Physiology of pain

Dr Prabhu Gandhimani

Consultant Anaesthetist and Pain Management

Kingston Hospital

Definition

- An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.

- Complex with physical, emotional and cognitive components

Types of Pain

- Acute pain
- Chronic pain
- Cancer pain

  (or)

- Somatic pain
- Visceral pain
- Neuropathic pain

Acute Vs Chronic

Acute

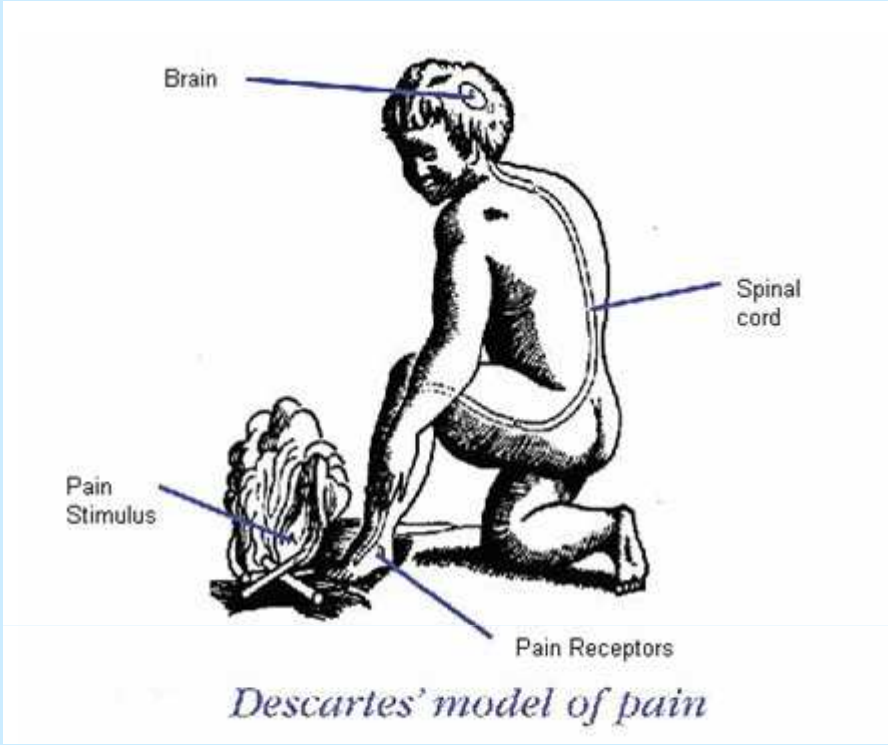
- Brief
- Resolves with tissue healing
- Protective response

Chronic

- >3 months
- Does’nt resolve with healing
- No useful purpose.
- Behavioural , emotional changes

Neuropathic pain

- Damage or injury to nervous system
- Pins and needles, burning, stabbing, shooting,lancinating…
- Allodynia,paresthesia, dysaesthesia
- Responds to unconventional medications- amitryptiline, pregabalin.



Descartes' model of pain

Pain is not a simple hard wired system

Present pain pathway

Pain Pathway

- There are four basic processes involved in nociception (McCaffery and Pasero, 1999). These are;
- transduction;
- transmission;
- perception;
- modulation.

Transduction

Specific pain receptors- Nociceptors

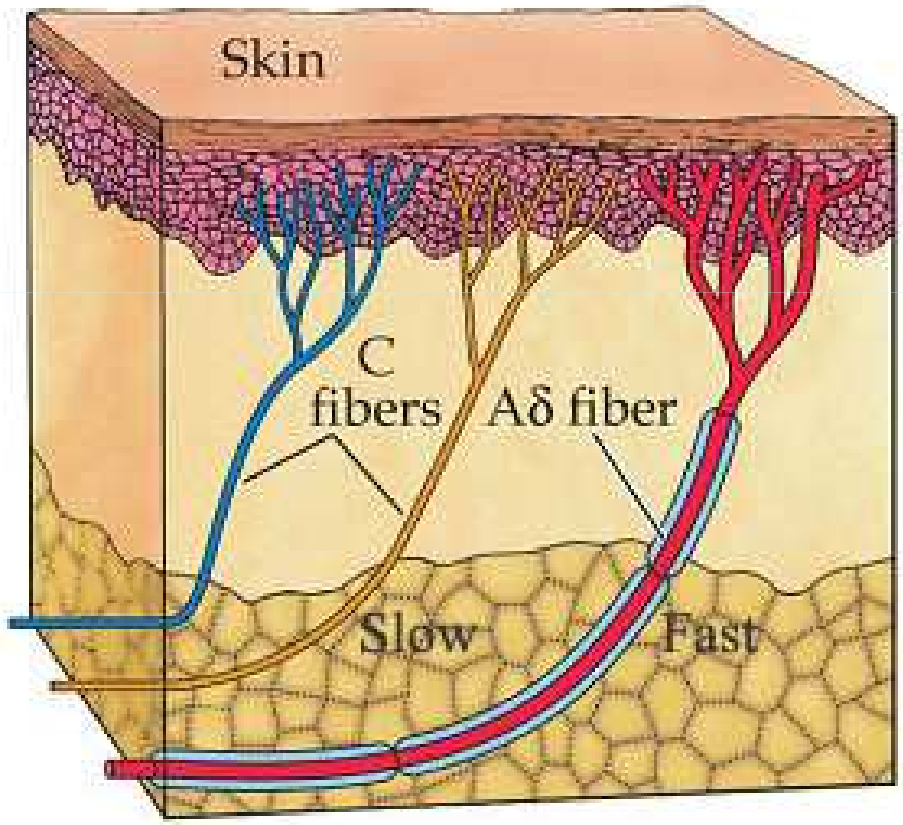
A Delta-

- sharp immediate pain ("first pain")
- Myelinated
- Velocity 6-30m/s
- Mechanothermal and thermal
- Terminate in lamina 2 & 5

C fibers-

- prolonged unpleasant burning pain
- Non myelinated
- Velocity<3m/s
- Polymodal (heat, chemical and mechanical)
- Terminate in lamina1 & 2

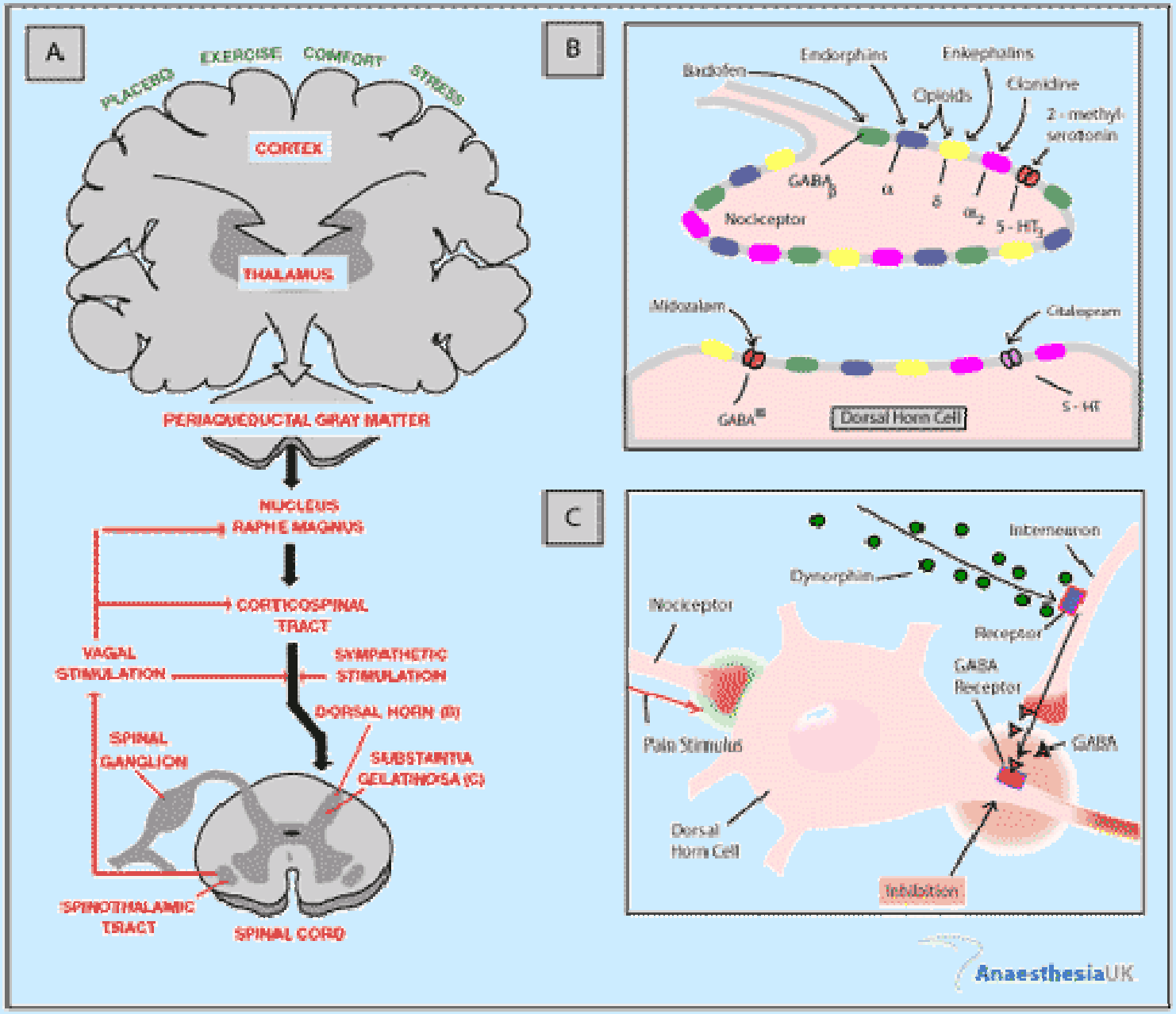
Transduction…



BIOLOGICAL PSYCHOLOGY, Fourth Edition, Figure 8.23 © 2004 Sinauer Associates, Inc.

Visceral Pain

- Distension and Ischaemia
- No A delta fibers in viscera
- Afferent- high and low threshold receptors
- Relay in lamina 1,2 5 and 10.
- Spinothalamic,spinohypothalamic,spinosolitary, spinoreticular and dorsal column.
- Difficult to localise- receptors are sparse.


A
PLACEBO
EXERCISE
COMFORT
STRESS
CORTEX
THALAMUS
PERIAQUEDUCTAL GRAY MATTER
NUCLEUS RAPHE MAGNUS
CORTICOSPINAL TRACT
VAGAL STIMULATION
SYMPATHETIC STIMULATION
DORSAL HORN (B)
SPINAL GANGLION
SUBSTANTIA GELATINOSA (C)
SPINOTHALAMIC TRACT
SPINAL CORD
B
Buprenorphine
Endorphins
Enkephalins
Opioids
Clonidine
2 - methyl serotonin
GABA$_B$
α
δ
α$_2$
5 - HT$_3$
Nociceptor
Mirtazalam
Citalopram
GABA^B
Dorsal Horn Cell
5 - HT
C
Interneuron
Dynorphin
Nociceptor
Receptor
GABA Receptor
GABA
Pain Stimulus
Dorsal Horn Cell
Inhibition
AnaesthesiaUK

Sensitisation

- normally most nociceptors lie dormant
- Inflammation sensitizes this vast population of nociceptors, making them far more sensitive to stimulation (hyperalgesia).

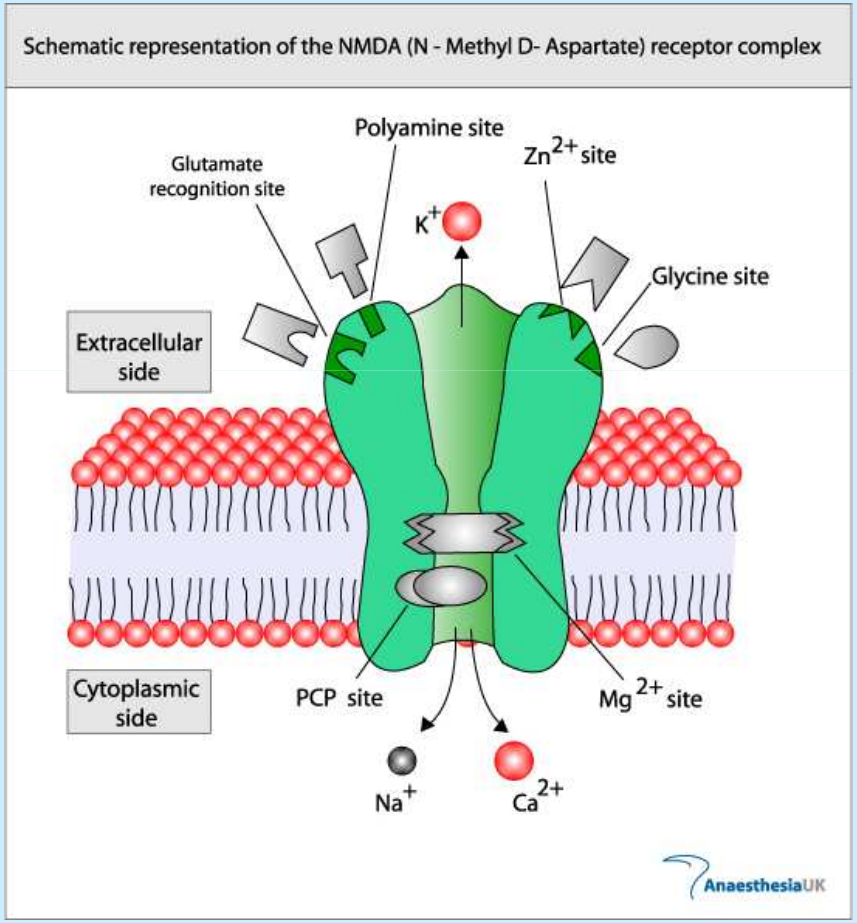
Hyperalgesia

- Primary
  - Felt at the site of stimulation,
  - Peripheral sensitisation- release of intracellular contents of injured cells and by mast, macrophages.
- Secondary
  - Felt at a site remote from the original injury,
  - Sensitisation of dorsal root ganglia (wind up)

Wind up

- Repetitive stimulation of nociceptive neurons results in sensitisation of dorsal horn neurons-
  - Expansion in receptive field size
  - More response to same painful stimuli (hyperalgesia)
  - Reduction in threshold- normal non painful stimuli results in pain (allodynia)
- May be because of NMDA activation

NMDA



- The NMDA receptor is normally inactive
- Frequent stimulation of C-fibre opens this channel and an there is a dramatic and long-lasting central response.
- Glutamic,Aspartic acid & CGRP

Preemptive analgesia

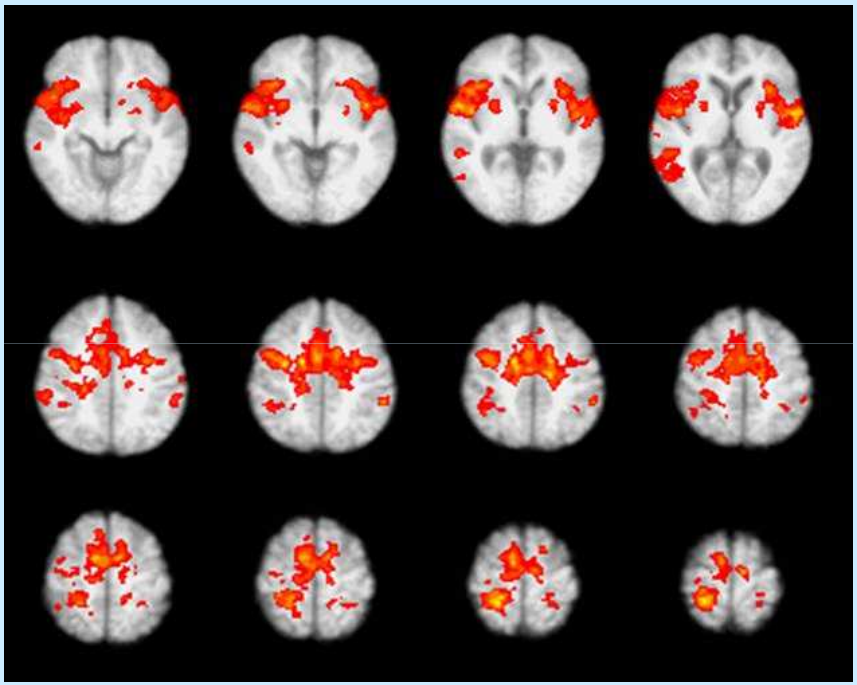
- Analgesia before a painful stimulus results in less analgesic requirements and prevents wind up and sensitisation
- Phantom limb pain
- Research- Preemptive pregabalin
  - Epidural ketamine

Transmission

- Spinothalamic tract- lamina 1,4 & 5 terminate in VP and medial thalamic nuclei
- Spinoreticular tract, spinomesenchalic tract- terminate in periaqueductal gray and stimulate descending inhibitory pain pathway.
- Posterior column- ? visceral pain
- Spinoparabrachial-Amygdala system-emotional aspect of pain

Perception of pain

- Perception of pain is the end result of the neuronal activity of pain transmission and where pain becomes a conscious multidimensional experience
- Functional MRI

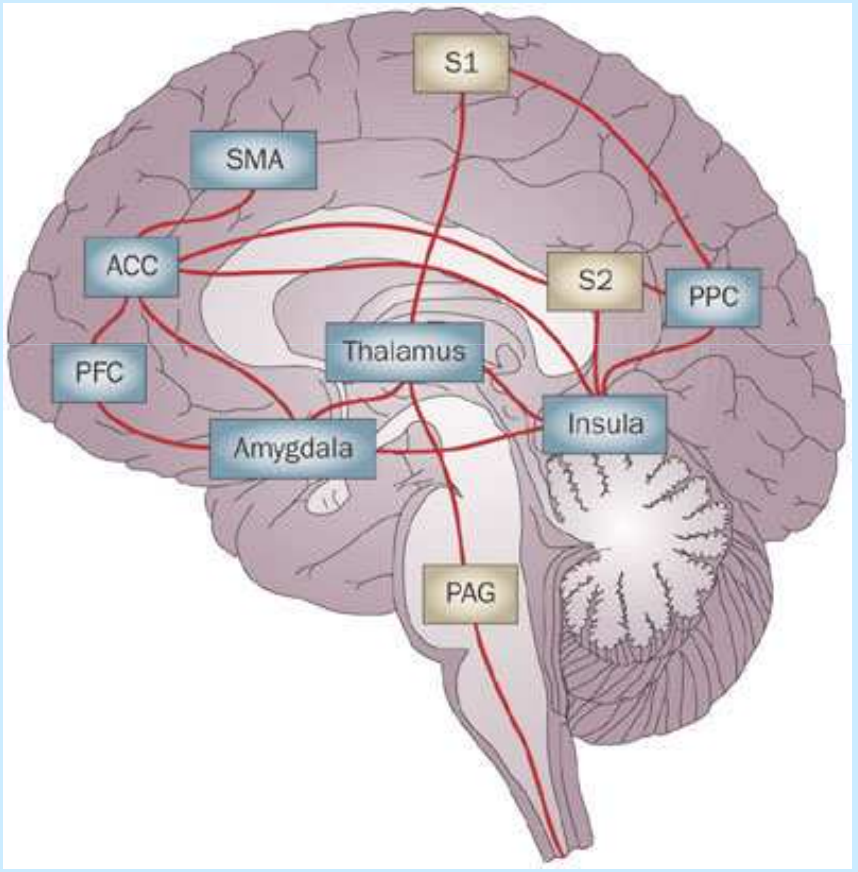


Pain Perception

- The thalamus is the 'central switching station' of the brain.
- The lateral nuclei deal mainly with sensory/discriminative aspects
- The medial ones with 'affective' pain.

Pain Perception

- Fibres from thalamus relay in higher cortical structures:
- The primary sensory cortex, S I –Localisation of pain
- The secondary sensory cortex, S II –affective
- The anterior part of the insula - affective
- The cingulate gyrus- affective



Modulation

Modulation of pain

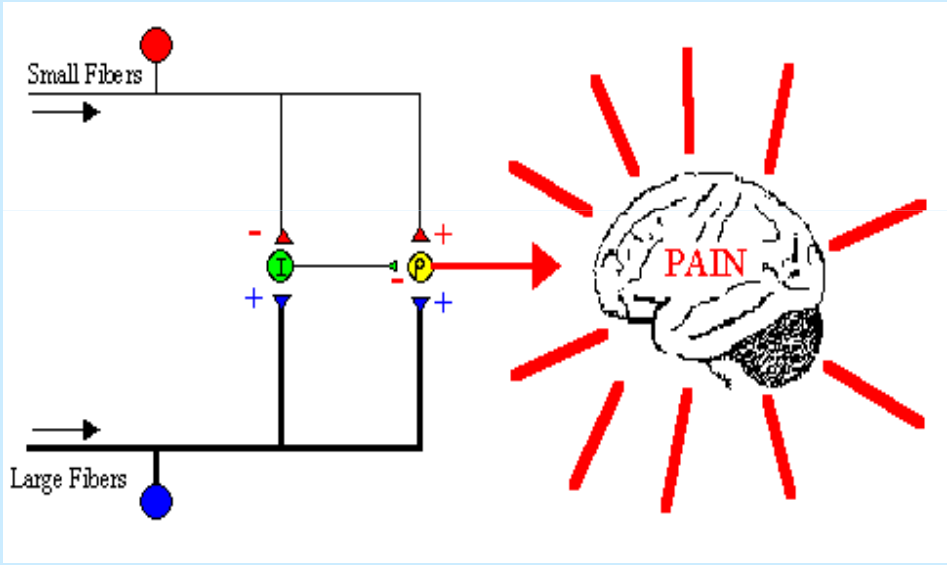
- Tissue injury does’nt always lead to pain(eg) soldiers injured in battle do not always complain of pain.
- The modulation of pain involves changing or inhibiting transmission of pain impulses in the spinal cord.
- Spinal or Supraspinal level.

Pain Modulation

Spinal:

Gate control theory
(Melzack & Wall)

- Activation of large fibres can suppress conduction in small fibres
- Interneurons in lamina 2 regulate output of lamina 1& 5- TENS, SCS, rubbing,acupuncture.

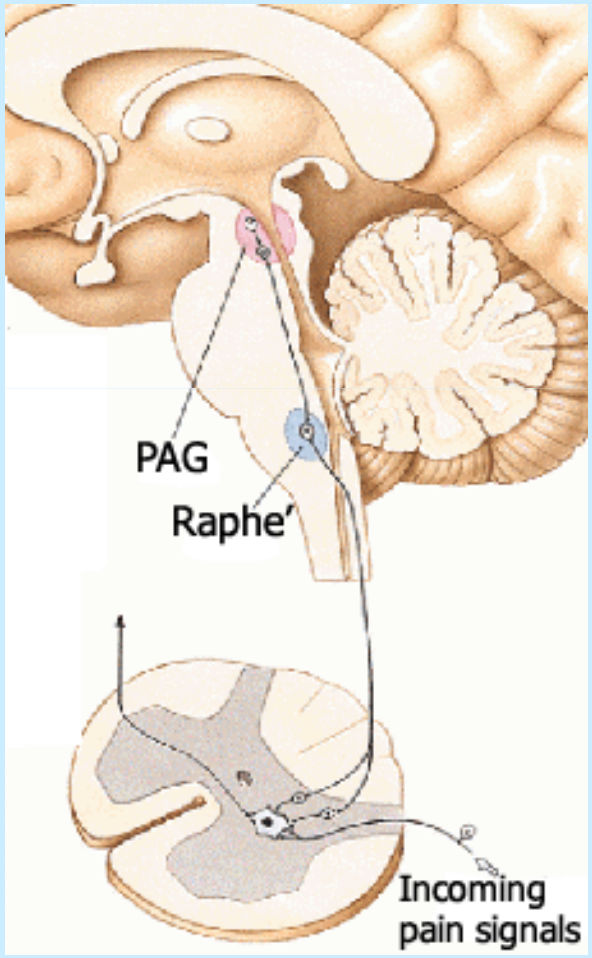


Pain Modulation…

Supraspinal:

Descending inhibitory control

- Excitatory connections from Periaqueductal gray to medulla(Raphe Magnus) rich in 5HT. 5HT axons inhibit firing in lamina1 and 5
- There are parallel nor adrenaline induced descending inhibitory control.



Modulation…

Neurotransmitters:

- endogenous opioids (enkephalins and endorphins);
- serotonin (5-HT);
- norepinephirine (noradrenalin);
- gamma-aminobutyric acid (GABA);
- neurotensin;
- acetylcholine;
- oxytocin.

Neurobiology

Excitatory neurotransmitters

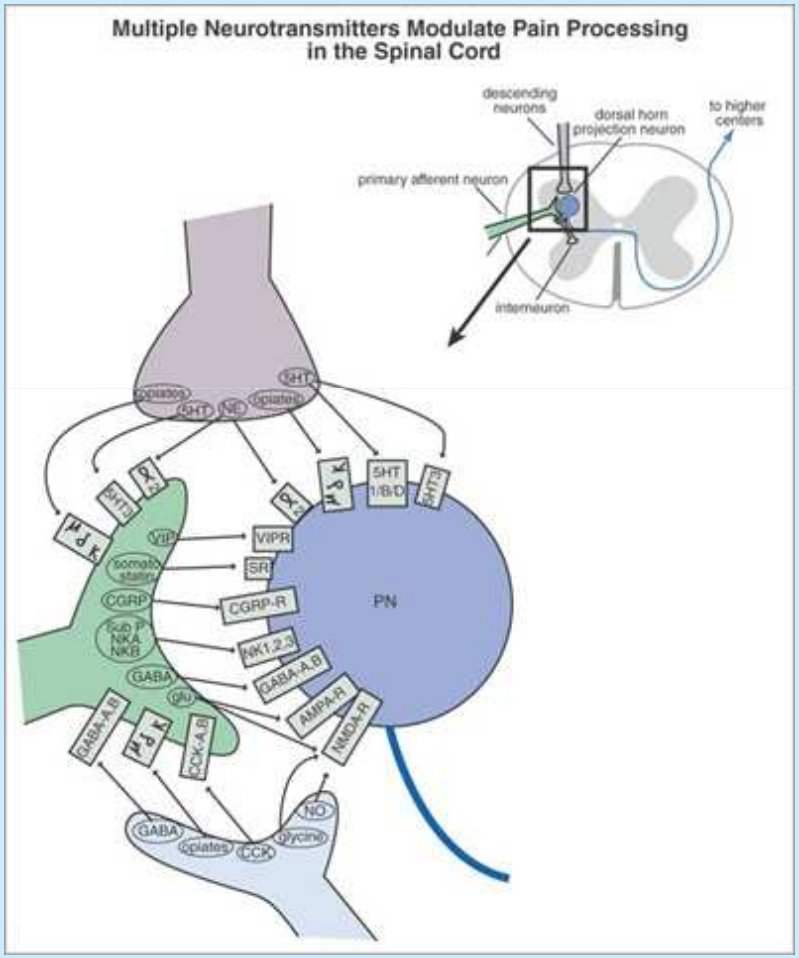
- **Glutamate,aspartate**
- **tachykinins (eg)** substance P ('P is for pain'), neurokinin A & neurokinin B.
- calcitonin gene-related peptide,
- vasoactive intestinal polypeptide,
- somatostatin and bombesin.

Inhibitory neurotransmitters

- Gamma amino butyric acid (**GABA**) Over forty percent of inhibition in the central nervous system is GABAergic.

Descending Pain Regulation

- **noradrenaline** (norepinephrine)
- **serotonin** are prominent.



Recent Advances- cfos

- Probably the most significant discovery in the field of pain has been the gene c-fos.
- CNS c-fos expression correlates extremely well with painful stimulation.
- Generically, Fos is one of the **inducible transcription factors** (ITFs) that controls mammalian gene expression.
- **We now have a molecular marker for pain**.

C fos

- "anaesthesia”without analgesia (for example the combination of halothane and N2O) does *not* suppress production of c-fos.
- Fentanyl reduces c-fos production by about 50%
- Neuraxial block with local anaesthetic agents can almost totally ablate the c-fos response.

Stress response

- Neuro endocrine response initiated by tissue trauma and pain.
- Symphathetic overactivity-↑cathcolamines
- ↑renin angiotensin- ↑cotisol and aldosterone
- ↑GH,ACTH,vasopressin, prolactin and endorphins
- Resulting in a hypercatabolic state
- Increase myocardial O2 demand
- Hypercoagulablity
- Immunosuppression.

Analgesic Drugs

NSAIDs

- COX inhibition- periphery
- NSAIDs may have central antinociceptive effects.
- Descending serotonergic pathways seem to be activated by NSAIDS, and part of the central action of NSAIDs in animal models appears to be prevented by naloxone!
- In addition, NSAIDs may even reduce c-fos expression!

Paracetamol

- COX 3 inhibition- central effect.

Analgesic Drugs…

- Opioids act by stimulating mu, delta and kappa receptors.
- Brian(periaquaductal grey and periventricular areas), spinal cord, peripheries
- 70% bind to presynaptic 1st order neurons and hyperpolarises and prevents release of neurotransmitters.
- 30% bind to postsynaptic 2nd order neurons

Analgesic Drugs…

Tramadol:

- **opioid receptors,**
- **prevents reuptake of seratonin and noradrenaline(descending control mechanism)**

Ketamine:

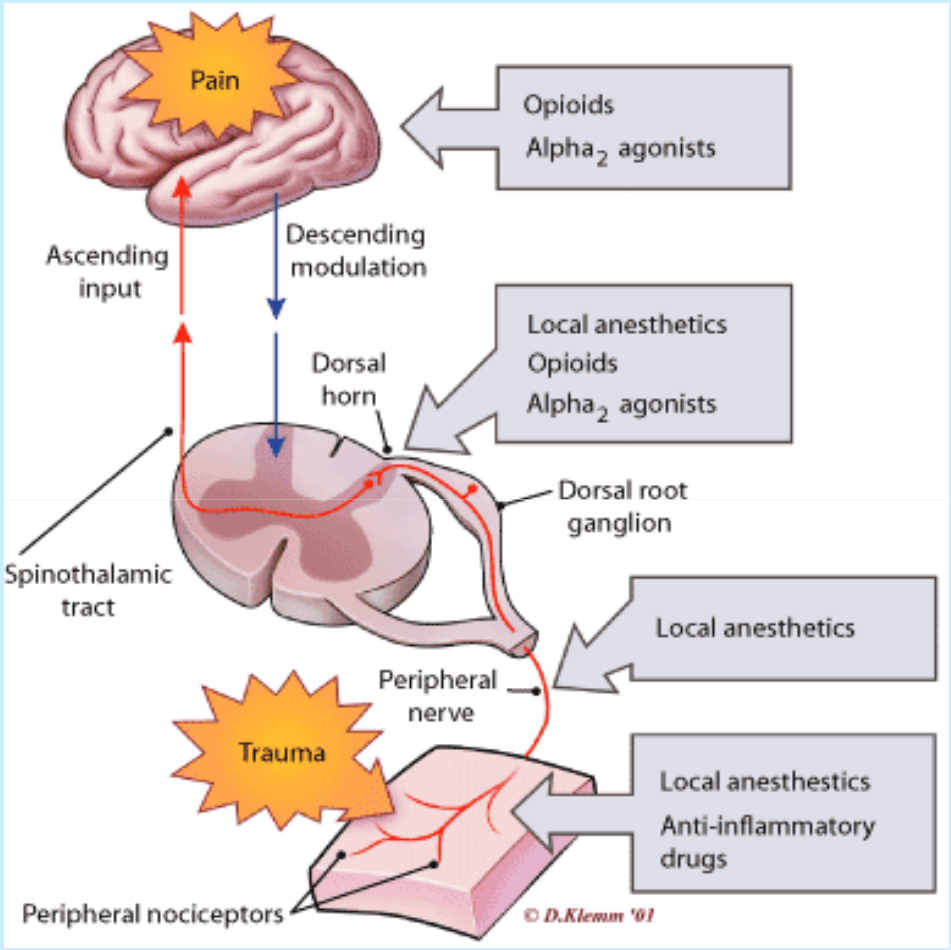
- NMDA antagonist
- Central and spinal cord

Gabapentin and pregabalin - Calcium channel blockers

Local anaesthetic- Sodium Channel blockers

Capsaicin- depletes substance P

Clonidine: alpha agonist- spinal cord


Pain
Opioids
Alpha2 agonists
Ascending input
Descending modulation
Local anesthetics
Opioids
Alpha2 agonists
Dorsal horn
Dorsal root ganglion
Spinothalamic tract
Local anesthetics
Peripheral nerve
Trauma
Local anesthestics
Anti-inflammatory drugs
Peripheral nociceptors
© D.Klemm '01

Acute to chronic

Risk factors:

- Untreated severe acute pain
- Intra operative nerve injury
- Pre existing psychological problems

Thankyou