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Analgesics – Antipyretic Analgesics; Non-Steroidal Anti-Inflammatory Drugs; Opioid Analgesics.

Lecture

Pharmacology II

Autumn 2023

Metabolism of Arachidonic Acid

- Location in cell membranes
- It is released from neutrophil granulocytes, mast cells, endothelium, and thrombocytes during inflammation
- Arachidonic acid is released from the membrane phospholipids by activated **phospholipase A2 (PA2)**
- Metabolism of arachidonic acid – 3 ways:
- **Cyclooxygenases** – synthesis of prostaglandins, prostacyclins, thromboxanes
- **Lipooxygenases** – formation of leukotrienes and other products
- **Cytochrom P450**

Cyclooxygenases

- **COX-1** (constitutive) synthesizes prostanoids involved in physiological processes and inflammatory reactions: prostaglandins (e.g. PGE2, PGF2), thromboxane A2 (TXA2)
- **COX-2** (inducible) is activated during inflammation (activation by pro-inflammatory factors e.g. IL-1, IL-2, TNF-α, oncogenes, etc.) mainly in macrophages, neutrophils, in the endothelium → inflammation, pain (sensitization of nociceptors), fever; production of prostacyclin (PGI2)
- **COX-3:** CNS and myocardium – role in the central MoA of analgesics-antipyretics ??

Prostaglandines

– **Functions**

- Mediators of inflammation (vasodilatation, increased permeability of blood vessels)
- Pain and fever (hypothalamus) – increase the sensitivity of nociceptors to bradykinin, histamine, serotonin, etc.
- Inhibition of gastric HCl secretion, promotion of gastric mucus secretion
- Vasodilation – reduce systemic arterial pressure
- They stimulate the contractions of the myometrium
- They inhibit the resorption of water and Na^+ in the collecting duct

2. Prostacyclines

- Vasodilatation (→ also regulation of glomerular filtration)
- Reduction of platelet aggregation

3. Tromboxanes – synthesized in platelets

- Vasoconstriction (TXA2)
- Increase in platelet aggregation

Lipooxygenase Pathway

- The effect of 5-lipooxygenase creates a group of leukotrienes
- (LTA4, LTB and LTC4, D4, E4)

- Leukotrienes have a very strong bronchoconstrictive effect
- They increase the permeability of blood vessels
- Chemotaxis and activating function on leukocytes (mainly eosinophils and monocytes)
- They regulate vasoconstriction

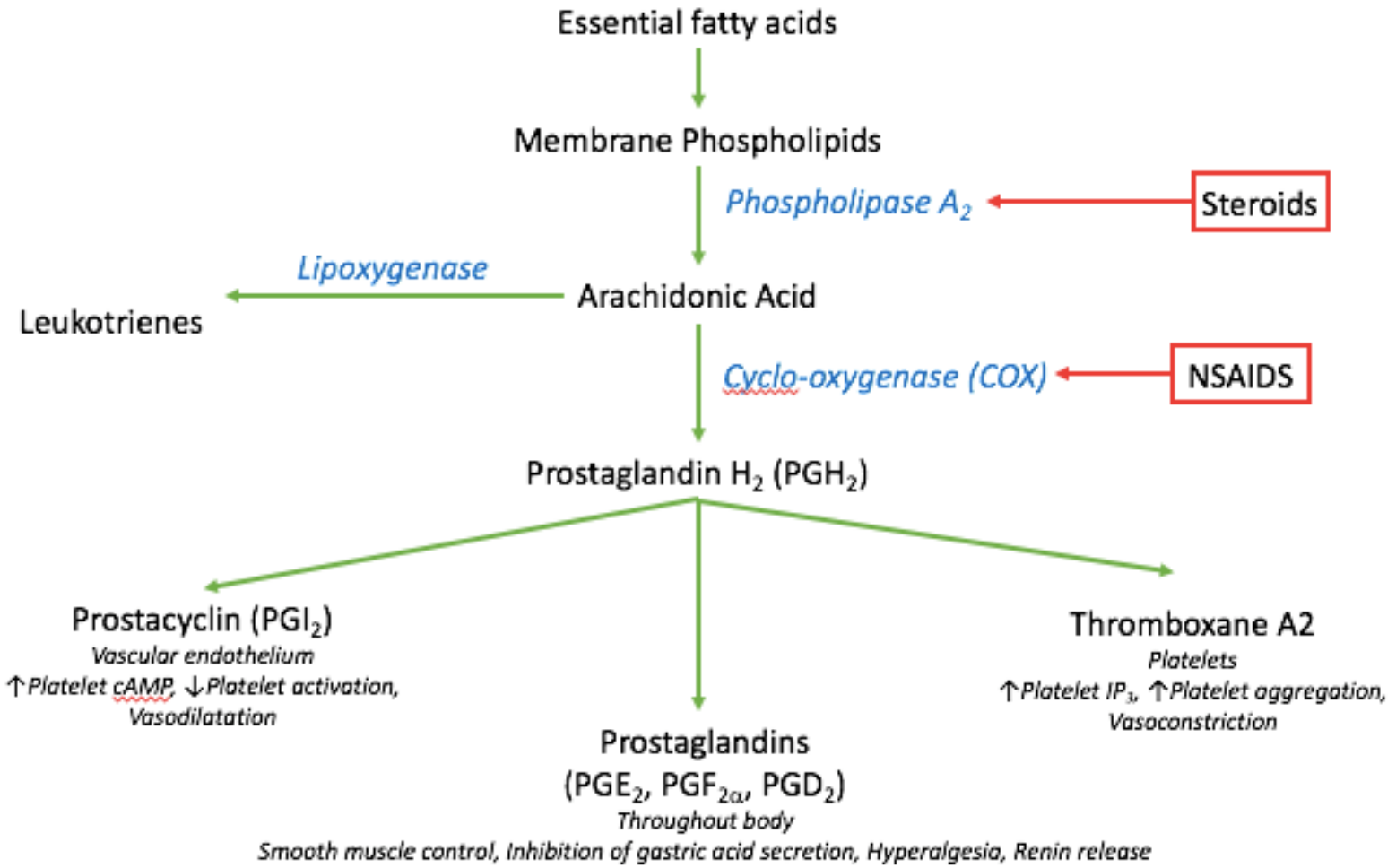

Figure 1. Prostaglandin synthesis.
Diagram adapted from T. E. Peck & S. A. Hill. Pharmacology for Anaesthesia and Intensive Care 2014 (4th edition). Cambridge University Press.

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Antipyretic Analgesics
Non-Steroidal Anti-Inflammatory Drugs

Non-opioid analgesics

Antipyretic Analgesics

- Substances that reduce the perception of pain (mainly through a peripheral mechanism) and at the same time reduce elevated body temperature (by acting on the hypothalamus)
- The exact mechanism of action is still not fully understood

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Antipyretic Analgesics

Paracetamol (acetaminophen)

- Analgesic, antipyretic effect – no anti-inflammatory effect !!
- MoA: the exact mechanism of its effect is not fully clarified, inhibition of COX (COX3), influence on descending serotoninergic pathways or modulation of the endogenous cannabinoid system, TRP ion channels, etc.
- I: mild to moderate pain, fever (drug of choice for fever and pain in children)
- Fki: good absorption (p.o., p.r.), low binding to plasma proteins, fast onset of effect
- AEs: rare after therapeutic doses (skin rash)

Antipyretic Analgesics

- Contraindication: hepatopathy, renal failure
- CAVE reduced liver and kidney function; Gilbert syndrome
- Risk of intoxication at high doses: after depletion of glutathione

→ N-acetylbenzoquinonimine (↑ formation in combination with alcohol) – reaction with hepatocytes – toxic liver necrosis

- Antidote – N-acetylcysteine

- Part of combined preparations: + tramadol; phenylephrine; guaifenesin; caffeine; propyphenazone; acetylsalicylic acid

Propyphenazone

- Pyrazolone derivative – no risk of carcinogenicity
- It acts mainly as an analgesic and antipyretic
- Compared to NSAIDs, it exhibits lower gastrotoxicity and practically does not affect the aggregability of platelets
- Part of fixed analgesic mixtures (+ paracetamol, caffeine)

Metamizole

- Analgesic, antipyretic and slight spasmolytic effect
- MoA: not clarified in detail, central and peripheral effects are assumed
- AEs: rarely leukopenia, agranulocytosis or thrombocytopenia
- Combination with spasmolytics

Non-Steroidal Anti-Inflammatory Drugs

- A chemically heterogeneous group
- Analgesic, antiphlogistic and variously strong antipyretic effect
- MoA: still not fully clarified
- **Inhibition of arachidonic acid metabolism** → inhibition of cyclooxygenase isoenzymes (COX-1, COX-2)
- Suppression of the function of phagocytic cells
- Inhibition of the effect of chemotactic substances, the release of proteases, pro-inflammatory factors, free radicals, etc.

+ central mechanism of analgesic and antipyretic effect

Differences between NSAIDs

- **Pharmacodynamics**
- Selectivity for COX isozymes
- **Pharmacokinetics**
- Biological half-life – onset of effect, duration of effect
- **Indications**
- Acute/chronic pain, anti-inflammatory effect (rheumatoid arthritis, etc.)
- **Adverse effects (GIT, CV)**

Indications

- **Analgesics**
- Mild, moderate pain (muscle pain, toothache, headache, dysmenorrhoea, rheumatism)
- **Antipyretics**
- Acetylsalicylic acid, ibuprofen
- **Antiaggregation**
- Acetylsalicylic acid (low doses – prevention of aggregation)
- **Antiphlogistics, mainly antirheumatic**
- They mainly affect the acute phase of inflammation
- **Dermatology**
- Keratolytics (salicylic acid)

Pharmacokinetics

- Lipophilic substances, weak acids
- Good absorption from GIT
- Small volumes of distribution, high plasma protein affinity (up to 99% in some cases) risk of drug interactions!, mostly metabolized by liver
- Differences in speed of absorption, onset of effect and mainly in biological half-life – acute x chronic pain
- Distribution to the site of inflammation with a lower pH

Adverse Effect	Pathophysiological background
Gastrointestinal tract Dyspepsia (nausea, vomiting, pain), erosion of gastric mucosa, gastroduodenal ulcer, microbleeding	Reduction of PGE2, PCI2 synthesis, local effect on mucous membranes
Kidneys Dysfunction, ↓ glomerular filtration, fluid retention	Decreased COX function in the kidneys
Inhibition of platelet aggregation	Reduced formation of thromboxane
Hypersensitivity reaction Asthma provocation, bronchospasm, skin reaction, photosensitisation	Predominance of leukotriene synthesis
Reye's syndrome	??
Liver (hepatopathy), cardiovascular system – increased blood pressure, bone marrow – cell damage – rare today	
CNS – during long-term treatment with indomethacin – rare	

Drug Interactions

- Risk of displacement from binding sites on plasma proteins (valproic acid)
- Potentiation of risk of bleeding into the GIT - Antiplatelet agents (ASA, clopidogrel, etc.), anticoagulants (warfarin, heparin, etc.) – displacement from binding to plasma proteins (warfarin)
- Increased incidence of GIT bleeding – SSRI type antidepressants
- Reduction of the effect of diuretics and antihypertensives (e.g. ACEIs and beta-blockers)
- Increased efficacy and toxicity due to reduced clearance (lithium, methotrexate)
- Sulfonylureas – hypoglycemia
- Co-trimoxazole – acidification of urine
- Glucocorticoids increase the risk of GIT AEs
- Simultaneous administration of two NSAIDs increases the risk of AEs

Contraindications

- Active and recurrent peptic ulcer disease
- In patients with acute heart failure, renal failure
- In pregnancy in the third trimester (inhibition of uterine contractions → prolonging, complications during childbirth; risk of premature closure of *ductus arteriosus*)
- CAVE chronic bronchitis, asthma, COPD; liver diseases

Classification of NSAIDs according to COX selectivity

- **COX-1 selective** – ASA in low doses (max. 100 mg/day)
- **COX-nonselective** – e.g. ASA higher doses; piroxicam; naproxen; indomethacin, ibuprofen; diclofenac etc.
- **COX-2 preferential**
- meloxicam
- nimesulide
- **COX-2 selective**
- celecoxib
- rofecoxib

Non-selective COX Inhibition

- Inhibition of both types of COX
  - The affinity of specific substances to individual types varies

- A higher occurrence of AEs is associated with a higher affinity to COX-1 due to a high inhibition of the formation of constitutive prostaglandins

Acetylsalicylic acid

- **Antiplatelet** effect already at a dose of 50–100 mg/day (secondary prevention of myocardial infarction)
- MoA: by irreversible blockade of COX-1 inhibits the synthesis of thromboxane A2 (after degranulation ↓ amount in plasma) → irreversibly inhibits the activation of platelets (they are not capable of synthesizing new cyclooxygenase) – the effect lasts as long as the platelet survives in the bloodstream (full recovery of the effect 4–5 days)
- **Antipyretic** 500 mg
- **Analgesic** 500 mg (after 4 – 6 h)
- **Antiphlogistic** above 3 g per day
- With an increase in the dose, the effect also increases in AEs

Acetylsalicylic acid

- Fki: absorption at pH < 3.5 (stomach, or the proximal part of the duodenum)
- Salicylic acid is a metabolite (deacetylation possible already in the GIT)
- Salicylate intoxication = salicylism (headache, dizziness, tinnitus, confusion, sweating, vomiting, diarrhea, fever)
- AEs: see previous (GIT, bronchospasm, skin rash, hepatopathy, nephropathy)
- Contraindications: children under 12 years of age – Reye's syndrome (hyperpyrexia, metabolic acidosis, vomiting, convulsions, neuropsychiatric disorders, hepatic impairment)
  - Asthma; blood clotting disorder; gastroduodenal ulcer
- Drug Interactions: see previous

Propionic acid derivatives

Ibuprofen

- Analgesic, antipyretic (400 mg 3 times per a day) and mild antiphlogistic effect (max 2.4 g/day)
- I: treatment of inflammatory and degenerative joint diseases, treatment of fever, treatment of backache, toothache, dysmenorrhoea, etc.
- Onset of action within 30 min after p.o. administration
- AEs, drug interactions, contraindications see previous
- Well tolerated, few AEs
- p.o., p.r., local application

Propionic acid derivatives

- **Ketoprofen**
- Antiphlogistic effect, analgesic
- I: inflammatory diseases (rheumatoid arthritis, arthrosis, etc.), post-operative, post-traumatic pain
- p.o., p.e., local application
- **Tiaprofen**
- Strong antiphlogistic effect, analgesic
- I: rheumatic diseases, post-operative, post-traumatic pain, osteoarthrosis – more gentle towards metabolic processes x e.g.. indomethacin – lower effect on the synthesis of proteoglycans and hyaluronic acid
- Good penetration into synovial fluid
- **Flurbiprofen** – currently registered only as a local analgesic, antiphlogistic – in oral cavity

Propionic acid derivatives

Naproxen

- Analgesic (mild, moderate pain), antiphlogistic effects
- I: headache, toothache, backache, dysmenorrhea, post-traumatic pain, osteoarthritis, rheumatoid arthritis
- Well tolerated
- Longer biological half-life (14h), rapid onset of action
- AEs: mainly in GIT, but lower risk of cardiovascular toxicity x other NSAIDs

Acetic acid derivatives

Indomethacin

- Strong analgesic, antiphlogistic effect
- Frequent occurrence of AEs GIT, CNS, rarely disorders of hematopoiesis
- Only short-term treatment of acute problems
- p.r., local application
- I: acute attacks of gout, rheumatoid arthritis, arthrosis, painful swelling or inflammation after injuries
- Phlebitis, pericarditis
- Pharmacological closure of the ductus arteriosus

Acetic acid derivatives

Diclofenac

- Good analgesic, moderately strong antiphlogistic effect (also slightly antipyretic)
- Relatively common but mild AEs (more than ASA, less than indomethacin)
- Short biological half-life, rapid onset of action
- I: as a common analgesic, muscle, tooth, back pain; rheumatoid arthritis (well penetrates synovial fluid)
- p.o., p.e., local application

Acetic acid derivatives

Aceclofenac

- Analgesic, antiphlogistic effect
- I: pain and inflammation in osteoarthritis, rheumatoid arthritis
- Good GIT tolerability, lower risk of AEs
- Suitable for chronic therapy

Oxicams

Non-selective COX inhibitors

Piroxicam – strong antiphlogistic effect

- I: symptomatic treatment of osteoarthritis, rheumatoid arthritis
- Long biological half-life, risk of accumulation in case of elderly patients
- CAVE renal dysfunction

Lornoxikam – good therapeutic efficacy; short biological half-life

- I: acute mild to moderate pain
- Good safety profile – lower incidence of GIT AEs x other NSAIDs

Preferential COX-2 inhibitors

Meloxicam

- It belongs to the oxicam group
- I: rheumatoid arthritis or ankylosing spondylitis
- Long biological half-life, slower onset of action - suitable for the therapy of chronic problems
- Lower incidence of GIT AEs x non-selective NSAID

Preferential COX-2 inhibitors

Nimesulide

- MoA: Preferential inhibition of COX-2 + inhibition of the formation of free radicals, reduces the release of substances that damage connective tissue
- Good CNS penetration
- Shorter biological half-life, rapid onset of action
- Lower incidence of GIT AEs, but discussed hepatotoxicity (not for long therapy - max. 2 weeks)
- Not registered in many countries

Selective COX-2 inhibitors

Coxibs

- Some coxibs have up to 100 times higher selectivity to COX-2

→ lower GIT AEs, they do not affect kidney function and platelet aggregation

- BUT! risk of thromboembolic events
- **Rofecoxib**, **valdecoxib** withdrawn from clinical use (cardiovascular toxicity)
- **Celecoxib, etoricoxib, parecoxib**
- Contraindications: cardiovascular or cerebrovascular disease

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Opioid Analgesics

Opioid Analgesics

= Substances that can activate opioid receptors

- Effect at the level of the spinal cord, supraspinally
- Affect the somatic and even visceral pain
- Stronger effect than non-opioid analgesics
- Affect consciousness
- Can induce addiction
- Endogenous opioids (natural ligands of opioid receptors) – endorphins, enkephalins, dynorphin, endomorphins

Opioid Receptors

- 3 types of opioid receptors:
  - **μ** supraspinal analgesia, euphoria, respiratory depression, miosis, sedation, addiction, GIT effects
  - **κ** spinal + peripheral analgesia, sedation, dysphoria, miosis
  - **δ** spinal analgesia, respiratory depression, reduction of GIT motility

(**σ** hallucinations, dysphoria, anxiety)

Classification according to pharmacodynamic profile

- **Agonists** – affinity for the μ, κ and δ receptor with intrinsic activity (morphine, pethidine, fentanyl, oxycodone, alfentanil, sufentanil)
- **Partial agonists** – high affinity for μ receptors with lower intrinsic activity (buprenorphine)
- **Agonists-antagonists** – receptor affinity for κ and δ with expressed intrinsic activity and affinity for the μ receptor without intrinsic activity (pentazocine, nalbuphine, butorphanol)
- **Antagonists** – affinity for the μ but also the κ receptor and δ without intrinsic activity (naloxone, methylnaltrexone)
- **Atypical opioids** (tramadol)

Opioid Classification – a clinical perspective

➢ Weak opioids

- Weak μ agonists (codeine, dihydrocodeine, tramadol) or agonist-antagonists (pentazocine) with partial activity on κ receptors and antagonistic activity on μ receptors
- **Ceiling effect** - i.e. the dose beyond which there is no additional analgesic effect

➢ Strong opioids

- Potent opioids are full agonists at μ receptors and are intended for the therapy of strong, unquenchable pain that cannot be adequately relieved non-opioid analgesics or weak opioids
- No ceiling effect

Pharmacological Effects – Central

- **Analgesic**
- Sedation
- Euphoria/dysphoria
- Anxiety suppression
- Miosis
- Depression of the respiratory center, antitussive effect (the cough-control center in the medulla oblongata)
- Effect on neuroendocrine functions (↑ ADH, prolactin; ↓ GnRH, FSH, LH, ACTH, corticotropin etc.)
- Nausea, vomiting

Pharmacological Effects – Peripheral

- Increase of muscle tone in GIT → constipation
- Increase of detrusor and sphincter of the bladder → risk of retention of urine
- Delayed gastric emptying
- Histamine release – risk of bronchoconstriction, rash, itching, redness
- Uterus – ↓ tone and motility, risk of prolongation of labor
- Vasodilatation, orthostatic hypotension

Adverse effects of opioids

- Respiratory depression
- Nausea, vomiting
- Sedation and depression cognitive functions
- Constipation
- Itchy skin

➢ Quite fast adaptive **tolerance** to some AEs arises during therapy with opioids

!! Except tolerance to constipation

- Risk psychological and physical dependence

Opioid agonists

Morphine

- Reference analgesic for evaluation of efficiency and dosage of other opioids
- s.c., i.m., i.v., epidural administration for the therapy of strong, acute pain
- p.o. administration for therapy of acute or chronic pain
- Analgesically effective and toxic metabolites accumulating in renal insufficiency and in older age

Strong Opioid Agonists

Fentanyl

- Good CNS penetration
- Lipophilic
- AEs: depression of the respiratory center, ↓ risk of nauzea
- Indications: therapy of moderate/severe acute or chronic pain, in anesthesiology (neuroleptanalgesia = neuroleptic + opioid), analgosedation (combination of opioid + benzodiazepine)
- Transdermal application (TTS – transdermal therapeutic system)
- Transmucosal systems – due to lipophilic properties rapid onset of action (treatment of breakthrough pain)

Sufentanil, Alfentanil, Remifentanil

Strong Opioid Agonists

Oxycodone

- Agonist of μ and κ receptors
- Drug forms with controlled release
- I: chronic pain, neuropathic pain

Hydromorfon

Piritramid

Pethidin/meperidin

- I: for in acute colic pain, not for chronic pain
- ↑ risk of AEs, obsolescent

Methadone – I: treatment of Opioid Use Disorder

Moderately and weakly potent opioid agonists

Codein

- Antitussive effect, weak analgesic effect (combination with paracetamol)
- Biotransformation by CYP450 2D6 to morphine ! interindividual variability

Dihydrokodein

Partial Opioid Agonists

- Lower analgesic effect, but lower risk of addiction and other AEs
- Ceiling effect

Buprenorphine

- I: for treatment of strong chronical pain (in the form of TTS), substitution treatment for opioid dependence (in combination with naloxon)
- Not for p.o. administation

Atypical Opioids

Tramadol

- Dual mechanism of action → weak μ-agonism and inhibition of noradrenaline and serotonin reuptake
- In combination with paracetamol
- Drug interactions: in combination with MAO/SSRI/SNRI risk of serotonin syndrome

Tapentadol

- Stronger opioid
- MoA: μ-agonism + suppresses the reuptake of noradrenaline

Opioid Antagonists

Naloxone

- Antidote in case of acute intoxication by opioids
- i.v.

Naltrexone

- Adjunctive treatment for Opioid Use Disorder

Nalmefene

- Treatment of acute opioid overdose and alcohol dependence

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