Pain Mechanisms

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

The Somatosensory System

- Somatosensory cortex
- Thalamus
- Hypothalamus
- Ascending tracts
- Midbrain
- Periaqueductal gray matter
- Descending pathway
- Frontal cortex
- Medulla
- Spinal cord

Noxious stimuli activate receptors in periphery

Inhibitory & excitatory modulation
Cutaneous Nociceptors

- **Definition**
  - Morphological (light & electron microscope)
  - Physiological (patterns of response to stimuli)
- **Aδ - mechanical**
  - Thinline 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
Injury / inflamed tissue

NorAd from symp efferents

IL’s

Kinins

Nociceptors

↑ Cytokines

↑ Free radicals

Endothelial cell contraction

↑ Histamine

Platelet

↑ SP

Inflammatory milieu

Vasodilatation

Neurogenic oedema

Peripheral Activation

External Stimuli

Heat

Mechanical

Chemical

Voltage-gated sodium channels

Action potentials

**Processing pathways**

- Axons of A\(\delta\) (fast) and C (slow) fibres
- Mechanothermal
- Polymodal (thermal/mech/chemical)
- Dorsal root ganglion
- Synapse with interneurons
- BRAIN

**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

Peptides, e.g., SUBSTANCE P

Cell Damage

Aa K⁺ BK

PG

Nociceptor

Spinal cord

Mast Cell

Platelet

HISTAMINE

SEROTONIN

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)

**Pain sensitisation**


Injury

Pain intensity

Stimulus intensity

Hyperalgesia – heightened sense of pain to noxious stimuli

Allodynia – pain resulting from normally painless stimuli

**Tissue injury and Hyperalgesia**

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

Modulation of Central Neurons

C-fiber terminal

Dorsal horn neuron

Substance P

Glutamate

GABA

Glycine

AMP A

NMDA

Ca ++

PKC

(+)

PKC

(-)

COX-2

induction

PGE 2

Dorsal Horn Neuron

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
    - \( \Rightarrow \) another pathway must be involved

Glutamate

- Acts at
  - Ionotrophic, 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
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

Prolonged inflammation

Repeated stimulation

Sustained increase in sensitivity to heat

Increased gene expression

Signal to nucleus

Sustained Decrease in Neuron Firing Threshold

Prolonged Increase in Resting Membrane Potential

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-1\(\beta\) 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-1\(\beta\) 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-1\(\beta\), IL-2, IL-6, IFN-\(\gamma\), tumour necrosis factor (TNF)-\(\alpha\)) 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

Periphera l

$\uparrow$ COX-1

$\uparrow$ COX-2

Inflammatory stimulus

Inflammation

$\uparrow$ PGE$_2$

Central

Pain

Prostaglandins

$\uparrow$ PGE$_2$


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

Simple Representation of the Sensory Cortex

- Areas important for pain perception
  - Primary somatosensory cortex
  - Secondary somatosensory (S1 and S2)
  - Anterior cingulated cortex
  - Insular cortex

- 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)

- 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.