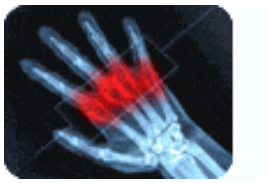
# Drugs and local hormones
# Pain

Dr K Outhoff



## Pain Overview





## Overview

- Neural mechanisms of pain
- Nociceptive afferent neurons
- Modulation in nociceptive pathway
  - Substantia gelatinosa and the gate control theory
  - Descending inhibitory controls
- Neuropathic pain
- Chemical signalling in nociceptive pathway
  - Bradykinin, prostaglandins, other peripheral mediators
- Transmitters in nociceptive pathway
  - Glutamate, GABA, 5HT, NA, adenosine
- Opioid receptors
- Morphine-like Analgesic drugs
  - Morphine analogues
  - Synthetic derivatives unrelated in structure to morphine



## Neural mechanism of pain

1. Peripheral nociceptive afferent neuron is activated by ‘noxious’ stimuli from direct tissue injury (nociception)

2. Disordered neural function not directly linked to tissue injury, but rather, the central and emotional mechanism whereby the afferent input generates a pain response (subjective response = pain)

## Stimulation of Nociceptive endings in periphery

Predominantly chemically mediated:

- Bradykinin
- Prostaglandins
- Neurotransmitters (5HT)
- Metabolites (lactate)
- Ions (K)
- Capsaicin (red hot chilli peppers)



## Neurotransmitters of primary nociceptor fibres

Fast neurotransmitters

- Glutamate
- ATP

Neuropeptides

- Substance P
- Calcitonin gene-related peptide (CGRP)

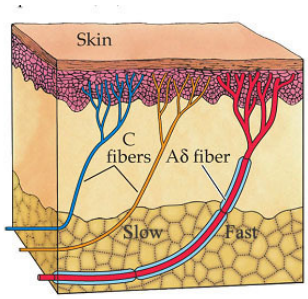


## Afferent nerve fibres involved in nociception

1. Slowly conducting unmyelinated C-fibres
2. Rapid fine myelinated Aδ fibres

- Activated by various stimuli:
  1. Mechanical
  2. Thermal
  3. Chemical
- Synapse in dorsal horn in spinal cord in laminae I, V and II (lamina II= substantia gelatinosa)
- Fibres in lamina I and V cross over to contralateral thalamus
- Substantia gelatinosa has short fibres to laminae I and V and functions as an inhibitory gate-keeper
- Gate mechanism also operated centrally from periaqueductal grey matter (PAG)in midbrain by descending pathways
- Similar inhibitory gate mechanism in thalamus



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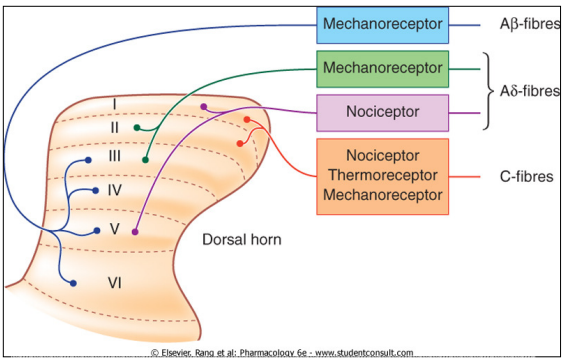


Figure 41-1 The termination of afferent fibres in the six laminae of the dorsal horn of the spinal cord.


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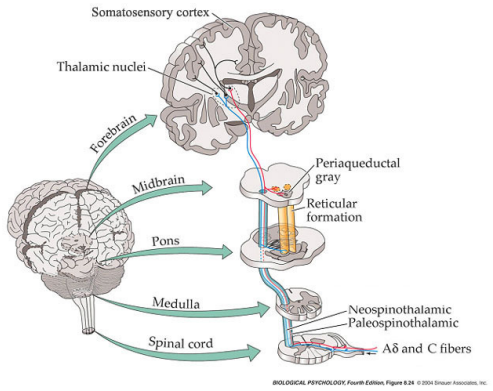
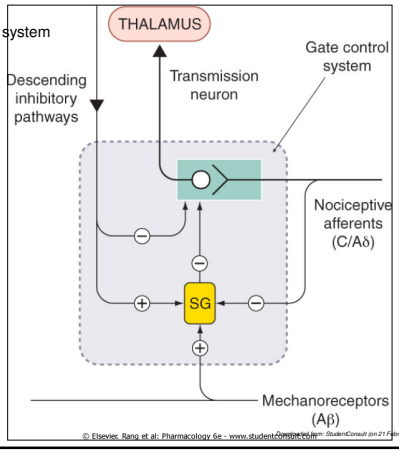





Gate control system

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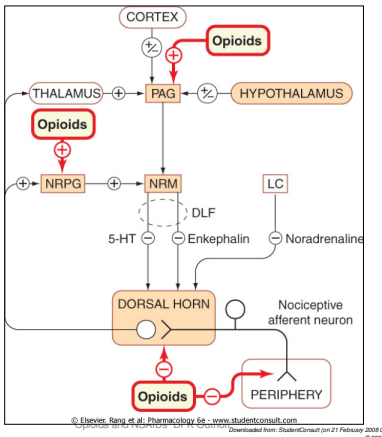
Descending Control System

Opioid action On pain transmission

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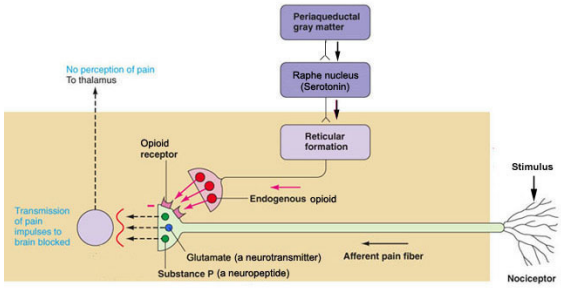
# Modulatory neurotransmitters (in descending inhibitory pathways)

- Opioid peptides in substantia gelatinosa, PAG, nucleus raphe magnus,
  - Met-enkephalin
  - Leu-enkephalin
  - Beta-endorphin
  - Dynorphin
- 5HT from nucleus raphe magnus to dorsal horn
- Noradrenaline in inhibitory fibres from locus ceruleus to dorsal horn





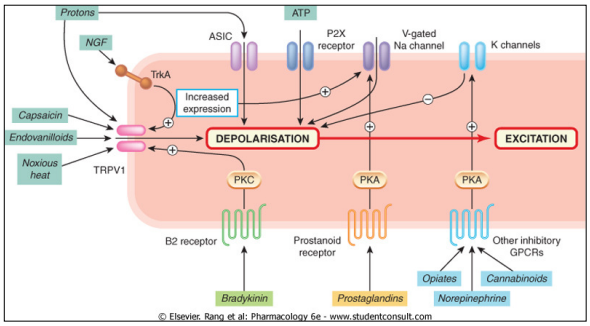



# Potential sites of action of analgesics

1. At the site of injury by interfering with nociceptive chemical mediators (eg prostaglandins)
   - NSAIDs
2. Transmission in local nerves
   - local anaesthetics
3. Transmission in the dorsal horn and thalamus
   - Opioids
   - Dual acting antidepressants
   - TENS
   - acupuncture
4. Pathways involved in the central appreciation of pain
   - Opioids
   - Antidepressants
   - Anticonvulsants



Channels, receptors, transduction mechanisms of nociceptive afferent neurons





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# The scope of analgesics

1. Paracetamol
2. NSAIDs
3. Opioids
4. Other (Neuropathic pain)
   1. Dual acting antidepressants (amitriptyline, mirtazepine)
   2. Anticonvulsants (carbamazepine, gabapentin, phenytoin)
5. Other
   1. NMDA antagonist ketamine
   2. Local anaesthetic lignocaine



# Opioid analgesics for the treatment of severe pain

Pain – inhibiting function of the opioid system



## G-protein-coupled Opioid receptors and effects

Three types:

1. **μ**
   - Analgesic effects (supraspinal, spinal, peripheral)
   - Respiratory depression
   - Euphoria
   - Sedation
   - Pupil constriction
   - Reduced GIT motility
   - Dependence

Affinity for these receptors parallels their analgesic potency

2. **δ**
   - Spinal analgesia
   - Respiratory Depression
   - Reduce GIT motility
3. **κ**
   - Peripheral analgesia
   - Sedation
   - Dysphoria

Functional heterodimers = combination of different opioid receptors!



## opioids

Morphine analogues:

- Pure Agonists: (μ)
  - Opium contains morphine (codeine and papaverine)
  - Morphine
  - Diamorphine (heroin)
  - Codeine
- Partial agonists (κ)
  - Nalorphine
  - Levallorphine
- Antagonists:
  - Naloxone
  - Naltrexone

Synthetic derivatives unrelated to morphine

- Pure agonists (μ)
  - Methadone (weak, long acting)
  - Pethidine
  - Etorphine
  - Fentanyl
- Partial agonists / mixed (κ andμ)
  - Pentazocine (partial agonist)
  - Buprenorphene (partial agonist)
  - Cyclazocine

- Loperamide does not cross BBB – inhibits peristalsis, no analgesia

## Morphine effects on the CNS

**Analgesia**
- Iv bolus (5mg) for MI and acute LVF
- Continuous infusion pump iv or subcut post-op / terminal illness
- Oral (pre-systemic metabolism)
  - 4 hrly with top-up doses
  - Sustained release
- Spinal (epidural, intrathecal) fewer systemic effects

**Euphoria**
**Respiratory depression**
**Depression of cough reflex**
  - Codeine preferred

**Nausea and vomiting**
  - Mediated by dopamine receptors in CETZ

**Pupillary constriction** (μ / δ receptors in Edinger –Westphal nucleus midbrain)



## Morphine effects on the GIT

- Increases tone
- Decreases motility, relieves diarrhoea
- Contracts gall bladder
- Constricts biliary sphincter

- Increase pressure in biliary tract
- Constipation and hard dry stool
- Delayed absorption of other drugs



## Morphine effects on other systems

Releases histamine from mast cells
- Local effects
  - Itching
  - Urticaria
- Systemic effects
  - Bronchoconstriction
  - Hypotension (vasodilatation)

Decreases adrenaline and noradrenaline from medulla
- Hypotension
- Bradycardia

Immunosuppressant effects
- Increased susceptibility to infections



## Tolerance and physical dependence

- Following repeated administration of an exogenous opioid, the sensitivity of the receptors decreases rapidly
- This necessitates an increase in dose to produce the same effect (tolerance)
- On withdrawal of the drug, endogenous opioids are not sufficient to stimulate the insensitive receptors
- This results in a withdrawal state
- Autonomic disturbances
- Pallor, runny nose, diarrhoea, shivering, pilo-erection (cold turkey)

## Morphine
## Other effects

Dependence

Overdose

- Depression respiratory centre
- Constricted pupils
- Coma
  - Rx: naloxone iv
  - (potential to precipitate acute withdrawal state)



## Morphine
## pharmacokinetics

- Variable oral absorption (cf codeine)
- Considerable first pass metabolism
- Half-life 3-6 hrs
- Hepatic metabolism
- Active, potent metabolite: morphine-6-glucuronide
- Enterohepatic circulation via bile
- Excreted in urine

Am. J. Ph.] 7 [December, 1901

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## Other opioid analgesics

**Diamorphine (heroin)**
- Converted to morphine
- Crosses BBB more rapidly (rush)
- Greater solubility (smaller volumes required)

**Codeine**
- More reliable absorption
- Less potent analgesic (20%)
- Does not cause euphoria
- Rarely addictive
- Mild pain, anti-tussive



## Other opioid analgesics

**Pethidine**
- Causes restlessness rather than sedation
- Anti-muscarinic effects (dry mouth, blurred vision)
- Euphoria
- Active metabolite has hallucinogenic and pro-convulsant effect
- Used for analgesia in labour as does not reduce force of uterine contraction
- Naloxone may be needed to reverse respiratory depression in newborn



## Other opioid analgesics

**Fentanyl**
- Rapid onset, short duration
- Used in anaesthesia

**Etorphine**
- 1000x more potent than morphine
- Used to immobilise large animals as only small volume required for dart



## Other opioid analgesics

**Methadone**
- Long duration
- Physical abstinence less acute
- Used for treating morphine and heroin addiction
- Euphoria absent when morphine / heroin used on top

**Buprenorphine**
- Partial agonist
- Long duration
- Used to control addiction

# Other opioid analgesics

**Tramadol**

- Metabolite of trazodone (antidepressant)
- Weak agonist of μ receptors
- Weak inhibitor of NA re-uptake

- Better tolerated than other opioids
- But Psychiatric reactions have been reported
- Po, im,iv for post-op pain



# Naloxone

- Pure opioid antagonist
- Affinity for all 3 opioid receptors
- No effect in normal subjects
- But produces rapid reversal of opioid effects of drugs
- No effect on pain threshhold in normal subjects
- But hyperalgesia when stressed of inflamed when endogenous peptides are produced
- Inhibits acupuncture analgesia
- Inhibits analgesia produced by PAG stimulation

- Rapidly metabolised
- Effects last 2-4 hrs
- Given repeatedly



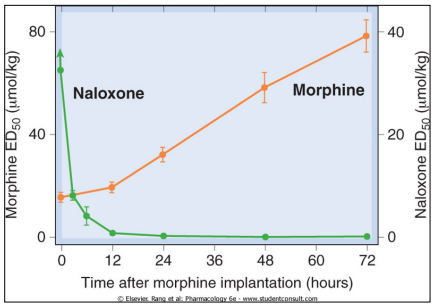



Figure 41-9 Development of morphine tolerance in mice. The median effective dose (ED50) for analgesia (hotplate test) produced by subcutaneous injection of a test dose of morphine (orange line) was measured at intervals after implantation of a slow-release pellet of morphine, the pellet being removed 8 hours before the assay in order to allow the circulating morphine concentration to fall to zero before the test dose was given. The ED50 increases about fivefold after 72 hours. Simultaneously, the dose of naloxone needed to precipitate withdrawal symptoms (green line) decreases very markedly. (From Way E L et al. 1969 J Pharmacol Exp Ther 167: 1.)

Pain medications vary considerably and each pain medication has its advantages and risks

ADAM.

# NSAIDs



## Some NSAIDs

- Aspirin
- Ibuprofen
- Diclofenac
- Indomethacin
- Meloxicam
- (Paracetamol)



## NSAIDs indications

- Chronic joint disease: osteo/rheumatoid arthritis
- Acute inflammatory conditions
  - Sport injuries
  - Fractures
  - Sprains
  - Soft tissue injuries
- Postoperative pain
- Dental pain
- Menstrual pain
- Headaches and migraine
- Etc



## NSAIDs primary action

- Inhibition of the fatty acid **COX enzyme** and its isoforms: COX 1 and COX 2

Thus ultimate inhibition of **thromboxane and prostaglandin** synthesis

## COX isoforms

COX – 1:
- Expressed in most tissues incl. Platelets
- Housekeeping role
- Tissue homeostasis
- Production of **prostaglandins** for:
  - Gastric cytoprotection
  - Platelet aggregation
  - Renal blood flow autoregulation
  - Initiation of parturition

COX – 2:
- Induced in inflammatory cells
- Production of **inflammatory cytokines**: IL-1 and TNF-alpha



## How do NSAIDs inhibit COX? background

- COX 1 and COX 2 are haem containing enzymes
- Situated in intracellular membranes
- They consist of long hydrophobic channel
- Into which **arachidonic acid** can dock
- So that (1) dioxygenation reaction may proceed
  - 2 molecules of oxygen incorporated into arachidonic acid
  - Results in highly unstable endoperoxide
- Second reaction is a (2) peroxidase reaction
  - Which results in a molecule that can be converted into other prostanoids by other enzymes



## How do NSAIDs inhibit COX?

**Inhibitors of initial dioxygenation reaction:**
- COX-1 : Rapid competitive reversible
- COX-2: slow, irreversible

- Some NSAIDs also have radical-scavenging effects
- Aspirin *irreversibly* inactivates COX-1 (exception) accounting for antiplatelet effect.
- Aspirin also inhibits expression of NF kappa B, thereby decreasing synthesis of inflammatory mediators



## NSAIDs pharmacological actions: therapeutic: COX 2 inhibition

- Analgesic effect
- Anti-pyretic effect
- Anti-inflammatory effect

## NSAIDs: Analgesic Effect

Two sites of action for mild –moderate pain:

Peripheral:
- Decrease production of prostaglandins that sensitise nociceptors to inflammatory mediators (bradykinin, 5HT)
- Main site of action

Central:
- Inhibit prostaglandin production within spinal cord
- Afferent fibres to dorsal horn neuron interrupted



## NSAIDs: Antipyretic Effect

- Hypothalamic thermostat balance interrupted in fever
- NSAIDs reset the thermostat
- NSAIDS inhibit E-type prostaglandin production in hypothalamus in response to pyrogen IL-1 in vascular endothelium
- Temperature regulating mechanisms able to adjust to new set point:
  - Dilatation of superficial blood vessels
  - Sweating



## NSAIDs: anti-inflammatory effects on pain, swelling, increased blood flow

Decrease production of prostaglandin E2 and prostacyclin derived from COX-2 in inflammatory and immune response which usually cause:

- Vasodilatation
- Oedema (increased permeability of blood vessels)
- Pain

No effect on progress of underlying disease

No effect on leukocyte migration, lysosomal enzyme release, toxic oxygen radical production (ie no effect on inflammatory cells)



## NSAIDs pharmacological actions: adverse effects: COX-1 inhibition

- Gastric irritation
- Renal blood flow compromised
- Prolonged bleeding by inhibiting platelet function
- ? Increase likelihood of thrombotic events by inhibiting PGI-2 synthesis

## NSAIDs
### common unwanted effects: GIT 40%

- Mainly from inhibition of gastric COX 1
- Therefore inhibition of prostaglandin synthesis
- Therefore loss of cytoprotection, including loss of inhibition of acid secretion:
- Gastric discomfort, dyspepsia, diarrhoea, nausea, vomiting, bleeding, ulceration
- Occurs whether drug is given locally or systemically
- But drug itself (aspirin) compounds the damage locally
- Selective COX2 inhibitors (COXIB) serious risk of increasing cardiovascular events: class effect; most withdrawn for this reason



## NSAIDs
### common adverse effects: skin + renal

Skin reactions:
- Idiosyncratic from mild to fatal
- Particularly with mefanamic acid and sulindac

Adverse renal effects;
- In susceptible people (neonates, elderly, cardiovascular, renal, liver disease) cause **acute renal insufficiency**
- By inhibiting biosynthesis of PGE2 and PGI2 which are involved in the regulation of renal blood flow
- (PGE2 compensatory vasodilation in response to NA and AngiotensinII)

- Chronic consumption: **analgesic nephropathy:**
  - Chronic nephritis
  - Renal papillary necrosis



## NSAIDs
### other unwanted effects

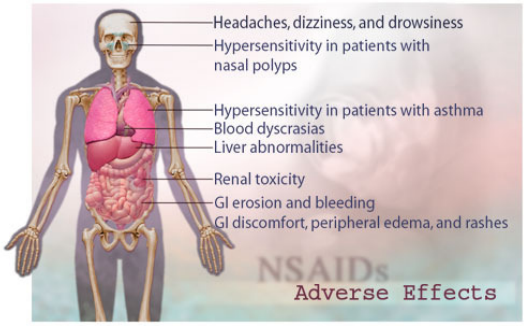
- CNS effects
- Bone marrow disturbances
- Liver disorders
- Paracetamol OD causes liver failure
- Aspirin sensitive asthma (5%) (cross reactivity with all COX-I)
- Prolongation of bleeding esp. Aspirin



## Agents selective for cyclo-oxygenase 2 (COXIBS)

- Celecoxib, Etoricoxib, Parecoxib
- Many withdrawn because of serious **cardiovascular effects**
- May only be prescribed if cardiovascular status of patient properly assessed
- Possible that GIT disturbances still occur because COX2 might be required for **healing of ulcers**
- **Rashes common**
- **Headache, dizziness**
- **Retention of fluid (oedema)**

## NSAID adverse effects




## Aspirin Indications

1. Inflammation
2. Cardiovascular disorders (medium dose, long term, 30% resistant)
3. Prevention of colo-rectal cancer
4. Alzheimer's disease
5. Radiation-induced diarrhoea



## Aspirin pharmacokinetics

- Aspirin is a weak acid
- Protonated in acid enviro of the stomach
- Therefore passage across mucosa facilitated
- But most absorption in ileum because of increased surface area provided by villi
- Rapidly hydrolysed by esterases in plasma and tissue (esp. Liver) to yield **salicylate**
  - 25% salicylate is oxidised
  - Some is conjugated with glucuronide or sulphate
  - 25% excreted unchanged, rate higher in alkaline urine
- Plasma half life dependent on dose
- Duration of action not related to plasma half life as irreversible inhibitor of COX1



## Aspirin unwanted effects

1. Salicylism: (with overdose)
   1. Tinnitus
   2. Vertigo
   3. Decreased hearing
   4. Nausea + vomiting
2. Reye's Syndrome
   1. Rare disorder of children
   2. Hepatic encephalopathy following acute viral illness
3. Poisoning

- Increased oxygen consumption, increased $CO_2$ production, stimulation of respiration and renal bicarb excretion: **respiratory alkalosis**
- Larger doses suppress respiratory centre, retention of $CO_2$: uncompensated **respiratory acidosis**
- Accumulation of pyruvate, lactate, acetoacetate: **metabolic acidosis**
- Hyperpyrexia, dehydration if vomiting
- Disturbances of haemostasis with bleeding

## Aspirin drug interactions

Warfarin:

- Displaced from plasma protein (pharmacokinetic)
- Anti-platelet effect (pharmacodynamic)

Uricosurics (probenicid, sulfinpyrazone)

- Decreased effect

Reduction of **urate excretion**



## Paracetamol

- Analgesic
- Antipyretic (inhibition of CNS prostaglandin production)
- Weak anti-inflammatory

- Very little gastric or platelet side effects
- (? Inhibition of CNS COX only)
- (? Interaction with cannabinoid receptors)



## Paracetamol pharmacokinetics

- Oral
- Well absorbed
- Peak plasma concentration within 30-60 min
- Half –life
  - Therapeutic dose: 2-4 hrs
  - Toxic dose: 4-8 hrs
- Inactivated in liver by conjugation with glucuronide or sulfate



## Paracetamol unwanted effects

Occ. Allergic skin reactions
Toxic dose (10-15grams)

- Fatal hepatotoxicity: 24-48 hrs later
- Enzymes saturated
- Therefore drug metabolise instead by mixed function oxidases
- Results in toxic metabolite, **NAPBI.**
  - Liver damage
  - Renal damage
- This is inactivated by conjugation with glutathione
- Rx: acetylcysteine iv or methionine orally within 12hrs to prevent liver damage

## W.H.O. approach to analgesia

Mild:
Paracetamol

Moderate:
Paracetamol + NSAID

Moderate-Severe:
Paracetamol + NSAID + mild opioid

Severe:
Opioid