NSAIDs (Aspirin)

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Non Steroidal Anti Inflammatory Drugs

- NSAIDs are used in the treatment of inflammation, fever and pain.
- Most currently available traditional NSAIDs (tNSAIDs) act by inhibiting the prostaglandin synthesis by inhibiting the cyclooxygenases (COXs).
- The inhibition of cyclooxygenase-2 (COX-2) is thought to mediate the antipyretic, analgesic, and anti-inflammatory actions of tNSAIDs.
- While the simultaneous inhibition of cyclooxygenase-1 (COX-1) largely accounts for unwanted adverse effects in the GI tract.

NSAIDS……

- There are two forms of COX, COX-1 and COX-2.
- COX-1, expressed constitutively in most cells, is the dominant source of prostanoids for housekeeping functions, such as gastric epithelial cytoprotection and platelet aggregation.
- Inhibition of COX-1 at this site is thought to account largely for the gastric adverse events that complicate therapy with tNSAIDs, thus providing the rationale for the development of NSAIDs specific for inhibition of COX-2.

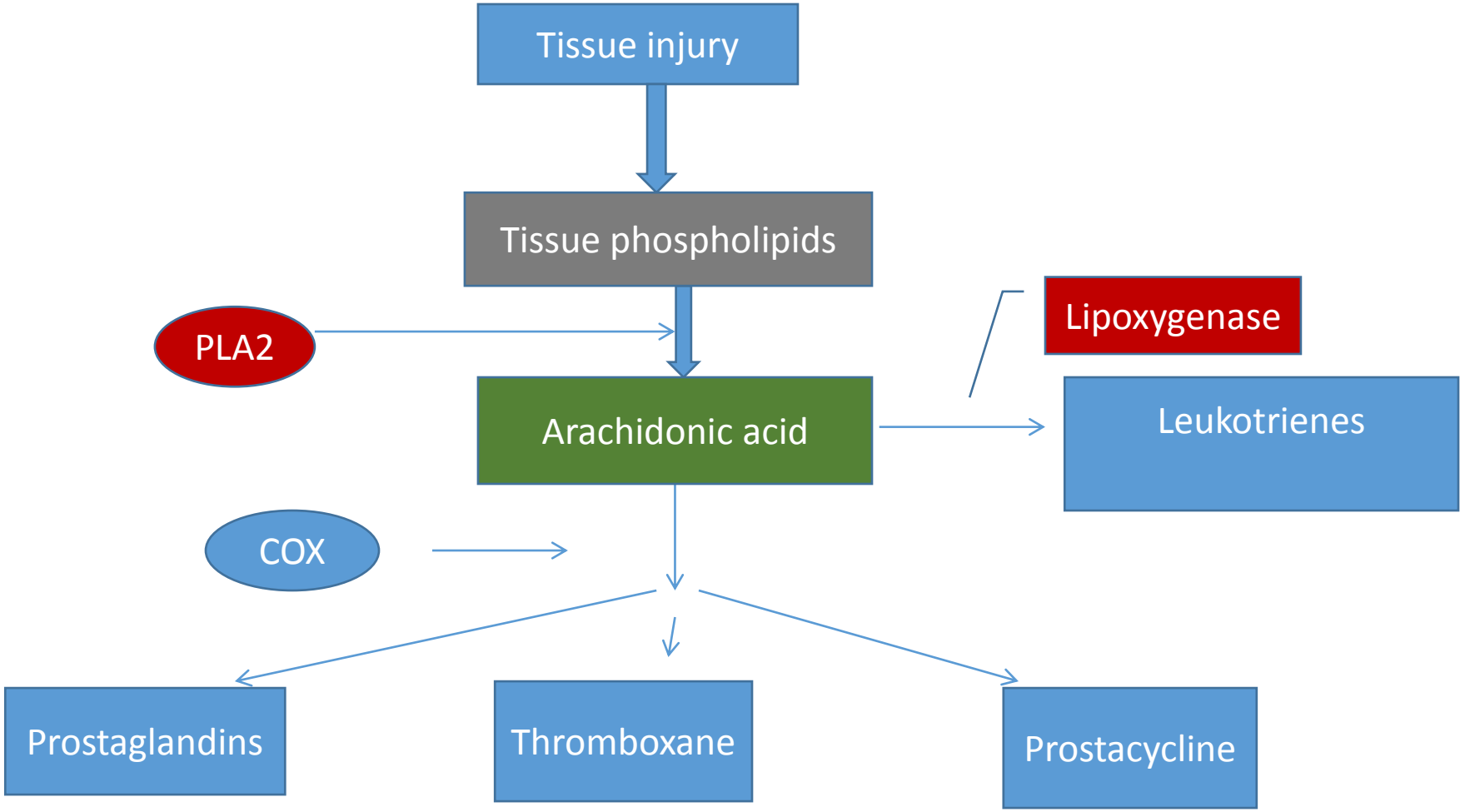
- Whereas COX-2, induced by cytokines, shear stress, and tumor promoters, is the more important source of prostanoid formation in inflammation and perhaps in cancer.

NSAIDs…….

- Aspirin irreversibly acetylates COX,
- Propionic acid derivatives (ibuprofen, naproxen), acetic acid derivatives (indomethacin), and enolic acids (piroxicam), all of which compete in a reversible manner with the arachidonic acid (AA) substrate at the active site of COX-1 and COX-2.
- Acetaminophen (paracetamol) is a weak anti-inflammatory drug; it is effective as an antipyretic and analgesic agent at typical doses that partly inhibit COXs.
- Acetaminophen has fewer GI side effects than the tNSAIDs.

NSAIDS……

- Aspirin and NSAIDs inhibit the COX enzymes and PG production; they do not inhibit the lipoxygenase (LOX) pathways of AA metabolism and hence do not suppress LT formation.
- Glucocorticoids suppress the induced expression of COX-2, and thus COX-2–mediated PG production. They also inhibit the action of PLA2, which releases AA from the cell membrane. These effects contribute to the anti-inflammatory actions of glucocorticoids.


Tissue injury
Tissue phospholipids
PLA2
Lipoxygenase
Arachidonic acid
Leukotrienes
COX
Prostaglandins
Thromboxane
Prostacycline

NSAIDS……

- At higher concentrations, NSAIDs also are known to

➢Reduce production of superoxide radicals,

➢Induce apoptosis,

➢Inhibit the expression of adhesion molecules,

➢Decrease NO synthase and pro-inflammatory cytokines (e.g., TNF-α, IL-1),

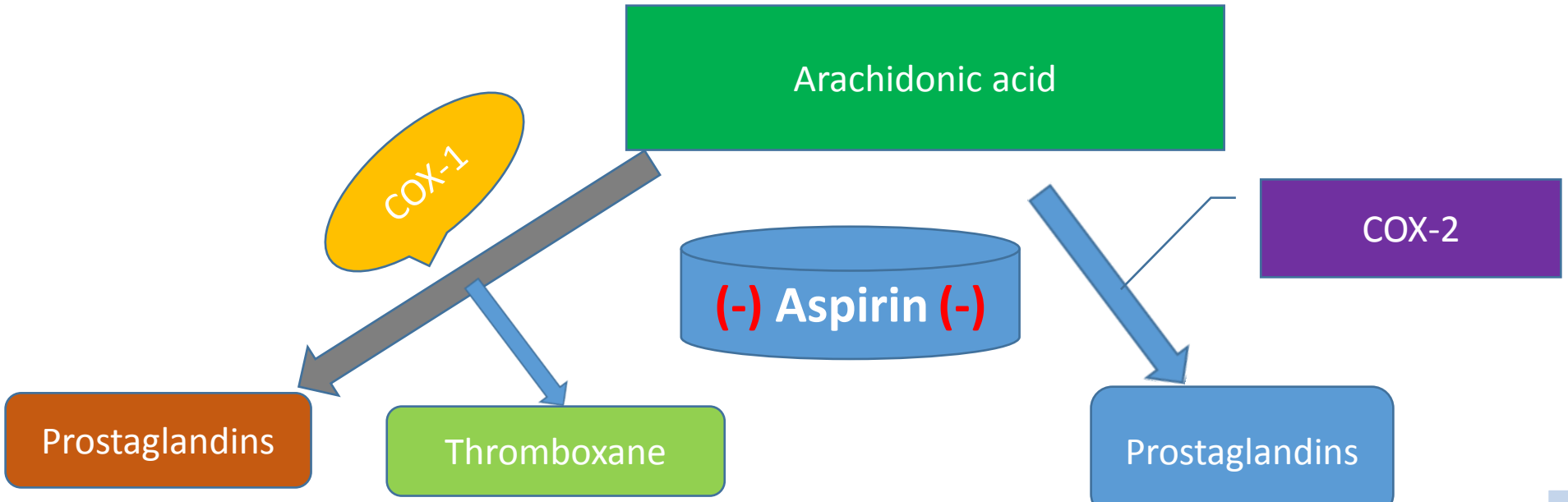
➢Modify lymphocyte activity,

➢Alter cellular membrane functions in vitro.

Mechanism of action of Aspirin

- Aspirin is a non selective inhibitor of cyclooxygenases.
- It covalently modifies COX-1 and COX-2.
- Aspirin acetylates serine at 529 position of COX-1, located high up in the hydrophobic channel. Interposition of the bulky acetyl residue prevents the binding of arachidonic acid (AA) to the active site of the enzyme and thus stop the ability of the enzyme to make PGs.
- Aspirin acetylates a homologous serine at position 516 in COX-2. Although covalent modification of COX-2 by aspirin also blocks the COX activity of this isoform.

Aspirin Mechanism of action



Aspirin-pharmacokinetics

- **Absorption**
- Orally ingested salicylates are absorbed rapidly, partly
- from the stomach but mostly from the upper small intestine.
- Appreciable concentrations are found in plasma in <30 minutes;
- The rate of absorption is determined by the disintegration and dissolution rates of the tablets administered, the pH at the mucosal surface, and gastric emptying time.
- Salicylate absorption occurs by passive diffusion primarily
- of undissociated salicylic acid or ASA across GI membranes.

Pharmacokinetics

- Distribution
- After absorption, salicylates are distributed throughout body tissues and transcellular fluids, primarily by pH-dependent passive processes.
- These are transported actively by a low capacity, saturable system out of the cerebrospinal fluid (CSF) across the choroid plexus.
- The drugs readily cross the placental barrier
- Aspirin can be detected within 30 minutes in the plasma only as a result of hydrolysis in plasma, liver, and erythrocytes;
- Only 27% of the total plasma salicylate are in the acetylated form.

Distribution/pharmacokinetics

- Methyl salicylate also is hydrolyzed rapidly to salicylic acid, mainly in the liver.
- Roughly 80-90% of the salicylate in plasma is bound to proteins,
- especially albumin, at concentrations encountered clinically
- Salicylate competes with a variety of compounds for plasma protein binding sites; these include thyroxine, triiodothyronine, penicillin, phenytoin, sulfinpyrazone, bilirubin, uric acid, and other NSAIDs such as naproxen

Pharmacokinetics……..

- **Metabolism and Elimination**
- The biotransformation of salicylates takes place in
- many tissues, particularly in the hepatic endoplasmic reticulum
- and mitochondria.
- The three chief metabolic products are salicyluric acid (the glycine conjugate), the ether or phenolic glucuronide, and the ester or acyl glucuronide. In addition, a small fraction is oxidized to gentisic acid (2,5-dihydroxybenzoic acid) and to 2,3-dihydroxybenzoic and 2,3,5-trihydroxybenzoic acids; gentisuric acid, the glycine conjugate of gentisic acid, also is formed.

Pharmacokinetics…….

- Salicylates are excreted in the urine as free salicylic acid (10%),
- salicyluric acid (75%), salicylic phenolic (10%) and acyl glucuronides (5%), and gentisic acid (<1%). However, excretion of free salicylates is extremely variable and depends on the dose and the urinary pH.
- In alkaline urine, >30% of the ingested drug may be eliminated as free salicylate, whereas in acidic urine, this may be as low as 2%.
- The plasma T1/2 for aspirin is ~20 minutes, and for salicylate is 2-3 hours at antiplatelet doses, rising to 12 hours at usual anti-inflammatory doses.

Pharmacokinetics……..

- Salicylate metabolism shows high intersubject variability due to the variable contribution of different metabolic pathways.
- Women frequently exhibit higher plasma concentrations, perhaps due to lower intrinsic esterase activity and gender differences in hepatic metabolism.

Pharmacological actions

- **Anti-inflammatory action**
- Aspirin produce this effect by irreversibly blocking the cyclooxygenase enzyme.
- Inhibit granulocyte adherence to injured tissue.
- Stabilizes lysosomes and inhibit the migration of leukocytes and macrophages into the cite of inflammation.
- By inhibiting kallikrein system.

Pharmacological actions of Aspirin

- **Analgesic effect**
- COX appeared in spinal cord and brain release prostaglandins.
- Bradykinin, serotonin, substance P, leukotrienes, and prostaglandins involve in eliciting pain.
- Inflammatory mediators increase the sensitivity of nociceptors and potentiate pain perception.
- PGE2 and PGI2 reduce threshold to stimulation of nociceptors, causing peripheral sensitization.
- Aspirin by inhibiting synthesis of these PGs, reduce pain of mild to moderate intensity and inhibit pain stimuli at subcortical site.

Pharmacological actions of Aspirin…….

- **Antipyretic effect**
- Pyrogens release interleukin-1 which in turn promote the synthesis and release of PGE2 which increases body temperature.
- Aspirin reduces elevated body temperature and normal temperature is slightly affected. Antipyretic effect is mediated by inhibition of both PGs and interleukins-1
- **Anti-platelet effect**
- Aspirin prolong bleeding time by inhibiting platelet aggregation through irreversible inhibition of platelet cyclooxygenase.
- Its effect last for 8-10 days.

Pharmacological actions of Aspirin……

- **Effect on respiration**
- Aspirin increases alveolar ventilation which in turn increases oxygen consumption and carbon dioxide production in skeletal muscles.
- This is due to uncoupling of oxidative phosphorylation in skeletal muscles.
- Metabolic acidosis occur due to accumulation of lactic and pyruvic acid production.
- **Effect on GIT**
- Normally, PGE1 and PGI2 inhibit gastric acid secretion whereas PGE2 stimulate synthesis of protective mucous in both stomach and intestine.
- In the presence of Aspirin, these prostanoids are not formed, resulting in increased gastric acid secretion and diminished mucous production.

Pharmacological actions of Aspirin……

- **Effect on uterus**
- Normally, PGF2α increases rate of uterine contraction whereas in the presence of Aspirin, rate of uterine contraction decreases.
- **Effect on kidney**
- Both renal medulla and renal cortex synthesize prostaglandins that perform auto regulatory functions.
- PGE2, PGI2 increases GFR through their vasodilating effect. Aspirin cause retention of sodium and water.
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