By Adam Hollingworth

Pain

Introduction

- Pain = an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage
- Duration of pain defines acute (<30d - 6months) ⟹ subacute (1-6months) ⟹ chronic (>6-12months)
  ↳ arbitrary lengths
- hyperalgesia = noxious stimuli producing more pain than normal expected:
  - primary hyperalgesia = due to periph sensitisation where stimulus at site produces more pain
  - secondary hyperalgesia = ↑ed responsiveness in a zone surrounding injured tissue
    ↳ due to central sensitisation
- allodynia = previously non painful stimuli is now very painful

Multimodal Analgesia

- =use of number of drugs/analgesics/adjuvants in combo to achieve best pain relief possible
- Pain complex construct with sophisticated transmission pathways through nervous system
- Main targets of modulating pain transmission:
  - Peripheral receptors:
    - LA's
    - NSAIDs
  - ascending pathways
    - Opiates
    - NSAIDs
    - NMDA receptor antagonists
    - gabapentinoids
  - Descending pathways
    - Tramadol
    - Clonidine
    - 5HT3 antagonists
  - Central perception
    - Opioids
    - paracetamol
- Combination of drugs means can reduce total dose of any one drug

Pre-emptive Analgesia

- Transmission of pain signals evoked by tissue damage leads to sensitisation of complex peripheral & central pain pathways
- Pre-emptive analgesia given before surgery aims to limit this sensitisation
- Theory that preventing cascade of sensitisation will limit subsequent doses of analgesia
- Theory holds for nociceptive stimuli associated with tissue damage
  ↳ this leads to
    - Peripheral (nociceptors) sensitisation - by inflam response - substance P/prostaglandins/serotonin/bradykinin/histamine
    - Central sensitisation - by sustained afferent activation & upregulation of transmission ⟹ 'pain memory'
- Drugs & evidence:
  - Opioids - no evidence for pre-emptive
  - Ketamine - no evidence
  - Epidural -

        - single shot - some evidence reduction in analgesic demand postop
        - Continuous - no change post op analgesic demand
    - Caudal block - no evidence
    - Peripheral LA's:
        - Pre-op incisional LA - no evidence compared to post op LA infiltration
        - Nerve blocks - very limited evidence
- Pre-emptive analgesia & chronic pain:
    - 1 trial pre vs post incisional treatment showed sig ↓ chronic pain at 6months
- Summary: limited evidence to support pre-emptive analgesia at all but limited side effects & good scientific rationale

Pain Pathways

- ascending = mainly stimulating
- descending = mainly inhibiting

Ascending pathways

- start in periph tissues & terminate in contralateral somatosensory cerebral cortex (precentral gyrus)
- generally 3 orders of neurons - ie 3 synapses in pathway

1st order Neurons

- Aδ - and C-fibers
- cell bodies lie in dorsal root ganglion
- terminate on second order neurons in dorsal horn
- C fibres terminate in lamina 1 & 2 aka substantia gelatinosa
- Aδ terminate lamina 1 + 5
- myelinated:unmyelinated = 1:4 for cutaneous nerves
- pain receptors (nociceptors) respond to various stimuli eg mechanical, chemical, thermal:
    - Aδ = mechano-thermal
    - C fibre = polymodal

Interneurons

- stay at that spinal level
- integrate signal in spinal cord between laminae

2nd Order Neurons

- lie in dorsal horn (lamina 1-5)
- diff types of neurons:
    - nociceptive specific:
        - high threshold
        - located in superficial layers of dorsal horn
        - respond selectively to painful stimuli
    - wide dynamic range:
        - found in deeper laminae
        - respond to painful & non painful stimuli
        - ↑firing in proportion to intensity of stimulus in graded fashion
        - Do not signal pain in normal non-painful stimuli eg from A_{β}
            ↳ but if sensitized (allodynia) then non-painful stimuli may be perceived as painful
- form tracts up spinal cord:
    - may cross over at same level or after 1-2 segments
    - ascend up anterolateral funiculus as 1 of 3 tracts:
        - spinothalamic
        - (spinoreticular)
        - (spinomesencephalic)
    - synapse with 3rd order neurons at various levels

3rd Order Neurons

- lie in thalamus, brainstem or cortex
- spinothalamic - 2nd order terminate on 3rd order in thalamus:
  - anterolateral - discriminatory pain
  - medial - emotive-motivational pain
- spinoreticular -
  - terminate in several brainstem nuclei:
    - Nucleus reticularis paragigantocellularis lateralis,
    - nucleus subceruleus,
    - nucleus reticularis pontis caudalis
    - medullary raphe nuclei
  - responsible for:
    - activation of descending inhibitory pathways
    - arousal
    - activation motor & autonomic reflexes
- spinomesencephalic tracts:
  - terminate in:
    - superior colliculus
    - nuclei cuneiformis
    - periacqueductal grey (PAG)
  - impt in
    - activating descending inhibitory pathway & autonomic reflexes
    - coordinated affective motor responses to pain
- 3rd order neurons ⟹
  - somatosensory cerebral cortex (precentral gyrus)
    ↳ role of this not fully understood
  - cingulate gyrus - role in emotion

Descending Pathways

- arise from diff areas:
  - hypothalamus - ß endorphin neurones link ⟹ Nucelus Raphe Magnus (NRM)
  - periaqueductal grey (PAG) - α2 receptors eg in clonidine analgesia
  - locus ceruleus (LC)
  - (Nucleus paragigantocellularis lateralis)
- descend down dorsolateral funiculus, synapse in dorsal horn lamina 1,2,5
- in dorsal horn may release:
  - serotonin
  - NA
  - enkephalins
  - others eg substance P, GABA, CCK, thyrotrophin releasing hormone (TRH), somatostatin
- endogenous opiate system:
  - PAG & NRM ⟹ descending pathway to spinal level inhibitory interneurons
  - Mu opioid receptors found:
    - 1st order afferent presynaptic membrane
    - 2nd order afferent post synaptic membrane in thalamus
  - proenkephalin = endogenous ligand
- importance of descending pathways:
  - activation via external factors eg stress battle field
  - acupuncture
  - spinal cord stimulation
  - drugs eg tramadol - serotinergic & noradrenergic effects work here

Classification of Pain Fibres & Receptors

- Aδ fibres:
  - from high threshold mechanoreceptors
  - enter lamina 1,5,10 of dorsal horn
  - release glutamate
  - = small myelinated fibres 2-5um
  - fast conduction 6-30m/s
  - well localised & well differentiated pain ie fast pain
  - poor response to opioids
- C-fibres:
  - from polymodal nociceptors
  - enter lamina 1& 2 of dorsal horn
  - release substance P
  - smaller unmyelinated <2um
  - slow conduction 0.5-2m/s
  - poorly localised/burning pain follow acute injury
  - good response to opioid
- Aß fibres
  - conduct non-noxious stimuli eg low threshold touch/pressure/machano/thermal stimuli
  - unmyelinated fibres
  - conduction velocity 30-70ms
  - sensitisation ⟹ normal Aß fibres input being interpreted as pain (allodynia)
- Sleeping/silent nocicpetors:
  - unmyelinated
  - chemically sensitive - only activated in inflam & tissue damage
  - only activated after high intensity prolonged stimuli (eg >10mins) BUT then remain active for hours
- sympathetic fibres:
  - may proliferate in DRG
  - ↑ed in chronic pain

NeuroTransmitters/Mediators

- released from traumatised tissue
- cause pain or ↓threshold for transmission

Endogenous Opioid Peptides

- encephalins - widely distributed in CNS but concentrated in lamina 1,2,5
- dynophins - 80% in L1, L5
- ß-endorphin -
  - concentrated in hypothalamus
  - a neurotransmitter & neurohormone
  - released from hypothalamus
  - prob responsible for battlefield phenomenon - blocked by naloxone

Neurokinins

- substance P:
  - pain, oedema, vasoD, accentuation of bradykinin
  - related to histamine & serotonin
- calcitonin gene related peptide (CGRP)
- neurokinin 1 (NK1)
- capsaicin:
  - depletes subatance P from nocicepter after transport up C fibre to nerve cell body
    ↳ ∴ 1st causes pain ⟹ then reduction in pain

Kinins
- bradykinin & kallidin:
  - MOA:
    - proinflam by releasing cytokines & degranulating mast cells
    - direct stim sensory neuron via
      - B2 receptor (bradykinin) ⟹ GPCR ⟹ ↑cAMP +/- cGMP ⟹ ↑Na permeability cell membrane
      - B1 (kallidin)

Histamine
- from mast cells
- H1 receptor ⟹ GPCR ⟹ ↑Ca permeability ⟹ ↑substance P release
- result:
  - low conc = itch
  - high conc = pain

Adenosine
- from breakdown ATP
- activates A2 receptors ⟹ GPCR ⟹ ↑cAMP ⟹ ↓K permeability & hyperexcitability

Serotonin
- from platelets & mast cells
- MOA:
  - 5HT3 receptor (ion channel) on sensory nerves ⟹ ↑Na permeability
  - 5HT2 receptor (GPCR) ⟹ ↓cAMP ⟹ ↓K permeability
    ↳ both serve to ⟹ hyperexcitability

Prostaglandins & Leukotrines
- from arachidonic acid by inducible cycloxygenase
- causeL
  - ↓threshold for activation
  - block glutamate reuptake @ spinal cord level ⟹ facilitate conduction of pain
    ↳ = excitatory aa

Cytokines , interleukins (IL1, IL6, TNFα)
- causes:
  - ↑bradykinin receptors
  - PG production
  - activate sympathetic nerves

Nerve Growth Factor
- tissue inflam ⟹ ↑NGF at site of injury ⟹ retrograde transport to cell body ⟹ NGF binds to tyrosine kinase receptor A

Glutamate
- binds to AMPA, NMDA, kainite, metabotropic glutamate receptors

Simple/Normal Pain Transmission
- eg pain from pinprick with no ongoing tissue damage or ongoing stimulation
- nociceptor (Aδ or C) stimulated ⟹ impulse conducted to dorsal horn ⟹
  - Aδ ⟹ **lamina 1 + 5** ⟹ 2nd order neuron synapse⟹project directly up to brain
  - C fibre ⟹ **lamina 1+2** (substantia gelatinosa) ⟹ interneurons ⟹ 2nd order neurons up to brain
- Aδ = pinprick & sudden heat ⟹ fast pain + withdrawal reflex
- C fibre = pressure, heat, chemicals + tissue damage ⟹ slow burning pain
- dorsal horn
  - transmitters:

    - excitatory aa's = glutamate & aspartate
    - neurokinins = substance P & CGRP
  - 3 main receptors:
    - AMPA - glutamate, fast Na channel
    - Neurokinin -receptor - substance P
    - NMDA

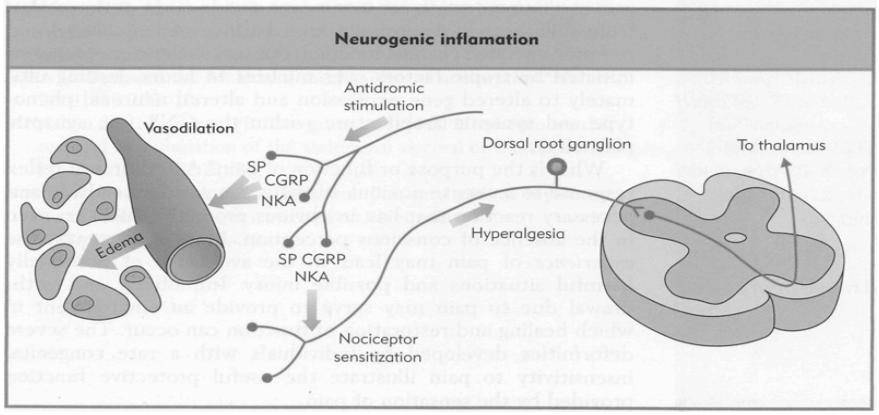
Altered Pain Perception

- may include:
  - attenuated acute pain eg hyperalgesia & allodynia
  - complex regional pain syndrome (CRPS)
  - chronic pain
  - phantom limb pain
- modulation of pain stimulus can occur peripherally and/or centrally

Peripheral Modulation

Peripheral Sensitisation

- tissue damage ⟹ local inflam response with release of:
  - mediators from damaged cells ⟹ 5-HT, bradykinin, potassium, PGs etc
  - macrophagues
  - lymphocytes
  - mast cells ⟹ histamine
- painful stim also leads to neurogenic inflam response from peripheral nerve terminals or nocicpetive afferents:
  - release of substance P, neurokinin-A & CGRP
- inflam soup ⟹ further vasoD & release of more inflam mediators eg NO, cytokines, PGs, leucotrines
- massive amount of mediators ⟹ sensitising sensory afferents (incl high threshold nociceptors) & sympathetic nerve fibres



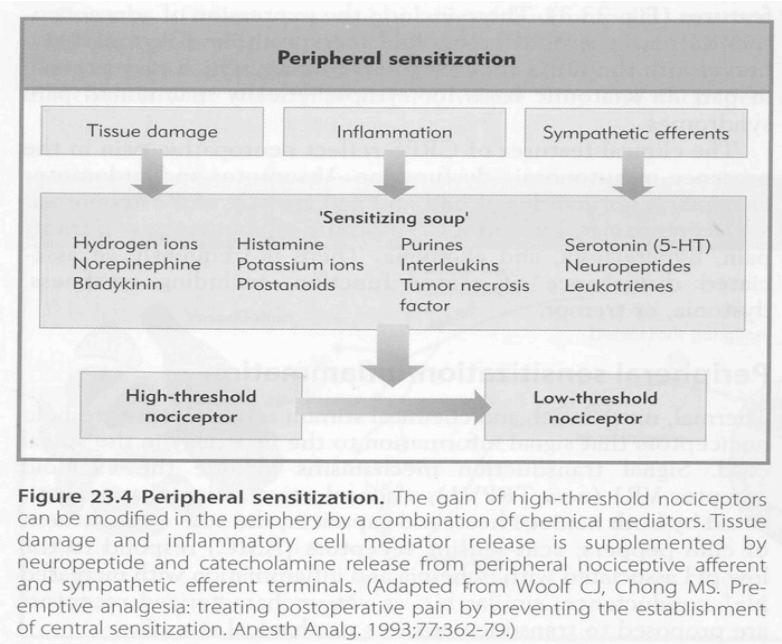
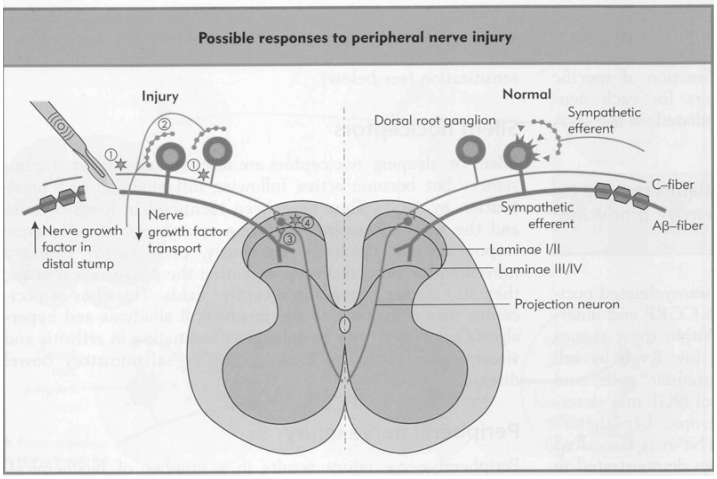


Figure 23.4 Peripheral sensitization. The gain of high-threshold nociceptors can be modified in the periphery by a combination of chemical mediators. Tissue damage and inflammatory cell mediator release is supplemented by neuropeptide and catecholamine release from peripheral nociceptive afferent and sympathetic efferent terminals. (Adapted from Woolf CJ, Chong MS. Pre-emptive analgesia: treating postoperative pain by preventing the establishment of central sensitization. Anesth Analg. 1993;77:362-79.)

Peripheral Nerve Injury

- transection or damage to periph nerve ⟹ biochemical, physiological, structural changes ⟹ focus of pain itself
- may cause ectopic discharge near site of damage
- release of nerve growth factor (NGF) may ⟹ neuroma ⟹ possible spont firing and/or altered pain sensation



Central Modulation

- complex and not fully understood
- would be Holy Grail of pre-emptive analgesia/chronic pain
- impulses can be:
  - potentiated eg wind up
  - inhibited - descending paths, Gate Theory

Central Sensitisation

- painful stimuli = repetitive or continuous ⟹ changes at dorsal horn level which augment pain transmission
- wind up = evidence to show low frequency (0.5Hz) painful stimuli activating C fibres ⟹ progressive ↑ of neuronal activity in dorsal horn (WDR) neurons throughout duration of stimuli
  - ↳ ∴ not simple stimulus-response relationship

↳ ∴ non painful stimulation within field of WDR neuron may be misinterpreted as pain in presence of ↑ed C fibre activity

- NMDA receptors:
  - central in wind up
  - ligand gated receptors for Ca influx
  - normally ion channel blocked by Mg ion
  - sustained activation of non-NMDA receptors (eg substance P or glutamate on AMPA/neurokinin receptors) ⟹ removal of NMDA Mg plug ⟹ glutamate can now activate NMDA receptor
  - ↑ed intracellular Ca
    - ⟹ ↑several second messengers ⟹ ↑signal transduction ⟹ ↑ed pain perception
    - examples of ↑Ca effects:
      - activation phospholipase A2 ⟹ frees arachadonic acid from membrance ⟹ COX pathway ⟹ PG creation which act on PG receptors on presynaptic C fibres terminals
        ↳ ie central & periph action for NSAIDs
      - activates NO synthase ⟹ ↑glutamate release at presynaptic terminals
      - activate protein kinase C & A ⟹ ↑activation of NMDA, AMPA receptors
      - activation or protooncogenes c-fos & c-jun ⟹ long term changes

      ↳ nerve cell may
        - die,
        - transmit pain all the time
        - sprout nerve growth factors

- wide dynamic range (WDR) neurons also get sensitised & contribute to secondary hyperalgesia
- ∴ wind up contribute to ⟹ allodynia & secondary hyperalgesia ⟹ may lead to sub-acute or chronic pain
- long term potentiation:
  - = strengthening of efficacy of synaptic transmission following activity across synapse
  - similar to memory formation in cortex
  - strong contributor to chronic pain
- periph nerve injury:
  - redistribution of central terminals of myelinated afferents in DH ⟹ move terminal from lamina 4 to lamina 2
  - ∴ non-noxious transmission can be interpreted as noxious (alodynia)

Gate Theory Of Melzack & Wall

- transmission of pain signals is subject to modulation at all levels of neuraxis
- afferent impulses arriving at DH initiate inhibitory mechanisms which limit subsequent impulses
- inhibition occurs via:
  - inhibitory interneurons
  - descending inhibitory pathways from brain
- Gate theory propose that
  - transmission cells (T) in DH output to ascending brain pathways
  - T cell output is regulated by inhibitory interneurons in substantia gelatinosa
  - Inhibitory interneuons (IINs) activity depends on input:
    - large diameter (Aß) non-noxious stimuli ⟹ ↑action of IINs ⟹ ↓output T cells
    - small diameter (C) noxious stimuli ⟹ ↓action of IINs ⟹ ↑output T cells
- theory good for helping understand pain modulation
- doesnt explain all pain phenomena eg pain after complete loss of afferent input eg complete spinal cord transection

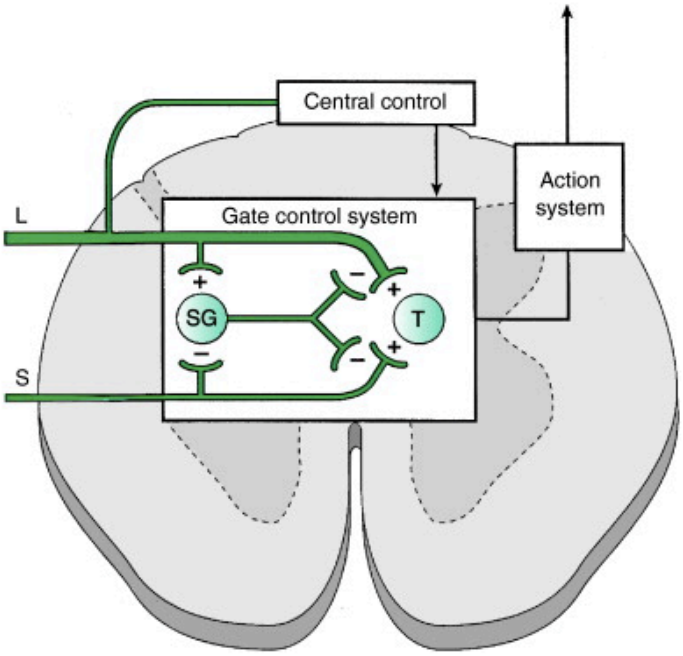


FIGURE 20-1

Gate control theory of pain. Activity in small-diameter afferents (S) stimulates transmission cells in the spinal cord (T), which send signals supraspinally and results in the perception of pain. Small-diameter afferents also inhibit cells in the spinal cord substantia gelatinosa (SG), the activity of which reduces excitatory input to T cells. Activity in large-diameter afferents (L) also stimulates T cells in a manner that is perceived as nonpainful and excites SG cells to "close the gate" and reduce S afferent activation of T cells. The gate mechanism is under regulation by central sites.

Pain in the Elderly

- impt factors to consider in elderly:
  - pharmacokinetic changes:
    - ↑fat mass,↓mm,↓body water,↓blood volume
      - effects:
        - lipid soluble drugs:
          - ↑duration of action with wider Vd
        - water soluble drugs:
          - ↓Vd ⟹ ↑plasma conc at same doses ⟹ ↑frequency of side effects
    - ↓albumin ⟹ ↑free drug available in highly bound drugs eg NSAIDs
    - change in metabolism:
      - ↓ed hepatic phase I reactions: oxidation, hydrolysis, reduction
        ↳ compared to phase II reactions : acetylation, glucuronidation, sulfation, glycine conjugation
        - ∴ drugs which undergo sig 1st pass metab will exhibit ↑ed plasma conc
        - egs:
          - SSRIs & SNRIs both inhibit cyctochrome system ⟹ buildup of other drugs
          - high dose opioids also act as enzyme inhibitors
    - ↓renal clearance - largest pharmacokinetic effect
      - caution in drugs which undergo primary renal clearance eg gabapentin
  - pharmacodynamic changes:
    - ↑sensitivity to CNS drugs
    - adrenergic & cholinergic autonomic nervous systems have ↓sensitivity eg ßblockers
  - change in body systems:

    - CNS - varied neurological dysfunctions eg parkinsons dementia,
    - liver ∴ prolonged elimination of drug
    - renal - decline in renal function in >40 at 1%/yr
        ↳ but clinical function of kidney in healthy elderly is preserved
    - pain threshold with age:
        - ↑threshold with somatosensory pain
        - ↓threshold with pressure pain
        - no change heat threshold
    - poor compliance
- chronic pain in elderly often accompanied by:
    - social isolation
    - depression
    - poor memory
    - denial