B. 4 Non-steroidal anti-inflammatory analgesic drugs

a. Describe the prostaglandin pathway

Prostaglandins and other eicosanoids (thromboxanes, leukotrienes, lipoxins, hydroperoxyeicosatetraenoic acids etc.) are synthesized from saturated membrane phospholipids derived from dietary linoleic and linolenic acid. They are not stored, but are synthesized as required either by cleavage of phospholipids by phospholipase A₂ (which can also give rise to PAF) or by phospholipase C and diacylglycerol lipase. The production of arachadonic acid is the rate-limiting step in the production of prostaglandins. Production of arachadonic acid may be stimulated either by specific receptors in some tissues or by general cell damage.

Arachadonic acid is oxidized to PGG₂ by cyclooxygenase and then reduced to PGH₂ by peroxidase. These steps are both catalyzed by prostaglandin endoperoxide synthetase. Which prostaglandins are synthesized from PGH₂ depends on the enzymes present in the tissue. In platelets thromboxane synthetase produces TXA₂, in endothelium prostacyclin synthetase produces PGI₂, in macrophages predominantly PGE₂ is formed. The subscript 2 refers to the number of saturated bonds in the fatty acid backbone of the molecule. Small quantities of prostaglandins are synthesized from dihomo-γ-linolenic acid or eicosapentanoic acid, giving one or three saturated bonds.

In lung, platelets and leukocytes, lipoxygenases convert arachadonic acid to 5-HPETE and then LTA₄, which is subsequently converted to other leukotrienes: important chemotactic factors.

Prostaglandins are metabolized either by specific uptake and inactivation in the lung (in the case of PGE₂), renal metabolism (in the case of PGI₂) or spontaneous decay to inactive substances (TXA₂ → TXB₂).

b. Classify the non-steroidal anti-inflammatory drugs

The NSAIDs are classified by chemical structure

- Salicylic acids
  - aspirin, diflunisal

- Propionic acids
  - naproxen, ibuprofen, ketoprofen

- Acetic acids
  - indomethacin, sulindac, diclofenac

- Fenamates
  - mefenamic acid, meclofenamic acid

- Oxicams
  - piroxicam, tenoxicam

- Pyrazolones
  - phenylbutazone, azopropazone

- COX-II selective
  - celecoxib

- Paracetamol

Paracetamol is an analgesic and antipyretic with no anti-inflammatory effect. It is a weak prostaglandin inhibitor. It is the most commonly used analgesic and is available without prescription.

Class

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History

Physical

- a white powder, sparingly soluble in water

Chemical

Paracetamol
structural formula above, empirical formula C₈H₉N₂O₂, a para-aminophenol derivative

Pharmacokinetics
administered orally or rectally (variable absorption)
IV preparation available overseas: proparacetamol
bioavailability close to 100%
peak concentration 30-60 min
Vₐ 1 l/kg
little protein binding (20-50%)
plasma t½ 2-4 h
clearance 5 ml/kg/min
eliminated by conjugation and hydroxylation in the liver followed by renal excretion
metabolism pathway is saturated in overdose, resulting in production of N-acetyl-p-benzoquinone which is hepatotoxic in the absence of glutathione. N-acetyl-cysteine administration within 8 hours of overdose is protective by regenerating hepatic glutathione.

Pharmacodynamics
little effect on peripheral prostaglandin synthesis
no antiinflammatory action
no gastric/renal toxicity
no antiplatelet activity
central effect, presumably prostaglandin moderated
analgesic
antipyretic

Clinical uses
dosage 10-30 mg/kg orally, less in hepatic impairment
up to 100 mg/kg/day in children, up to 40 mg/kg PR
duration of action around 4 hours
analgesic of choice for mild musculoskeletal or superficial pain without an inflammatory component
synergistic with opiates in severe pain
antipyretic of choice in children
no significant interactions

Adverse effects
hepatotoxicity in overdose
some constipation

d. Describe the actions of aspirin on prostaglandin synthesis in high and low doses and compare it with other NSAIDs

Class
the prototype non-steroidal anti-inflammatory drug

History
salicylates are present in willow bark, a traditional antipyretic described in 1763
aspirin was synthesized in 1853 and sold commercially from 1899

Physical/Chemical
a white powder sparingly soluble in water
calcium salts are readily soluble
structure above: acetylsalicylic acid
acidic pKa (3.5)

Pharmacokinetics
orally administered
high bioavailability
absorbed from stomach and small bowel, best in acidic conditions
hydrolyzed in the liver to salicylate t½ 15 min
salicylate is protein bound 80-90%

James Mitchell (December 24, 2003)
salicylate is conjugated with glycine in the liver
\( t^{1/2} \beta 2 \text{ h at low dose, up to 20 h at high dose} \)
both are renally excreted; unchanged drug is excreted rapidly in alkaline urine

**Pharmacodynamics**

- irreversibly acetylates cyclooxygenase
- inhibits production of PGL\(_2\), thromboxanes, other PGs
- impaired platelet function, analgesic, antipyretic
- salicylic acid reversibly inhibits cyclooxygenase
- high doses result in
  - PG-mediated
    - local gastric irritation or ulceration
    - CNS stimulation
      - seizures, hyperventilation, respiratory alkalosis
    - reduced GFR, Na\(^+\) and water retention, renal papillary necrosis
    - prolongation of labour
    - closure of PDA
- hepatotoxicity
- inner ear toxicity, tinnitus
- reduced prothrombin synthesis, increasing INR
- decoupling oxidative phosphorylation
  - metabolic acidosis, hyperthermia, dehydration
- anaphylactoid reactions are most common in asthmatics
  - cross-reactivity with other NSAIDs is common

**Clinical use**

**dosage**
- for anti-platelet activity 100 mg daily
- single dose for mild pain 300-600 mg
- anti-inflammatory dose 4-6 g/day

**toxicity**
- as above, plus
- protein-binding interactions, especially with warfarin
- Reye's syndrome in children
- marrow suppression

**blood levels are closely related to toxicity**
- <10 mg/dl analgesic, antiplatelet
- 10-40 mg/dl anti-inflammatory
- 50-80 mg/dl tinnitus, hyperventilation
- 80-100 mg/dl acidosis
- >100 mg/dl hypoprothrombinaemia, renal failure, coma

**indications**
- antiplatelet: IHD, carotid disease, CVA risk
- analgesic: mild pain, with or without inflammatory component
- synergistic with opiates

**contraindications**
- not generally used in children
  - Reye's syndrome: hepatic failure associated with viral illness
  - bleeding risk (e.g. proliferative retinopathy, warfarin)
  - renal impairment or hypovolaemia
  - peptic ulcer disease
  - asthma a relative contraindication
- gout (reduces uric acid excretion in low dose)

**overdose management**
- gastric lavage & charcoal
- correction of pH disturbance, dehydration or hyperthermia
- alkalinized diuresis
Other NSAIDs
Inhibit cyclooxygenase reversibly, so have less prolonged antiplatelet effect and are not known to be effective at low dose.
Exhibit the same adverse effects with variation according to selectivity for COX-I or COX-II. COX-II inhibition results in better selectivity for anti-inflammatory activity. Potency, metabolism, excretion and half life vary widely.

e. Describe the actions of parenterally administered NSAIDs and their side-effects.

Ketorolac
parenteral NSAID
propionic acid derivative

Pharmacokinetics
administered intramuscularly (sometimes IV)
oral bioavailability 80%
peak concentration 45 min after IM injection
99% protein bound
 clearance 30 ml/kg/min
hepatic glucuronidation and renal clearance
t1/2 5h

Pharmacodynamics
similar to other NSAIDs
analgesic potency: 30 mg ketorolac ≈ 12 mg morphine

f. Outline the pharmacology of acetic acid derivatives and propionic acid derivatives including their side-effects.