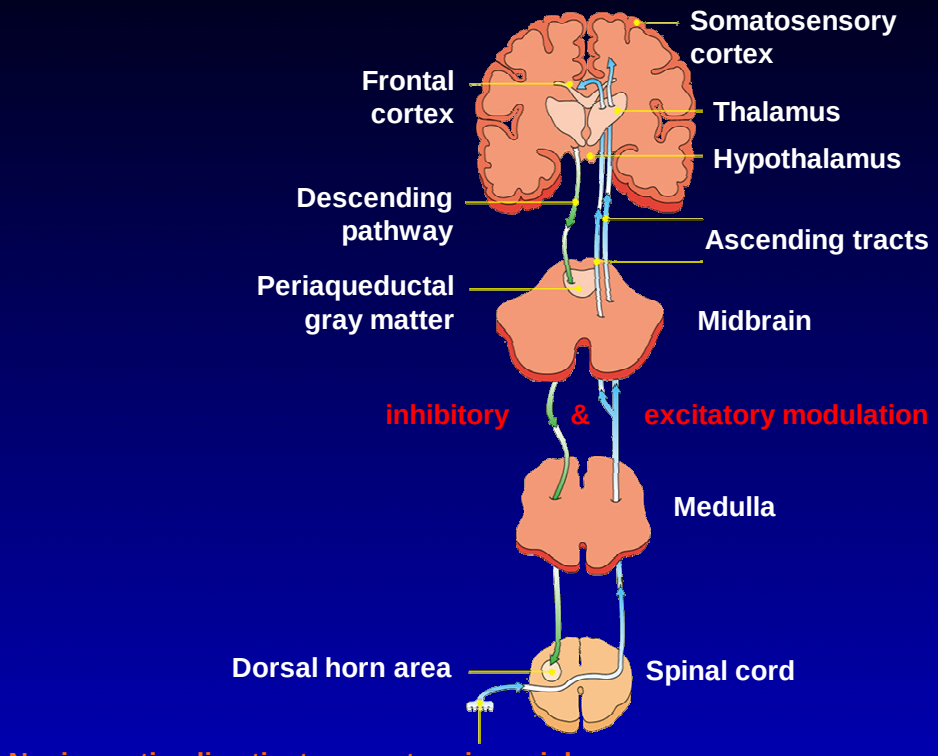


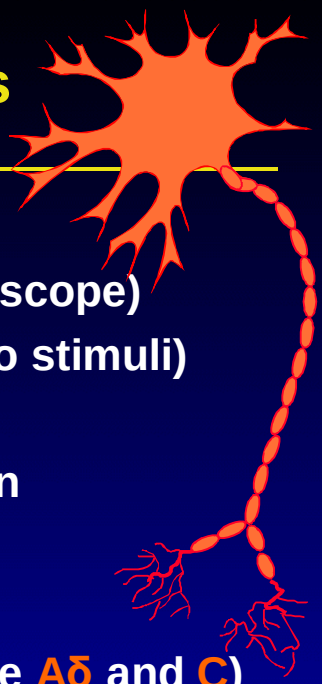
Pain Mechanisms

Prof Michael G Irwin MD, FRCA, FANZCA FHKAM
Head
Department of Anaesthesiology
University of Hong Kong

The Somatosensory System



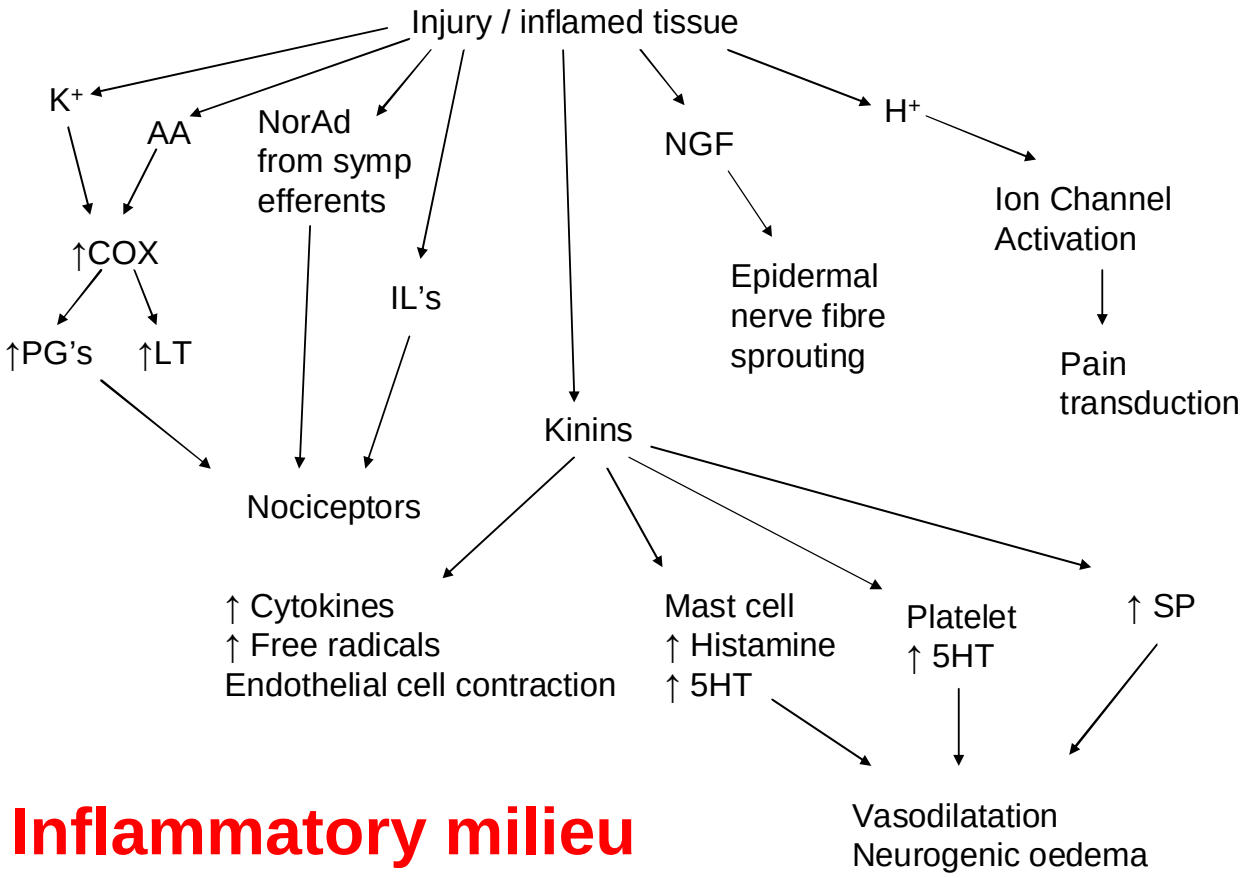
Cutaneous Nociceptors



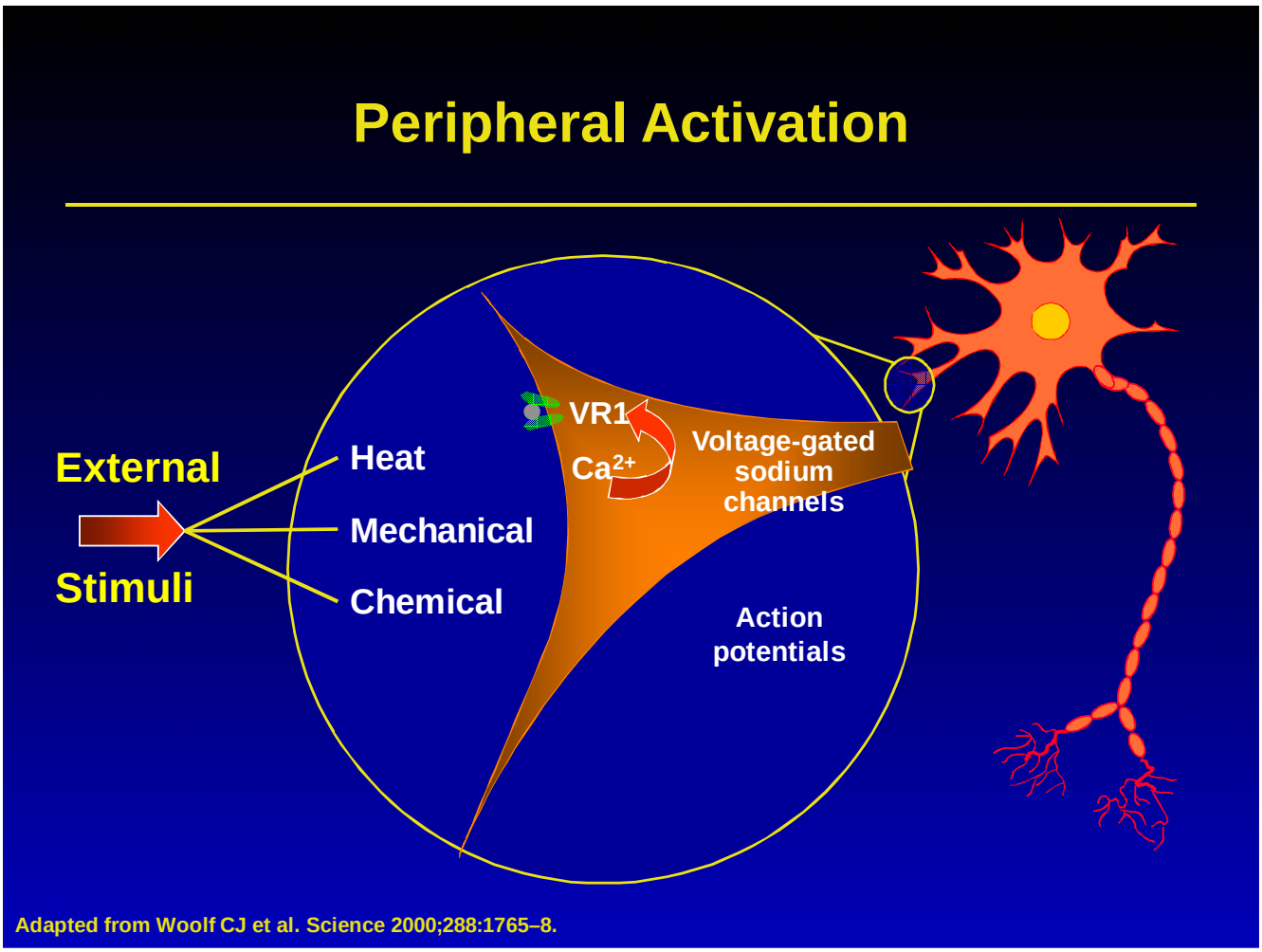
- Definition
  - Morphological (light & electron microscope)
  - Physiological (patterns of response to stimuli)
- Aδ - mechanical
  - Thinly myelinated, sharp/stinging pain
- C - Polymodal
  - Unmyelinated, dull/burning pain
- Silent/sleeping (mechanically insensitive Aδ and C)
  - Only active when tissue is injured
    - inflammatory conditions
  - 40% of C & Aδ are silent

Nociceptors

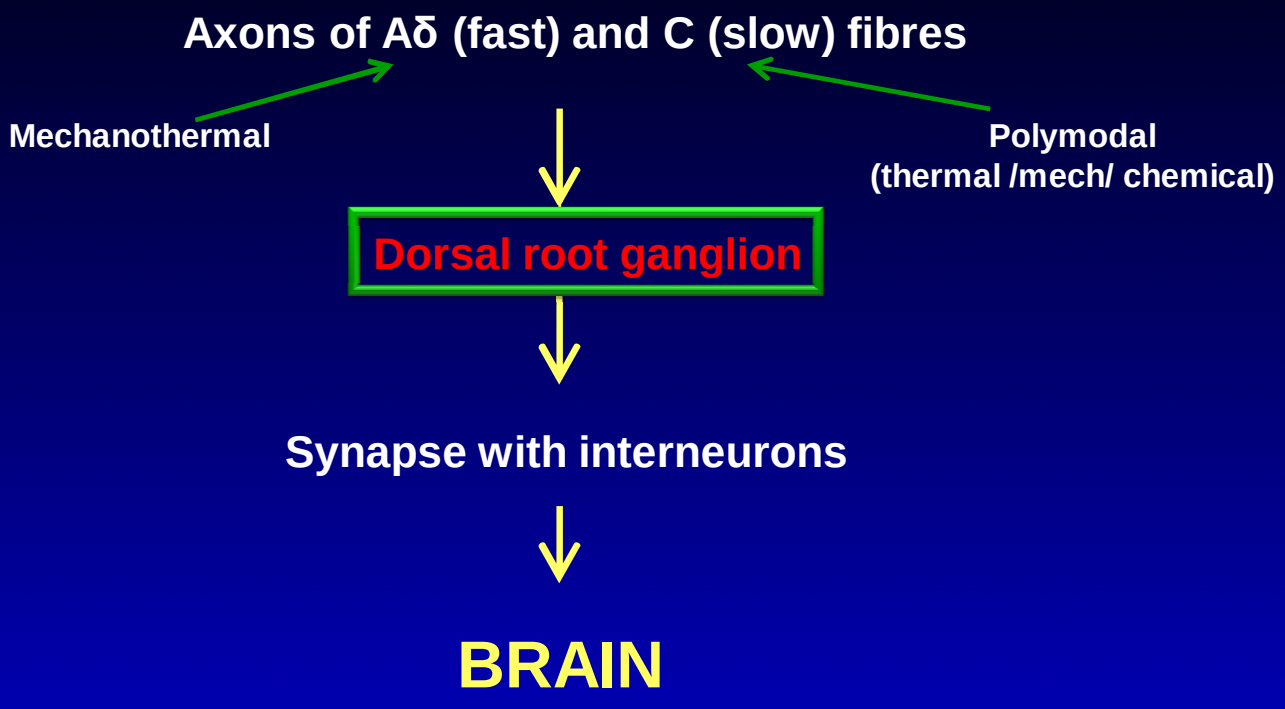
- Thermal nociceptors are activated by noxious heat (above 45˚C) or cold (below 5˚C)
- Mechanical nociceptors respond to excess pressure or mechanical deformation
- Polymodal nociceptors respond to damaging stimuli of a chemical, thermal, or mechanical nature
- Primary afferent nerve fibres transduce different forms of energy into generator potentials
  - If of sufficient magnitude, these generator potentials lead to action potentials
  - Action potentials → axon to the spinal cord



Inflammatory milieu



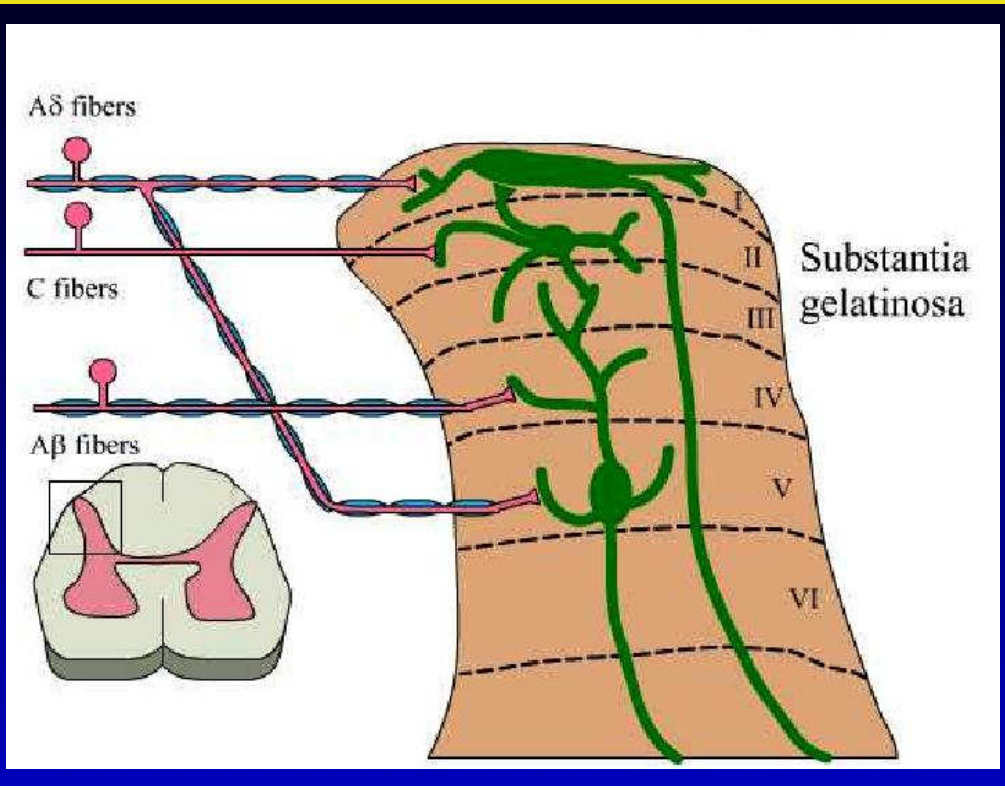
Processing pathways



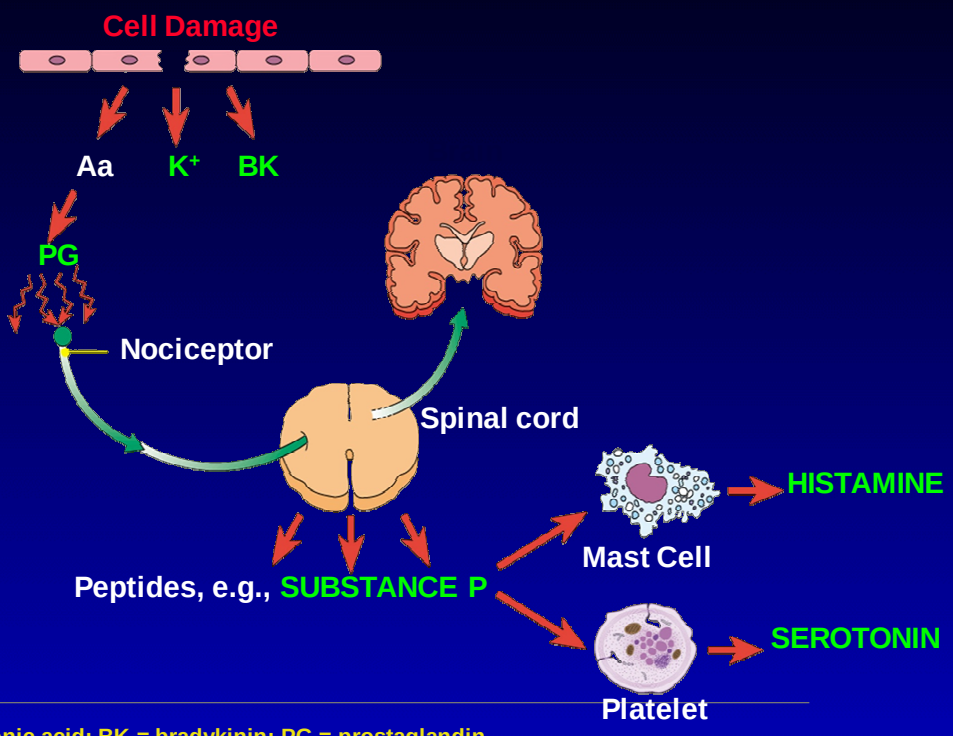
Dorsal Horn of Spinal Cord

- Transduction, transmission, and modulation of nociception occur here
- Focal point or “gate”
- Divided into laminae based on the types of neurons and their organization (physiologic not anatomic)
  - Lamina I (marginal zone)
  - Lamina II (substantia gelatinosa)
  - Laminae III-VI (nucleus proprius)

Nociceptor terminations in dorsal horn



Pain Mediators



Aa = arachidonic acid; BK = bradykinin; PG = prostaglandin

Nociceptor Sensitization (Hyperalgesia)

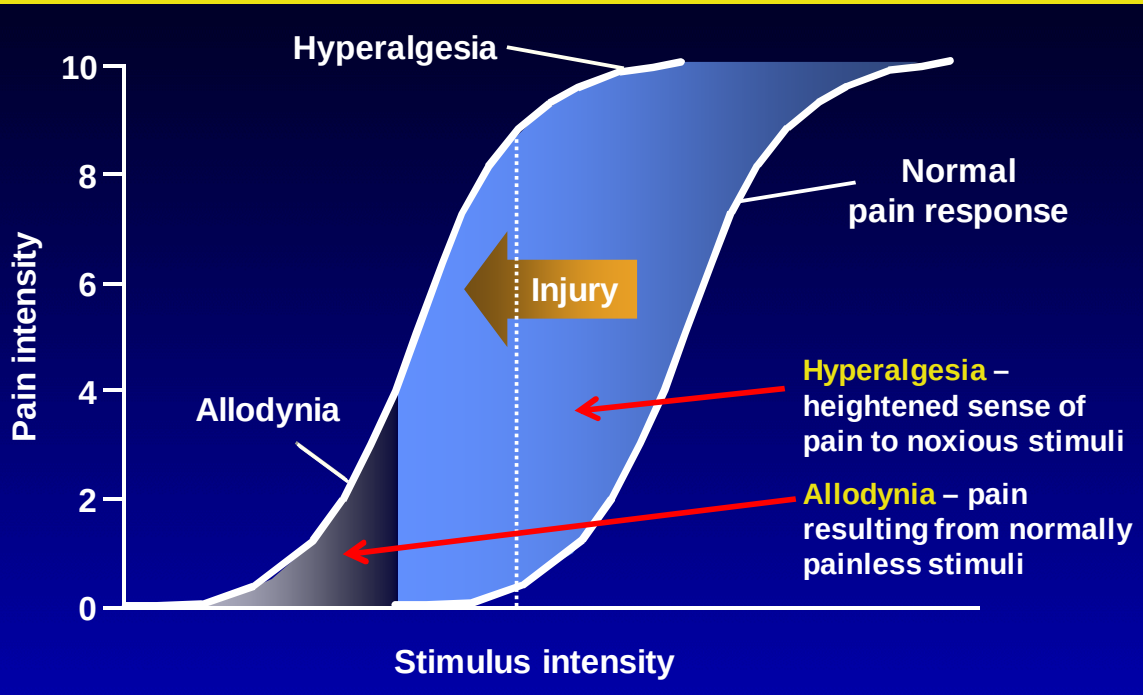
- Manifestation
  - ↓ threshold of activation after injury
  - ↑ intensity of response to injury
  - Emergence of spontaneous activity
- May occur within minutes and last for hours

Hyperalgesia

- Primary
  - Sensitization of primary neurons → ↓ threshold to noxious stimuli *within site of injury*
  - ↑ pain from suprathreshold stimuli
  - Spontaneous pain
- Secondary
  - Sensitization of primary neurons in *surrounding uninjured areas*
  - May involve:
    - Peripheral sensitization
    - Central sensitization (↑ excitability of central neurons)

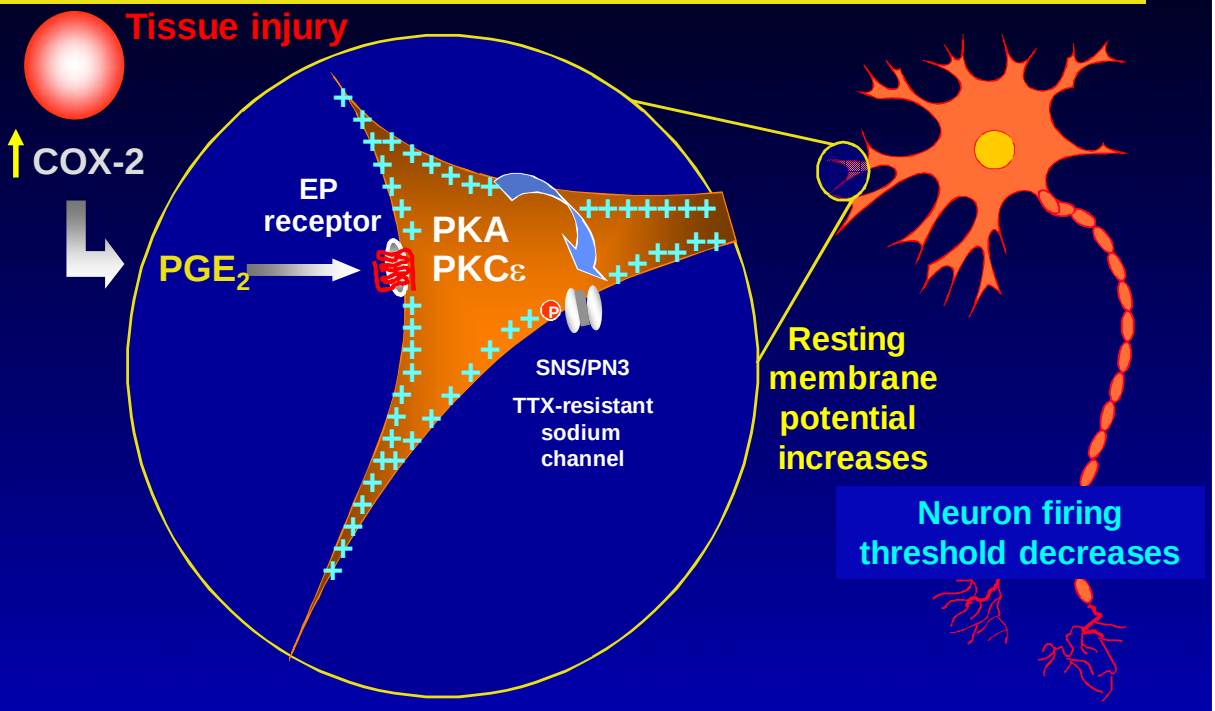
Raja SN, et al. In: Wall PB, Melzack R, eds. *Textbook of Pain*. 4th ed; 1999:11–57.

Pain sensitisation



Gottschalk A, Smith DS. Am Fam Physician 2001;63:1979–84

Tissue injury and Hyperalgesia

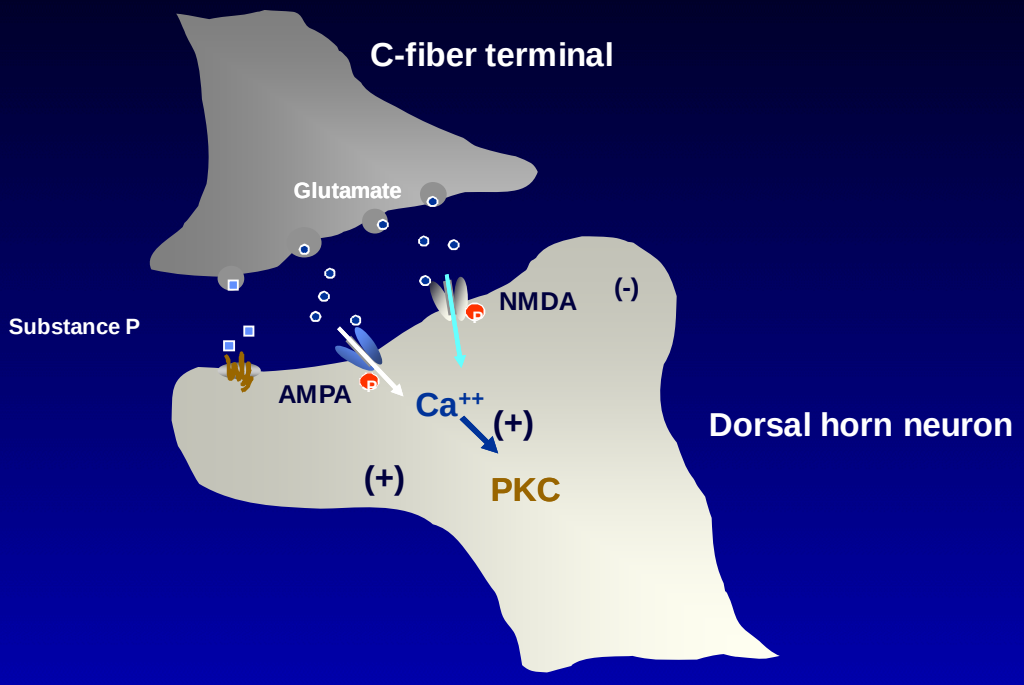


Samad TA et al. Nature 2000;410:471–5; Woolf CJ et al. Science 2000;288:1765–8;
Byers MR et al. In: Bonica's Management of Pain. Philadelphia: Lippincott Williams & Wilkins; 2001.

Central Sensitization

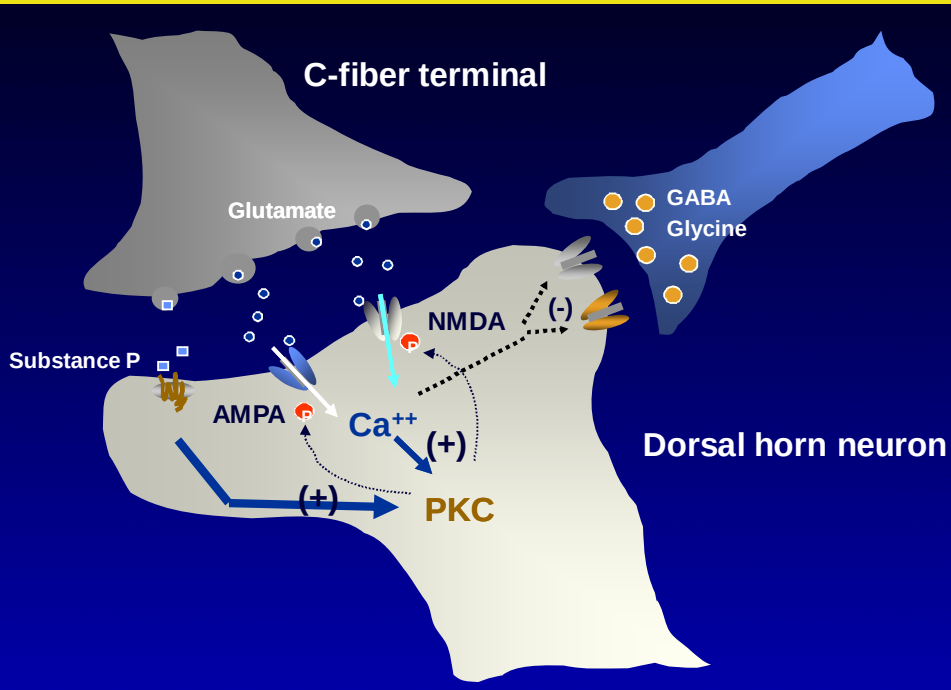
- ↑ afferent barrage
- Expansion of receptive fields of dorsal horn neurons
- ↑ release of peptides (e.g. SP, calcitonin gene-related peptide) & excitatory amino acids (mainly glutamate) neurotransmitters
  - Act at NK1 & NMDA receptors
- Postsynaptic morphologic changes also occur
- Neurochemical changes result in several plasticity responses including apoptosis (glial and neuronal cell death), axonal sprouting, and new afferent connections

Activation of central neurons



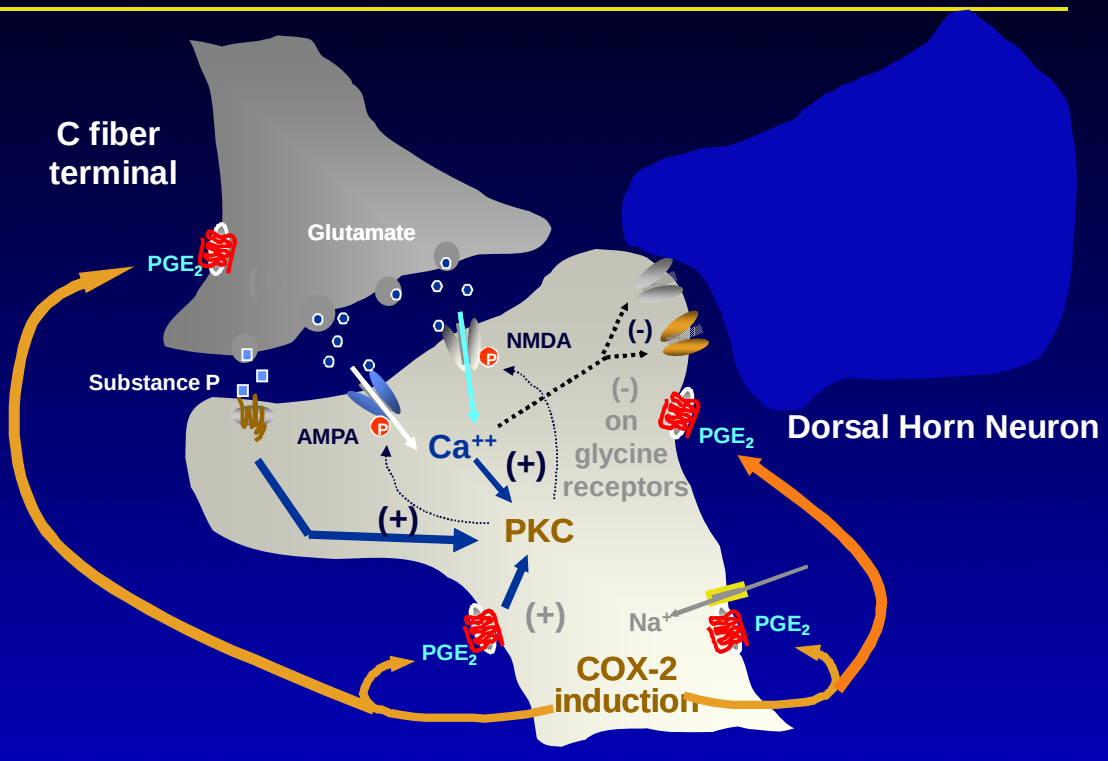
Woolf CJ, Salter MW. *Science.* 2000;288:1765-8.
Schwartzman RJ et al. *Arch Neurol.* 2001;58:1547-50.

Modulation of Central Neurons

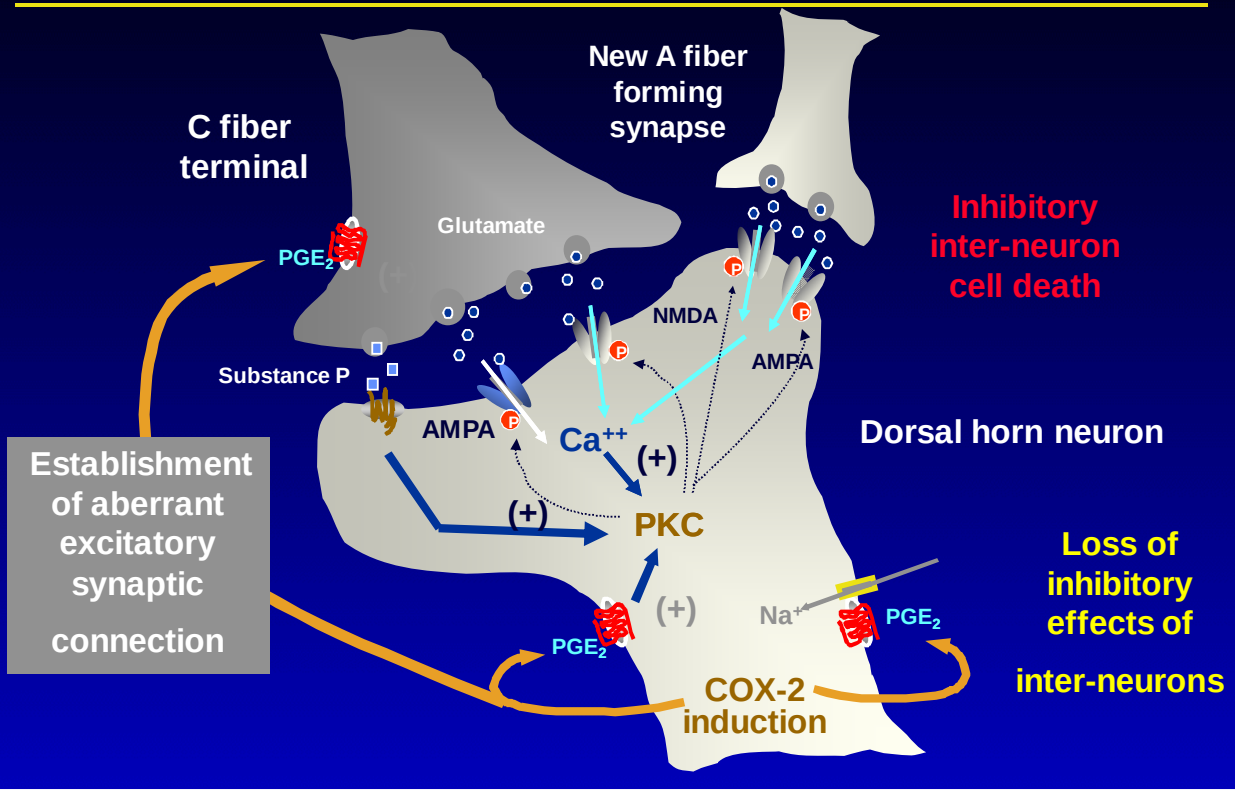


Woolf CJ, Salter MW. *Science* 2000;288:1765–8.Schwartzman RJ et al. Arch Neurol 2001;58:1547–50.
Terman GW et al. Bonica's Management of Pain 2001:73–152.

Modification of central neurons



Modification of central neurons



Evidence for Central Sensitization

- SP & glutamate most extensively studied
  - Synthesized in same nociceptor cell body in DRG
  - ↑ expression after tissue injury
  - Intrathecal administration causes pain like behaviour in animals
  - Antagonists block these effects

Substance P

- Neurokinin (NK)
- Acts at NK1 receptor
- NK1 antagonists
  - NOT analgesic
  - Significantly attenuate hyperalgesia
    - But only to ~50% of maximum
    - ⇒ another pathway must be involved

Glutamate

- Acts at
  - Ionotropic, cation-selective, ligand-gated receptors
  - Metabotropic G protein-coupled receptors
    - N-methyl- D-aspartate (NMDA) receptors
    - non-NMDA receptors (alpha-amino-3-hydroxy-S-methyl-4-isoxazolepropionate {AMPA})
  - NMDA and non-NMDA receptors are widely distributed throughout CNS & PNS

NMDA activation

- Substance P —glutamate→ NMDA activation
- Calcium entry into neurone
  - Generation of NO
  - Phospholipase activation
    - Spinal production of prostanoids

Neuronal Plasticity and Pain

- Neurons detecting and transmitting pain display "*plasticity*"
  - capacity to change function, chemical profile or structure
  - response to painful stimuli and inflammation
  - all contribute to altered sensitivity to pain

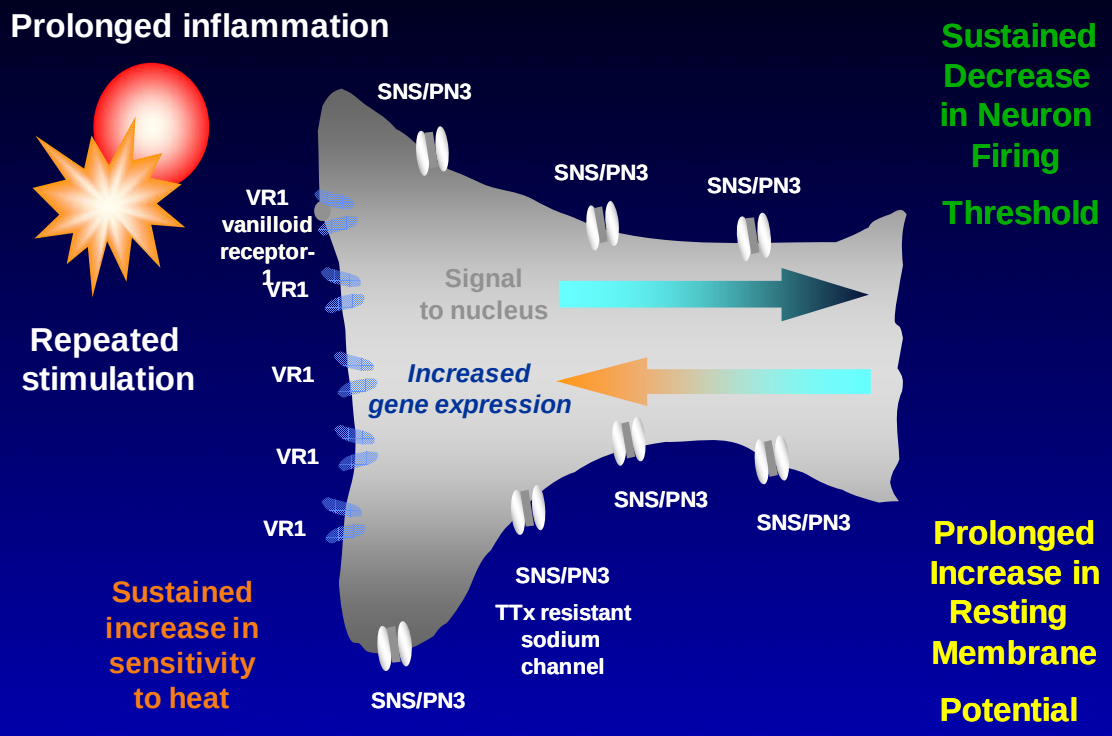
Woolf and Salter, Science 288: 1765-1768, 2000

Three Forms of "Neuronal Plasticity"

- **Activation**
  - rapid onset, substantial, readily reversible
    - *Autosensitisation and Wind-up*
- **Modulation**
  - follows repeated, intense stimuli, substantial, slowly reversible
    - *Peripheral and Central Sensitisation*
- **Modification**
  - follows prolonged, intense stimuli or nerve damage, very long-lasting
    - *Persistent, pathological (neuropathic) pain*

Woolf and Salter, Science 288: 1765-1768, 2000

Modification of Primary Sensory Neurons Resulting in Chronic Pain

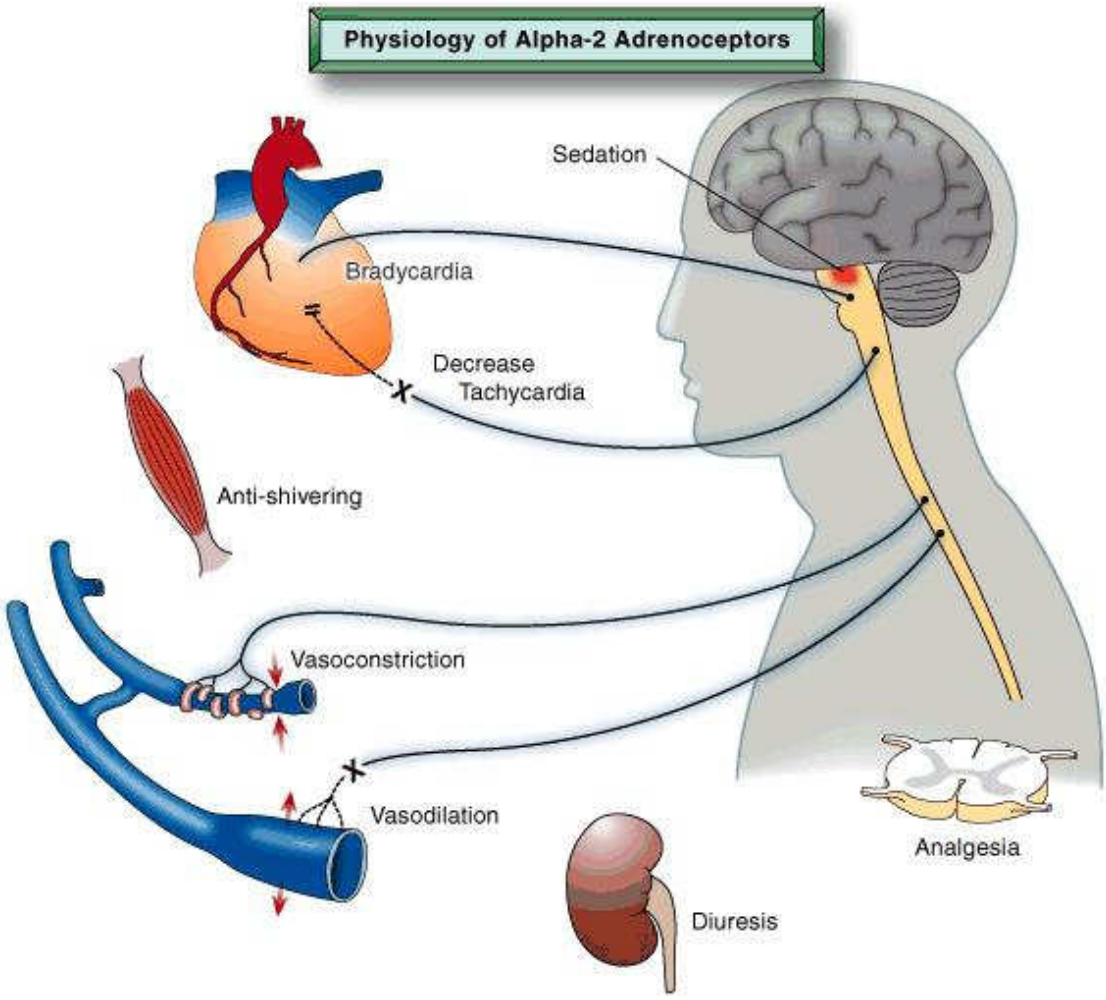


Adapted from Woolf and Salter, Science 288: 1765-1768, 2000

VR1: detects noxious heat

α2-adrenoceptors (subtype A)

- Descending noradrenergic inhibitory pathways modulate nociceptive transmission and spinal sensitisation after tissue injury
- α2-adrenoceptor agonists relieve mechanical hyperalgesia and depress nerve fibre action potentials
- Ca^{2+} channel auxiliary subunit α-2δ-1 plays important role in neuropathic pain processing (up-regulated in the DRG after spinal nerve injury)
- Pregabalin binds specifically to the α-2δ-1 subunit of voltage-dependent Ca^{2+} channels and reduces Ca^{2+} current



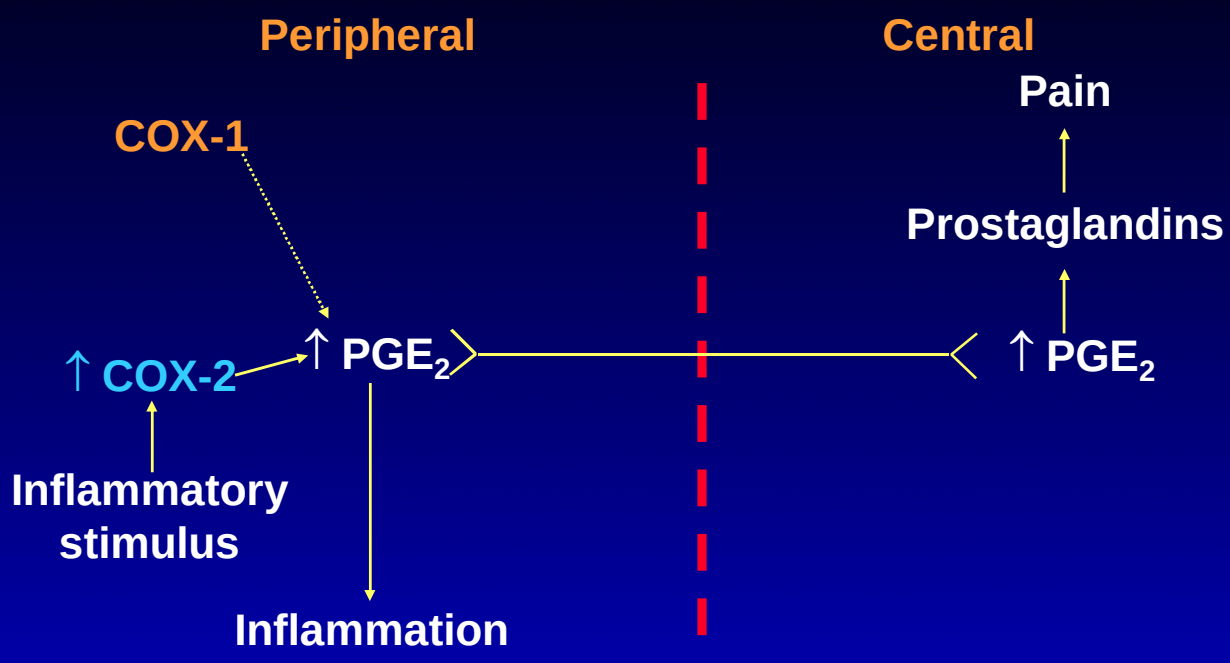
Opioid receptors

- Activation reduces neuronal excitability through the inhibition of voltage-dependent Ca^{2+} channels and adenyl cyclase, and opening of K^{+} channels
- Opioid induced reduction in excitability will lead to an inhibition of pain
- ATP sensitive potassium (KATP) channels are opened and modulated by both opioid and non opioid G-protein coupled receptors to also produce antinociception

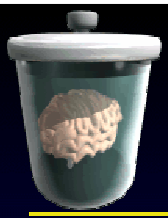
Humoral messengers

- Blood-brain barrier has components that enable a blood-borne cytokine to stimulate the production of PGE2
  - inflammatory mediator and powerful modulator of nociception
- These cells have receptors that specifically recognise IL-1β indicating that the activated immune system controls central reactions to peripheral inflammation through a prostaglandin-dependent, blood-borne cytokine-mediated pathway
  - Interestingly it is mainly the increase in CSF levels of IL-1β that mediates local inflammation in the brain and not the sensory inflow from nerve fibres
  - It has also been shown that high concentrations of pro-inflammatory cytokines (IL-1β, IL-2, IL-6, IFN-γ, tumour necrosis factor (TNF)-α) in the plasma correlate with increasing pain intensity
  - Chronic pain patients also show a significant increase in plasma levels of NO in comparison to healthy controls

Model for COX-1– and COX-2–Derived Prostaglandins in Inflammation and Pain



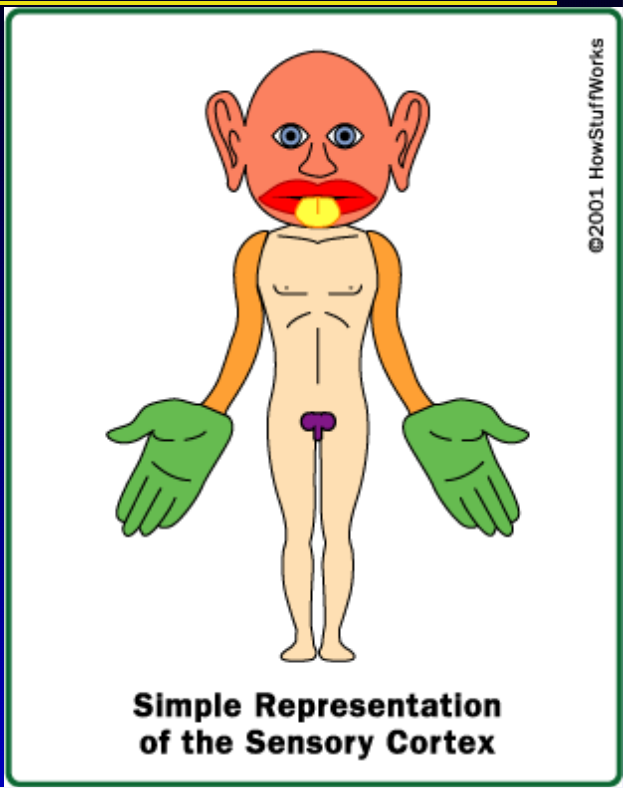
Smith CJ, et al. *Proc Natl Acad Sci U S A*. 1998;15:13313–13318.



Brain

- Information is sent from the spinal cord to the thalamus and the cerebral cortex in the brain
  - Thalamus, prefrontal cortex, premotor areas, cerebellum most commonly activated by pain stimuli
- Receptive fields of all pain-sensitive neurons are relatively large because detection of pain is more important than its precise localisation
  - Spatial, temporal and intensity aspects of pain perception are processed in the primary and secondary somatosensory cortex
  - Affective-motivational component - anterior cingulate cortex & insular cortex

Homunculus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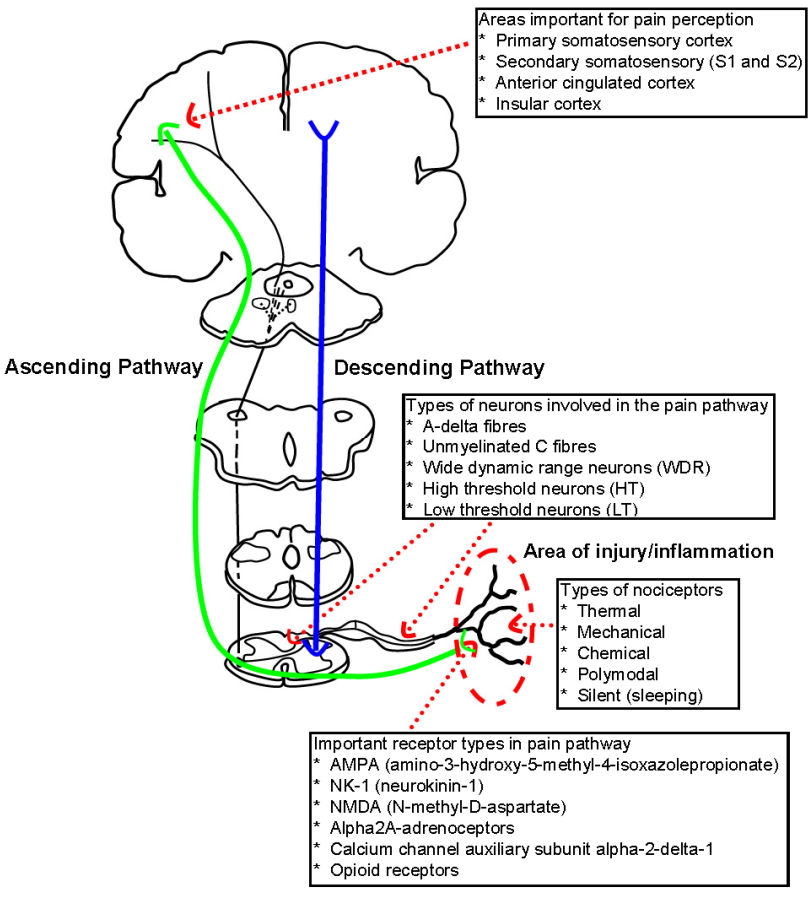
Simple Representation
of the Sensory Cortex


Areas important for pain perception
* Primary somatosensory cortex
* Secondary somatosensory (S1 and S2)
* Anterior cingulated cortex
* Insular cortex
Ascending Pathway
Descending Pathway
Types of neurons involved in the pain pathway
* A-delta fibres
* Unmyelinated C fibres
* Wide dynamic range neurons (WDR)
* High threshold neurons (HT)
* Low threshold neurons (LT)
Area of injury/inflammation
Types of nociceptors
* Thermal
* Mechanical
* Chemical
* Polymodal
* Silent (sleeping)
Important receptor types in pain pathway
* AMPA (amino-3-hydroxy-5-methyl-4-isoxazolepropionate)
* NK-1 (neurokinin-1)
* NMDA (N-methyl-D-aspartate)
* Alpha2A-adrenoceptors
* Calcium channel auxiliary subunit alpha-2-delta-1
* Opioid receptors

Summary

- Transmission of a pain signal from the periphery to the brain involves complex interactions between different types of neurons, through release of various neurotransmitters and receptor and ion channel activation
- Perception of pain is also affected by descending influences from the brain
- The components of the “pain pathway” have potential for modification both in terms of structure and function
- “Plasticity” in the system is responsible for the development of abnormal and chronic pain states, well beyond the duration of the inciting injury
- Understanding the neurobiology behind pain transmission is pivotal in the effective use of available analgesics and for the development of future therapy