NONSTEROID ANTIINFLAMMATORY ANALGESICS (NSAIDs)

2020

ANALGESICS

OPIODS

- narcotic
- morphine like
- major

NON-OPIOIDS

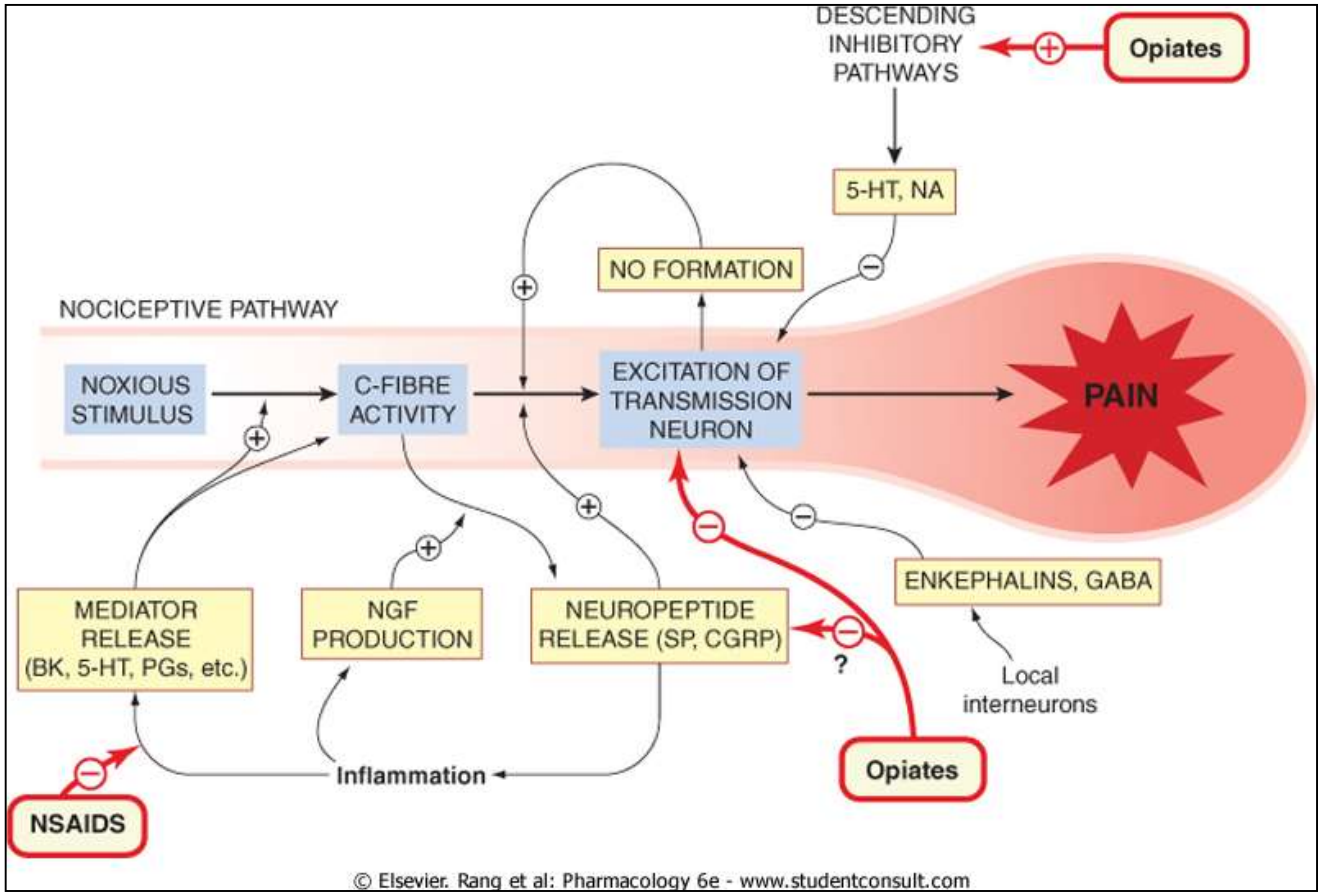
- non-narcotic
- ASA - like
- minor

•NSAID
+ antiinflammatory
antipyretic actions

ADJUVANTS

Therapeutical effects I

- **Analgesic – inhibition of the hyperalgesia induced by the PGs (PGE_2 and PGI_2), reduction of the sensitivity of nociceptors (peripheral effects)**

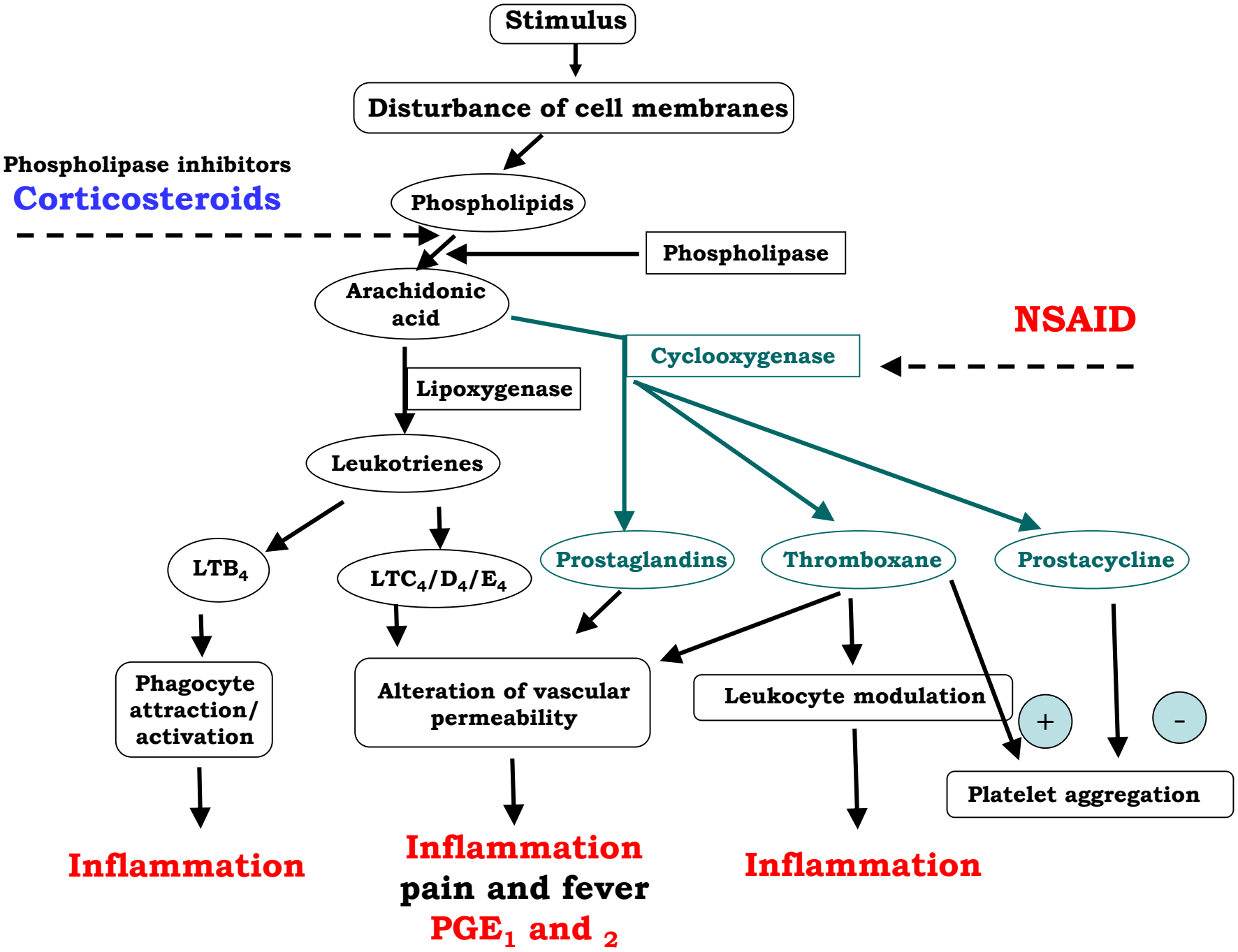


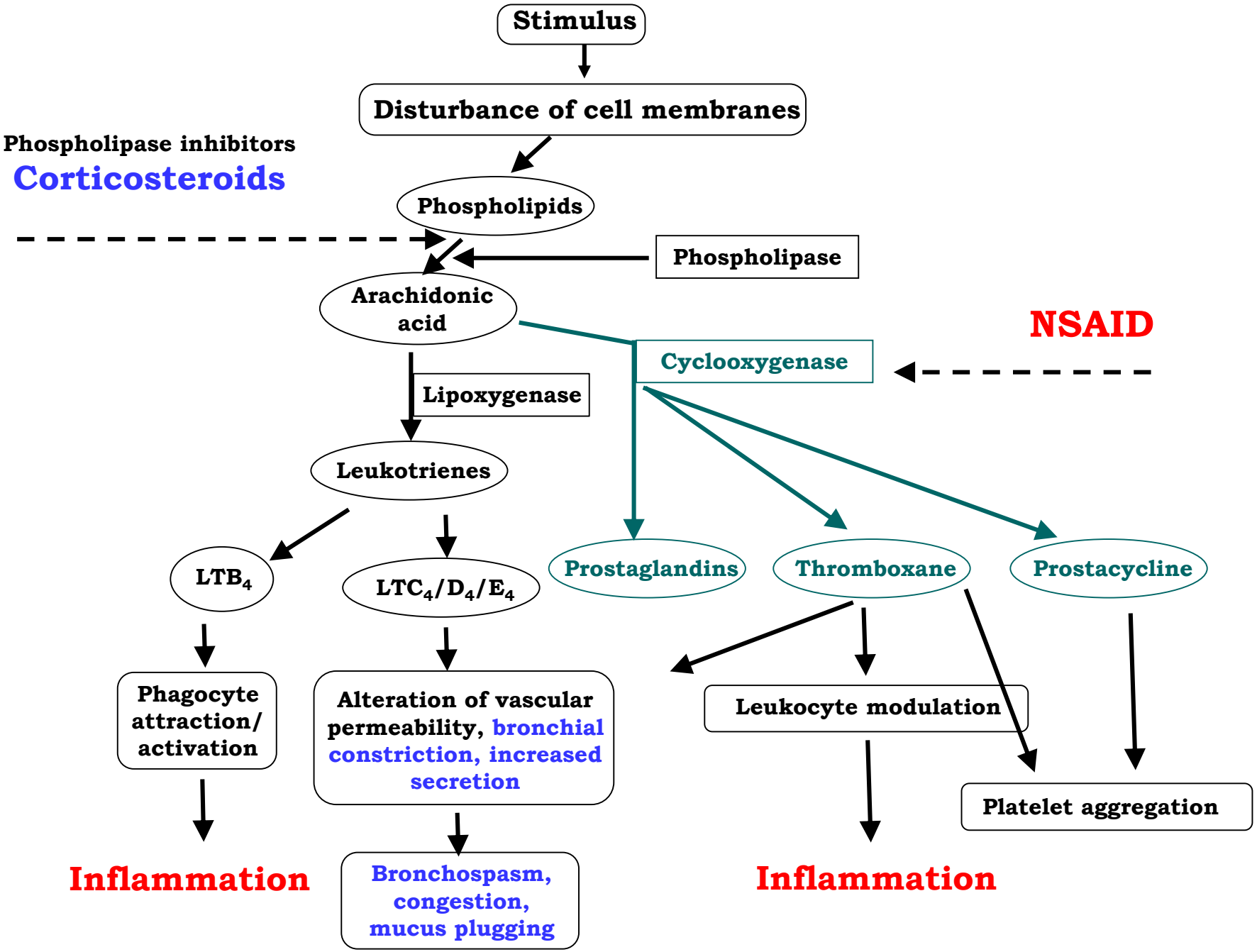
Therapeutical effects II

- **Analgesic – inhibition of the hyperalgesia induced by the PGs (PGE_2 and PGI_2), reduction of the sensitivity of nociceptors (peripheral effects)**

- **Antiinflammation – inhibition of the vascular effects of PGs** (vasodilation, changes in permeability)

NSAID compounds (in contrast to glucocorticoids) affect mainly the first phase of inflammation


Stimulus
Disturbance of cell membranes
Phospholipase inhibitors
Corticosteroids
Phospholipids
Phospholipase
Arachidonic acid
NSAID
Cyclooxygenase
Lipoxygenase
Leukotrienes
LTB4
LTC4/D4/E4
Prostaglandins
Thromboxane
Prostacycline
Phagocyte attraction/ activation
Alteration of vascular permeability
Leukocyte modulation
+
-
Platelet aggregation
Inflammation
Inflammation
pain and fever
PGE1 and 2
Inflammation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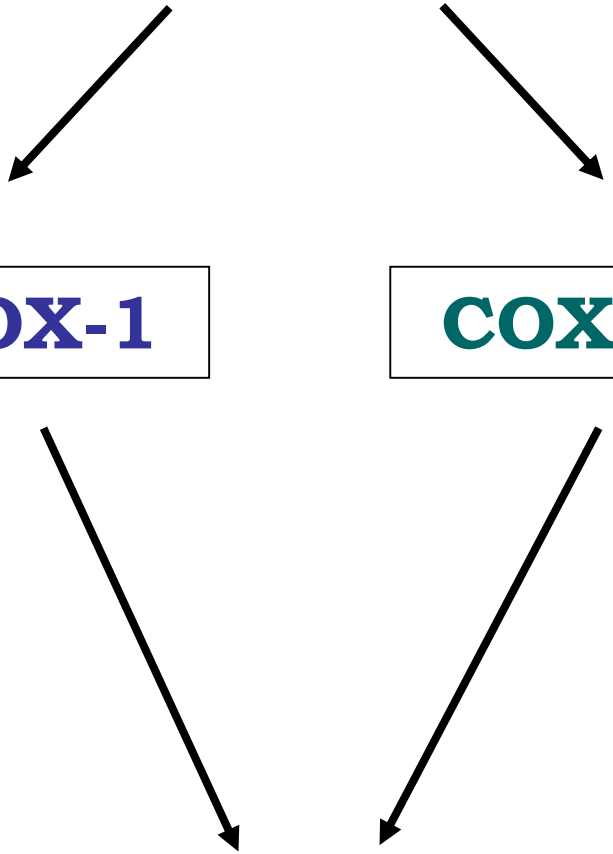
LTB4
LTC4/D4/E4
Prostaglandins
Thromboxane
Prostacycline
Phagocyte attraction/ activation
Alteration of vascular permeability, bronchial constriction, increased secretion
Leukocyte modulation
Platelet aggregation
Inflammation
Bronchospasm, congestion, mucus plugging
Inflammation

Arachidonic acid



COX-1

COX-2

constitutive in:
stomach
platelet
kidney

but is induced, too

induced by:
cytokines
endotoxins
mitogens

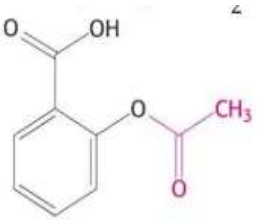
but constitutive in endothel (prostacyclin), in the kidney and also in CNS ?

prostanoids

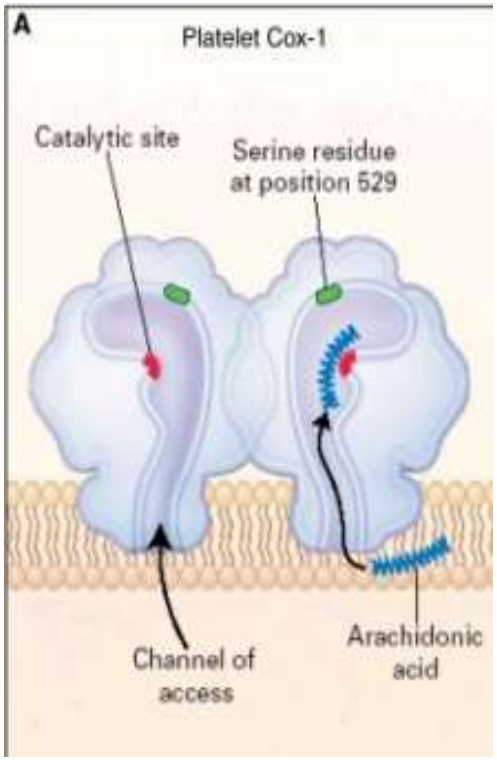
Therapeutical effects III

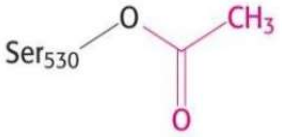
- **Antipyretic effect – inhibition of the hypothalamic PGE_2 effect (central)**
- **Inhibition of platelet aggregation – reduction of TXA_2 level (mainly COX-1 controlled effect)**

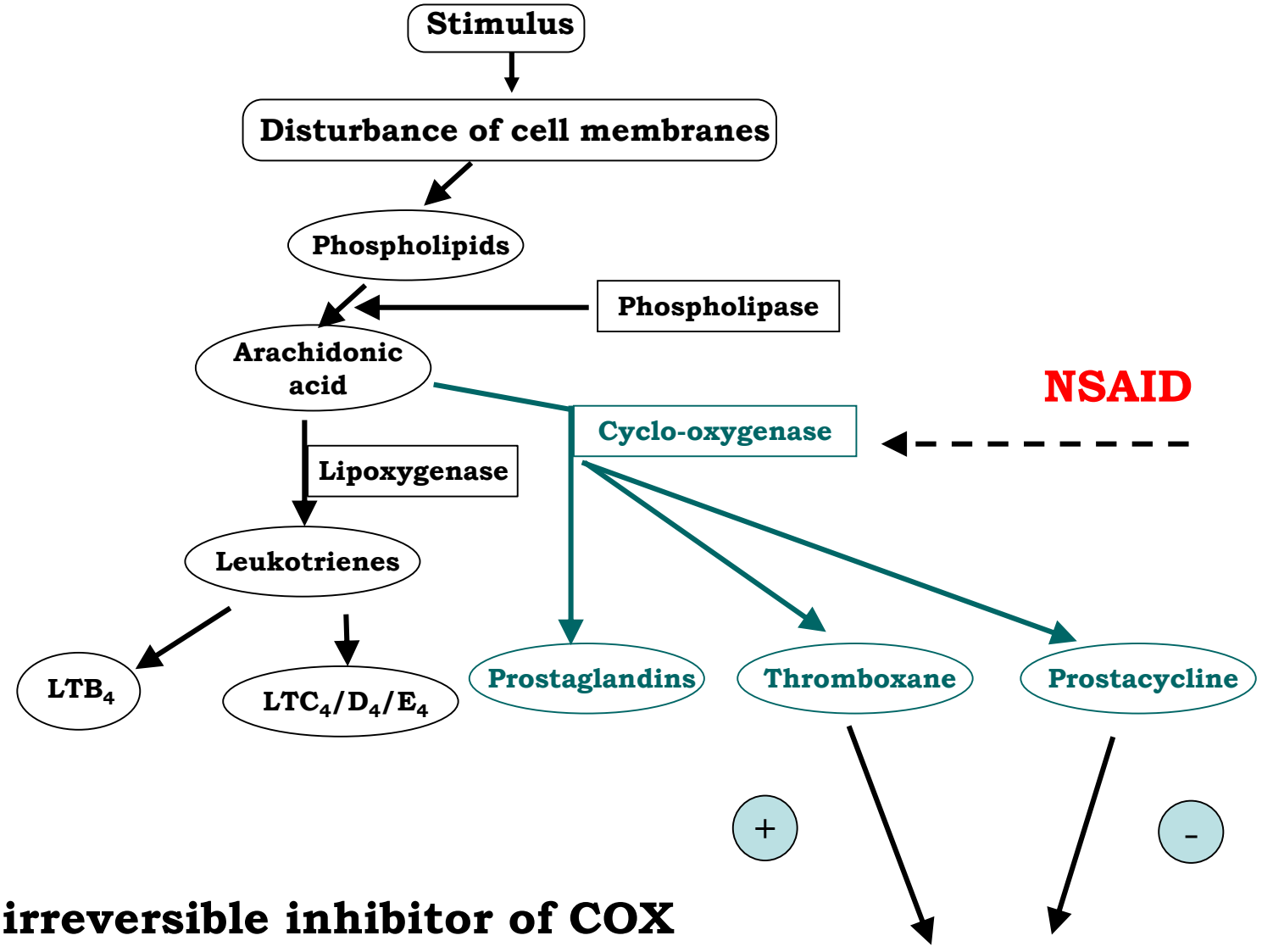
ASA is the most potent/most long-lasting



Aspirin
(Acetylsalicyclic acid)







aspirin – irreversible inhibitor of COX

Other effects

- **Relaxation of the uterus**
- **Closure of Ductus Botalli (arteriosus)**

Adverse effects

Ulcer (gastric, duodenum) – reduction of the level of defending PGs + local irritation (acidic character, diffusion into the cells of the mucosa, commutation, ionization

Impairment of kidney function, edema – GFR is reduced, during chronic usage the NSAID are accumulating in the kidney

Damage of cartilage – reduce of PGs results in enhanced formation of ROS ?

Allergic reaction – skin symptoms, bronchoconstriction
(probably because of enhanced leukotriene synthesis)

Early closure of Ductus Botalli

Decreased contraction of the uterus – slowing-down of delivery, intensified bleeding

Pharmacokinetic characteristics

- **good oral absorption**
- **high plasma protein binding**
- **high hepatic metabolism mainly by glucuronidation**
- **excretion mainly by kidney, in case of impaired kidney function slow elimination, risk of recyclization**

  excretion partly by the bile (e.g. diclofenac, indomethacin)
- **appearance in the synovial fluid (mainly those with short half life)**

CLASSIFICATION OF NSAIDs according to the antiinflammatory effect

analgesic and marked anti-inflammatory effect
(salicylates, pyrazolones, acetic acid derivatives, oxicams)

analgesic and mild/moderate anti-inflammatory effect
(propionic acid derivatives, fenamates

analgesic effect without anti-inflammatory effect
(para-aminophenol derivatives)

CLASSIFICATION according to COX selectivity

1. Relatively selective COX1 inhibitors (e.g. aspirin, indomethacin, naproxen, ketoprofen

2. Inhibitors having equal COX1/COX2 affinity (e.g. ibuprofen)

3. Inhibitors showing weak selectivity toward COX2 (<5 times difference , e.g. diclofenac, piroxicam)

4. Inhibitors showing medium selectivity toward COX2 (5-50 times difference , e.g. meloxicam, celecoxib)

5. Inhibitors with high selectivity toward COX2 (>50 times difference , e.g. etoricoxib, valdecoxib)

CLASSIFICATION according to COX selectivity

1. Short duration of action (less, than 10 hours)
   aspirin, indomethacin, diclofenac, ibuprofen

2. Long duration of action (more, than 10 hors)
   naproxen, piroxicam, nabumeton, meloxicam

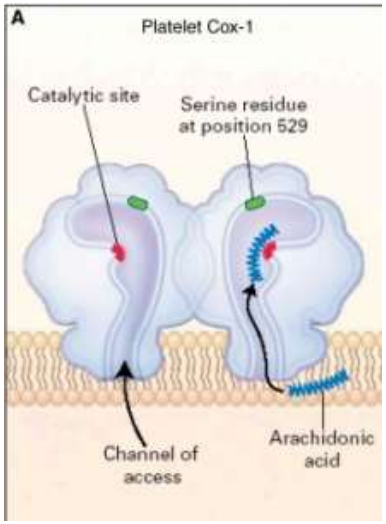
SALICYLATES I

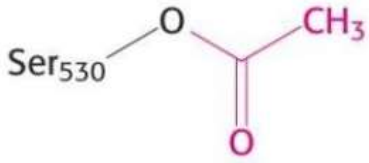
acetyl salicylic acid (aspirin)

analgesic and strong antiinflammatory

irreversible COX inhibitor, COX-1>COX-2

Aspirin
(Acetylsalicyclic acid)





Special kinetic - short half live, transformed to salicylic acid by esterase enzymes, which is metabolized in the liver.
In case of higher doses zero order kinetic, accumulation, metabolic acidosis

SALICYLATES I

acetyl salicylic acid (cont.)

THERAPEUTIC EFFECTS

- Inhibition of platelet aggregation (80-300 mg/day) for preventing/treating **arterial** thrombosis
- Analgesic (500 mg/day)
- Antipyretic (500 mg/day
- Anti-inflammatory (4-5 g/day)

SALICYLATES I

acetyl salicylic acid (cont.)

SPECIAL ADVERSE EFFECTS I

- Bleeding !!
- Hepatic effects - asymptomatic hepatitis, Reye's syndrome
- Hypersensitive reactions in CNS - tinnitus, vertigo, decrease of hearing, hyperventilation
- Hyperglycemia (with large doses)
- Hyperuricemia (contraindicated in gout)

Intoxication - metabolic acidosis, respiratory depression, hyperpyrexia), coma

Therapy NaHCO3 i.v. + symptomatic

OTHER SALICYLATES

Non-acetylated salicylates

Non acetylated salicylates are weaker, than the acetylated (smaller risk of adverse effect)

For topical application

salicylic acid – keratoplastic (2-3%), keratolytic (8-10%)
methyl salicylate – it induces hyperemia, used for joint/muscle pain

For systemic usage

diflunisal - not transformed to salicylic acid – $t_{1/2}$ 8-12 hrs.

5-aminosalicylic acid - IBD

ACETIC ACID DERIVATIVES

indomethacin, diclofenac, *sulindac, aceclofenac, tolmetin*

Short acting, strong antiinflammatory drugs

INDOMETHACIN

COX-1>COX-2 + inhibition of cell-migration and lymphocytes proliferation

antiinflammatory! anti-gout effect!

Special indications - Hodgkin disorder as antipyretic

management of patent ductus arteriosus (second line)

Severe adverse effects:

GI irritation, CNS (severe headache, depression, psychosis), hematologic reactions (aplastic anemia, thrombocytopenia, renal side effects

ACETIC ACID DERIVATIVES (cont.)

Diclofenac (COX-1 >/≈ COX-2)

anti-inflammatory (accumulates in synovial fluid!)
analgesic, antipyretic
Side effects – enhancement of the transaminase level

Sulindac

pro-drug, converted in the liver to a sulfide, which is excreted into the bile and then reabsorbed from the intestine. This may help to maintain a constant blood levels with reduced gastrointestinal side effects (?)
Long half-life

Bromfenac **- ophthalmic usage after surgery**

ENOL ACIDS (OXICAMS)

Long acting ($t_{1/2}$ 20-70 hr) antiinflammatory drugs

Piroxicam, *Tenoxicam*

very long half life (50 hours)!
extensive bound to plasma protein

Lornoxicam – short half life (3-4 hr)

Meloxicam - higher affinity towards COX2
half life about 20 hours

PROPRIONIC ACID

Better tolerated than the previous drugs, short duration of action, antiinflammatory (COX-1>COX-2)
accumulation in the joints

Ibuprofen/Dexibuprofen – used also for management of patent ductus arteriosus (first line drug) COX-1=COX-2

Naproxen – long duration of action (t1/2 - 14 h),

Ketoprofen (topical)**/Dexketoprofen** (oral)
some lipoxygenase inhibition, too;

Ketorolac tromethamine (injection, tabl. intraocular wash-out)

Flurbiprofen – also NO and TNFα synthesis inhibitor, oral and eye drop

Oxaprozin – half-life 58 hr

PYRAZOLONES I

Strong antiinflammatory action

Phenylbutazone

antiinflammatory!, analgesic, (antipyretic)

severe side-effects - used only in very severe inflammation, max. for 1 week (in Bechterew disease sometimes longer)
used also topically !

Sulfinpyrazone uricosuric
(presently discontinued)

PYRAZOLONES II

Weak antiinflammatory action

Methamizole (aminopyrine, dipyrone) is transformed in the GI by a non-enzymatic way to 4-methylaminophenazon, which is strong **analgesic** and **antipyretic**, but **weak antiinflammatory** + shows some smooth muscle relaxant effect, too

No acidic character, no ulcerogenic effect !

Side-effects - agranulocytosis! (genetic background ?)

Phenazone **eardrop**

Aminophenazone **analgesic and antipyretic**

FENAMATES

Mefenamic Acid, Flufenamic Acid, Niflumic Acid

Short duration of action

No advantages over others NSAIDs

Adverse effects - diarrhea, rarely sever skin symptoms (Steven-Johnson syndrome)

OTHER COMPOUNDS

Nabumetone (***Alkanon derivative)*** **– mainly antiinflammatory , less ulcerogenity (non acidic prodrug + higher effect on COX-2)**

Nimesulide (***Sulfonanilide)*** **– higher effect on COX-2, hepatotoxicity !!**

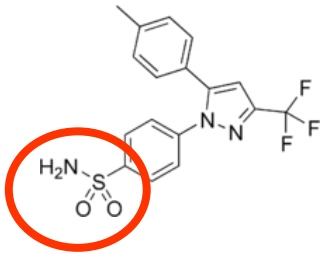
SELECTIVE COX-2 INHIBITORS (coxims)

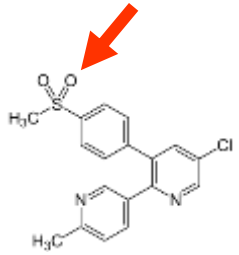
Substituted diaryl heterocyclic derivatives

Ulcerogenic action is small, cardiovascular risk is high

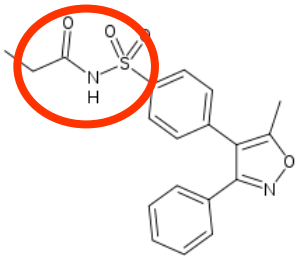
Celecoxib and etoricoxib

used mainly as antiinflammatory drugs, celecoxib - sulfonamide (allergy !)





Etoricoxib highest selectivity



Parecoxib - prodrug (valdecoxib) analgesic, inj.

SIDE EFFECTS OF COX-2 INHIBITORS

- **Cardiovascular**

  increased number of cardiovascular side effects

- **Renal**

  no significant difference in the renal complication of selective COX-2 and non-selective COX inhibitors

  risk!!! elderly, impaired renal function

- **Stomach**

  Healing processes are diminished

- **Psychiatric**

  confusion, hallucination, depression

OTHER MINOR ANAGESICS I

Para-amino-phenol (aniline) derivatives

THERAPEUTIC EFFECT: **analgesic, antipyretic**

NO ANTIINFLAMMATORY ACTION!

Short duration

no GI ulceration!
hypersensitivity occasionally!

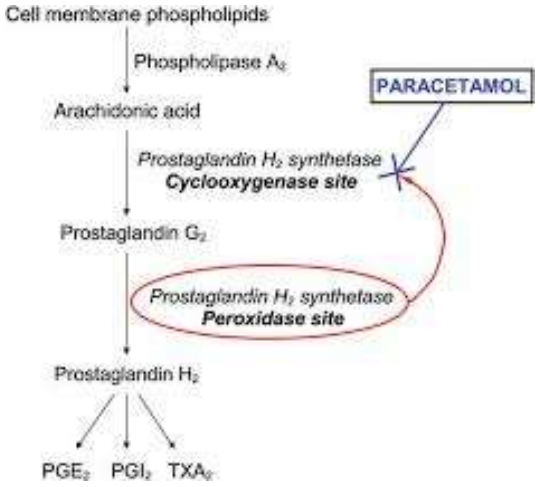
Phenacetin: renal tubular necrosis,
methemoglobinemia, hemolytic
anemia, euphoria only in mixtures

OTHER MINOR ANAGESICS II

Acetaminophen (paracetamol)

Mechanism of action – COX inhibitors but not antiinflammatory?

- COX inhibition in the brain (COX-3) ?
- It inhibits the peroxidase activity of COX enzymes, but not the endoperoxide synthase (cyclooxygenase) activity



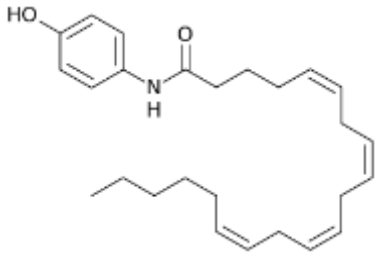
Peroxidase activity is higher in inflamed cells (and in CNS)

OTHER MINOR ANAGESICS II

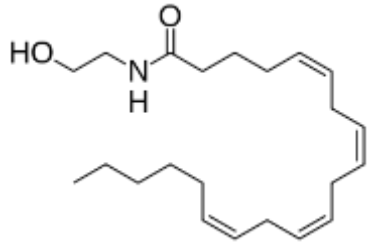
Acetaminophen

Mechanism of action – COX inhibitors but not antiinflammatory?

- perhaps other effects e.g. decrease of free radicals, inhibition of myeloperoxidase or action via the endogenous cannabinoids



AM404 (N-arachidonoylaminophenol) active metabolit of paracetamol



Anandamide – endogenous cannabinoid

OTHER MINOR ANAGESICS II

Acetaminophen

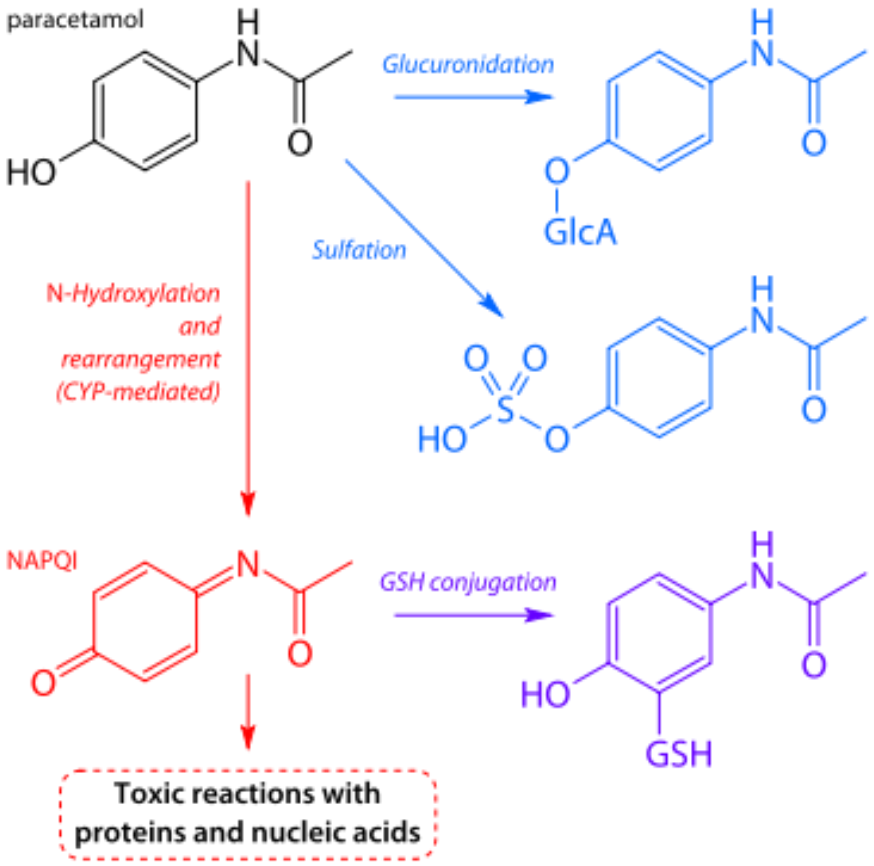
short duration of action
in case of not too high doses it is safe
can be administered to children/pregnancy

side-effects:

acute hepatic necrosis (might be fatal)
(dose-dependent, 10-15g, in children 6-8 g)

Alcoholics/children are much more sensitive

OTHER MINOR ANAGESICS II



N-acetyl-p-benzoquinon

Therapy of hepatic necrosis : SH compounds

N- acetylcysteine