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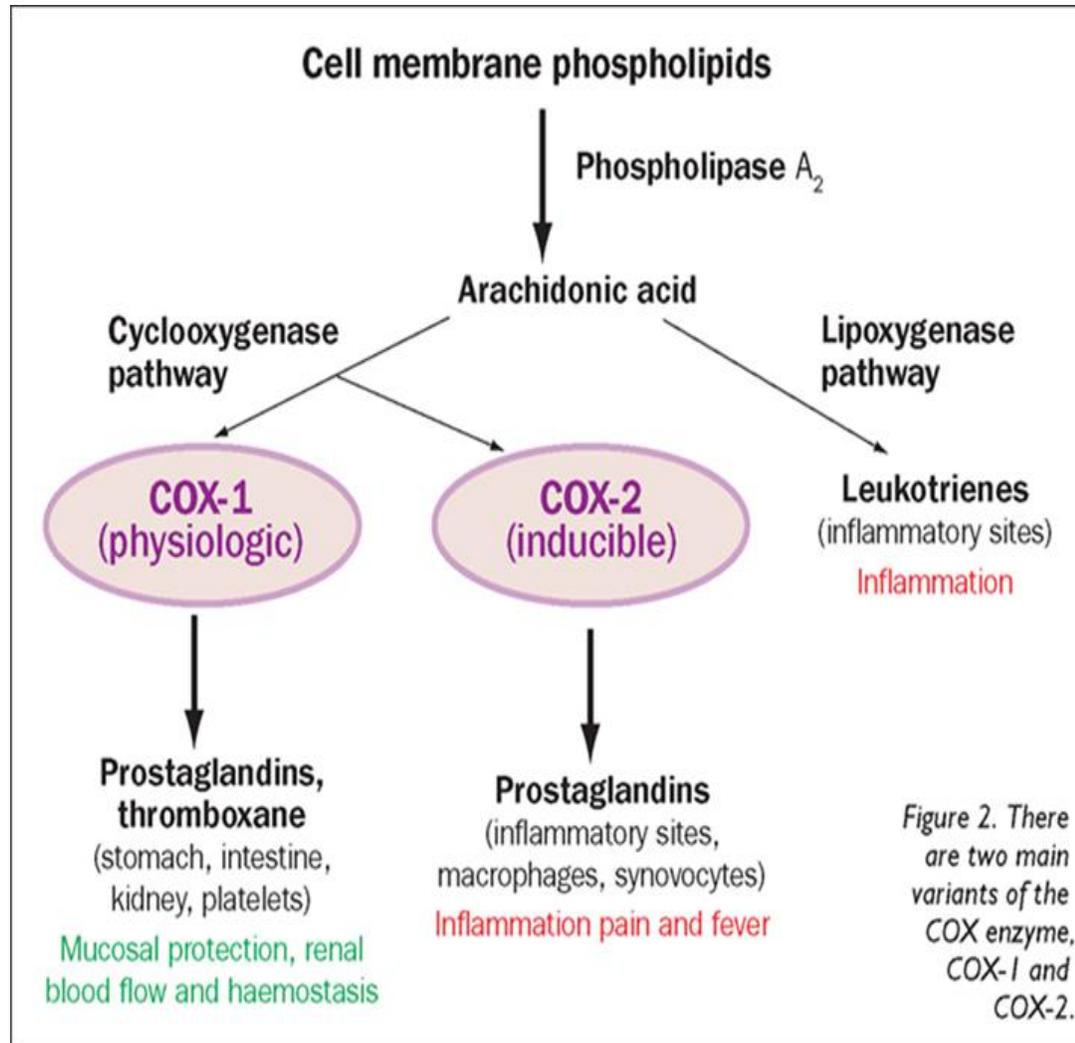
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Learning Outcomes

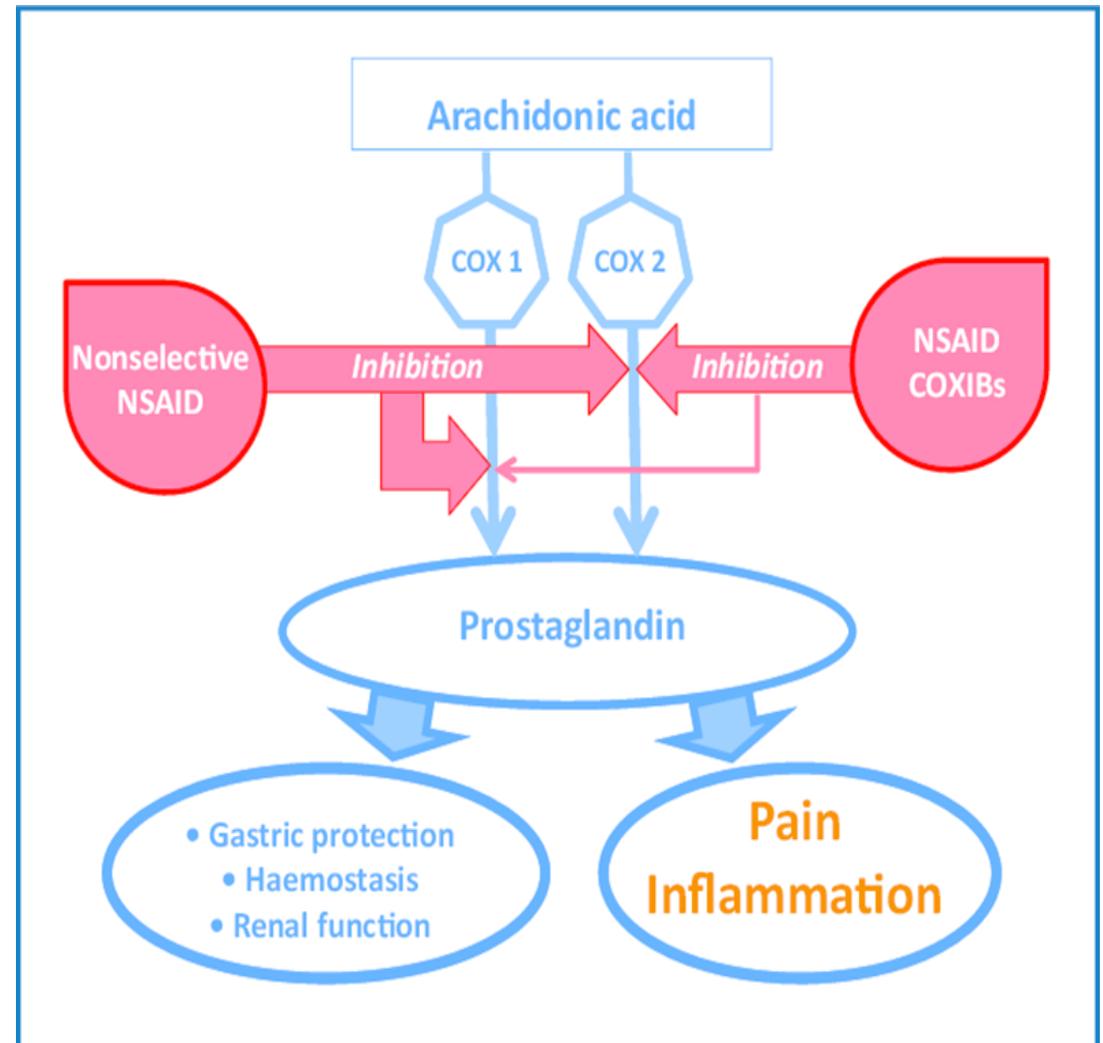
By the end of the lecture, the students will be able to:

1. Describe the effects of NSAIDs on prostaglandin synthesis.
2. Contrast the functions of COX-1 and COX-2.
3. Compare the actions and toxicity of aspirin, the older nonselective NSAIDs, and the COX-2-selective drugs.
4. Explain why several of the highly selective COX-2 inhibitors have been withdrawn from the market.
5. Describe the toxic effects of aspirin and NSAIDs.
6. Describe the effects and the major toxicity of acetaminophen (paracetamol).

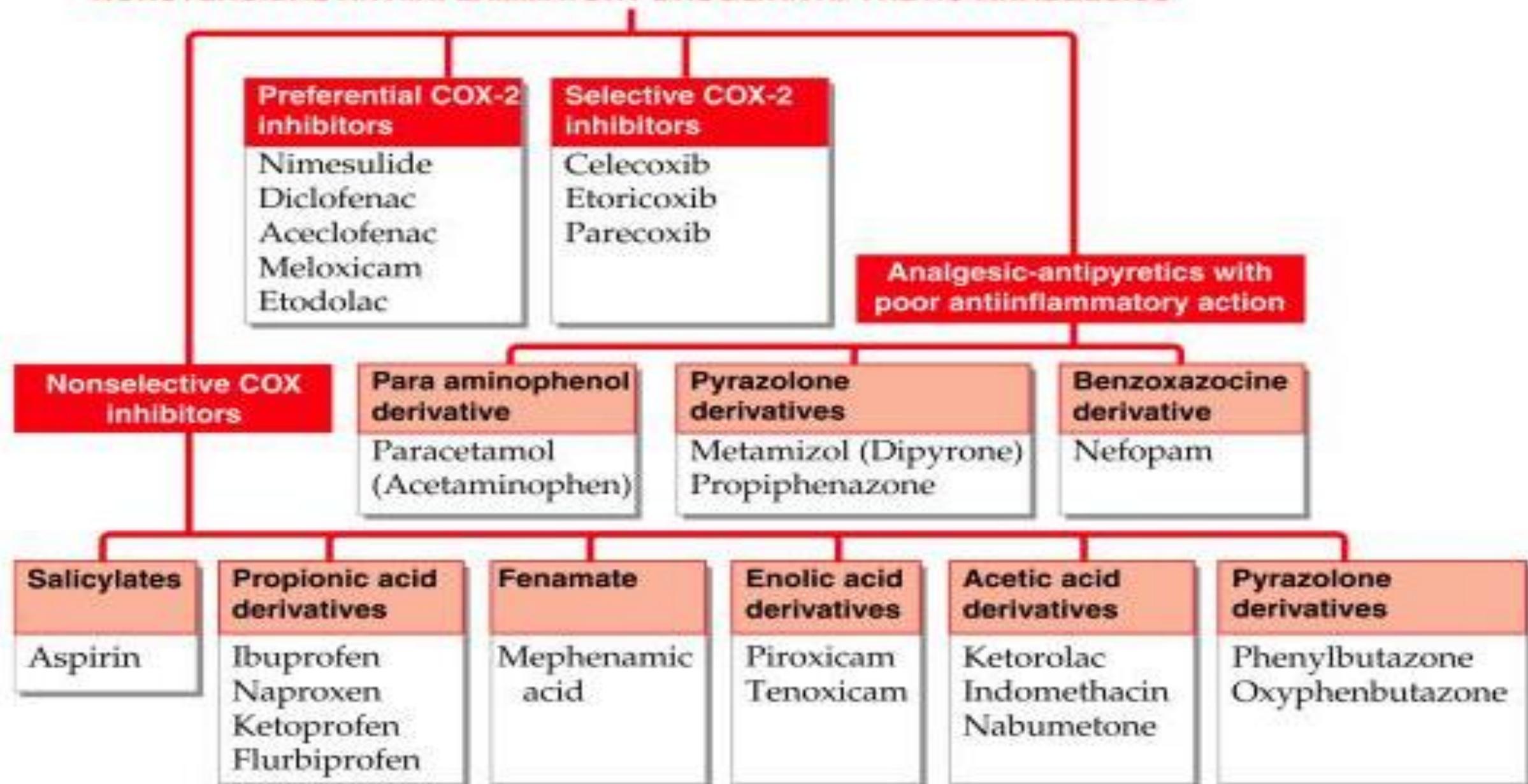
What are cyclo-oxygenase enzymes?



Nonselective & selective COX inhibitors



NONSTEROIDAL ANTIINFLAMMATORY DRUGS/ANTIPYRETIC-ANALGESICS



Non steroidal anti-inflammatory drugs (NSAIDs)

- **Non-selective COX inhibitors (inhibit COX-1 and COX-2):**

Aspirin

Diclofenac,

Ibuprofen, naproxen, ketoprofen,

Ketorolac, indomethacin,

Piroxicam

- **Selective COX-2 inhibitors:**

celecoxib, etoricoxib, meloxicam

Acetylsalicylic acid (Aspirin)



Chemistry

- White crystalline substance,
- Stable in dry air but *hydrolyses in moist air* to salicylic and acetic acids.



Pharmacokinetics:

□ Absorption:

- Oral absorption is complete; from the stomach and upper GIT.

□ Distribution:

- Widely distributed to all tissues including CNS.

□ Metabolism:

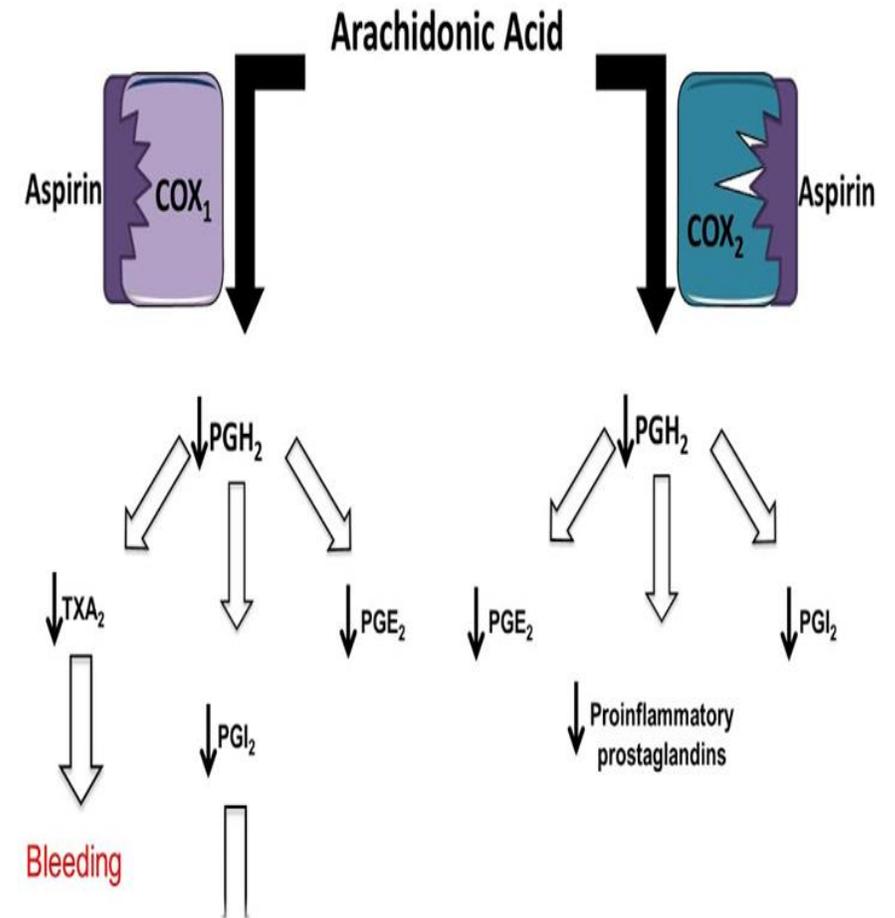
- Metabolism occurs by the hepatic microsomal enzymes.
 - At low doses, elimination is done by the first-order process.
 - At high doses, elimination is done by the zero-order process.

□ Excretion:

- Excretion is increased by alkalinization of urine (pH8) because in alkaline urine, most of aspirin is ionized and less re-absorbable.

Pharmacodynamics: Mechanism of action

- Aspirin and most of the non selective nonsteroidal antiinflammatory drugs (NSAIDs) inhibit both COX-1 and COX-2 isoforms, thereby decrease prostaglandin and thromboxane synthesis.
- Aspirin causes **irreversible** inhibition of COX.
- Rest of the NSAIDs cause **reversible** inhibition of the enzyme.



Pharmacological effects

1-Analgesic effect:

2-Antipyretic effect:

3-Anti-inflammatory & anti-rheumatic effects:

4. Antiplatelet effect of aspirin (CVS):

5- Respiratory effects: Aspirin induced asthma

6- GIT & liver effects:

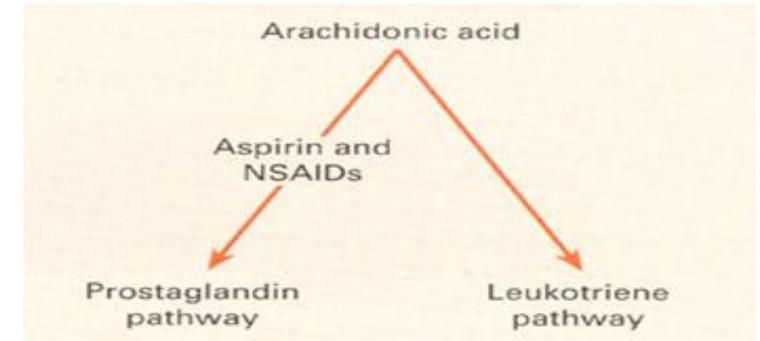
7- Renal effects:

8-Uterus:

➤ Prolongation of pregnancy and delay of labor due to inhibition of PGs necessary for uterine contraction during labor.

➤ The use of NSAIDs after 20 weeks of pregnancy is not recommended.

9-Local irritant action: keratolytic & counter-irritant



Analgesic action:

- for mild to moderate intensity pain (not severe pain).
- Mechanism:
- Peripheral effect: decrease PGs synthesis in the peripheral inflamed tissues.
- Central effect: decrease PGs synthesis in the subcortical sites (thalamus and hypothalamus).

Antipyretic effect:

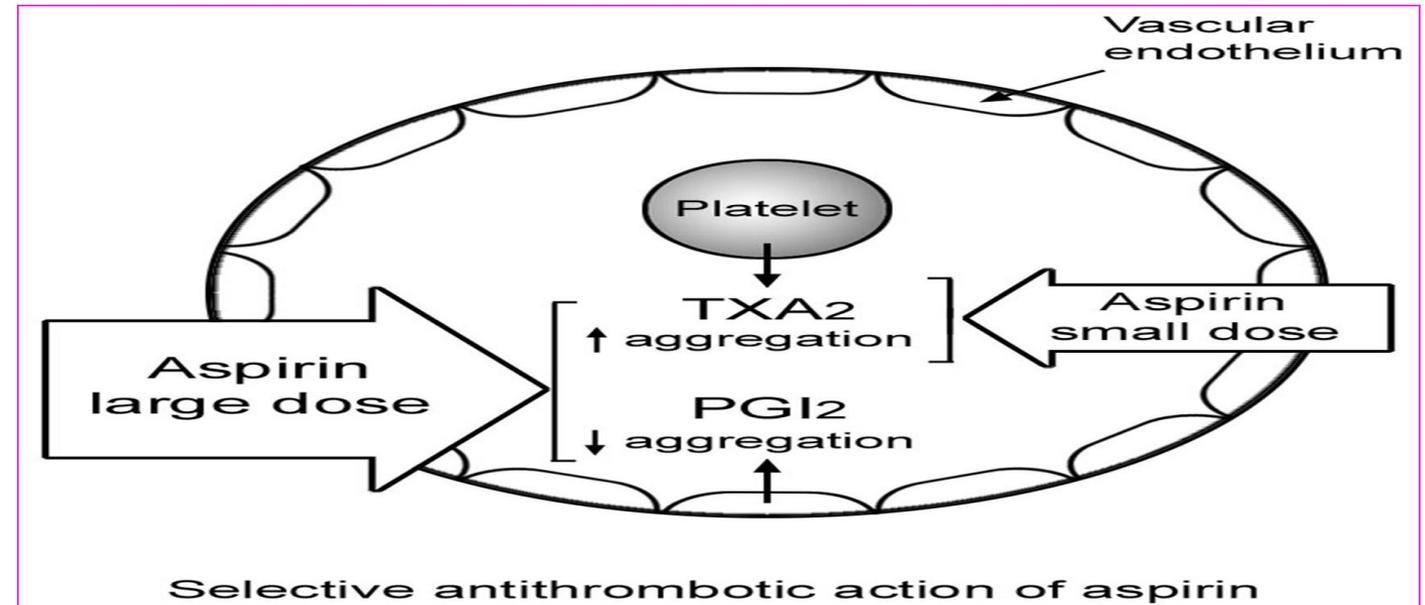
- Aspirin is antipyretic not hypothermic agent i.e. lower elevated body temperature but not normal body temperature.
- Mechanism:
- Decrease PGE₂ synthesis in the hypothalamus.
- Decrease the hypothalamic response to interleukin-1 (endogenous pyrogen).
- Cutaneous VD and increase sweating.

Anti-inflammatory:

- Mechanism:
- Decrease PGs synthesis and other inflammatory mediators (e.g. kinins).
- Analgesic and antipyretic effects.
- Decrease immune reaction.

Antiplatelet:

- In high doses (> 300 mg), aspirin inhibits both vascular PGI₂ and platelet TXA₂.
- In small doses (75-150 mg), aspirin inhibits only platelet TXA₂ → selective antiplatelet action. <https://www.youtube.com/watch?v=UVnQK-MWQ78>



❑ **GIT effects:** salicylates can produce **2** types of gastric ulcer:

a-Acute gastric ulcer:

- The pathogenesis is related to trapping of salicylate ions inside the gastric mucosal cells by the effect of pKa leading to acute, painful gastric bleeding.

b-Chronic gastric ulcer:

- The pathogenesis is related to chronic inhibition of the protective PGE₁, PGE₂ and PGI₂ synthesis leading to chronic ulceration and chronic blood loss.

❑ **Hepatic effects:** salicylates can produce **2** types of hepatic injury

a-Mild hepatic injury:

- It is dose-dependent, reversible and asymptomatic.

b-Severe hepatic injury:

- **“Reye’s syndrome”**: it is a rare and fatal condition occurs if aspirin is used to control fever of some viral infections (e.g. chicken pox, influenza, etc.) in **children below 12 years old**.

Renal effects:

Analgesic nephropathy:

- it is chronic renal failure due to chronic abuse of analgesics, which produce chronic renal ischemia due to decrease synthesis of renal PGE₂ and PGI₂.
- Renal failure is usually reversible on stoppage of therapy but rarely, NSAIDs may cause irreversible renal damage.

Salt and water retention:

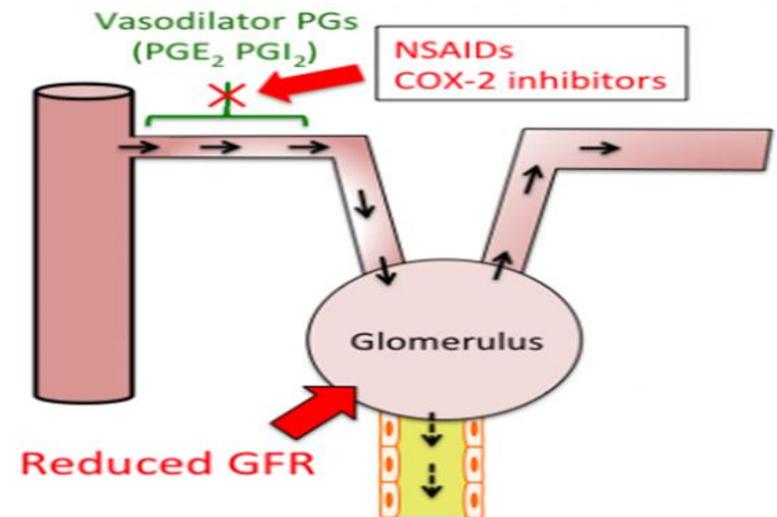
- due to decrease RBF and increase aldosterone

Antagonize diuretic effect of diuretics:

- due to decrease synthesis of vasodilator PGs.

Uric acid excretion:

- low doses decrease uric acid secretion and thus are contraindicated in gouty patients.



Therapeutic uses of salicylates

□As analgesic:

- in headache, arthritis, rheumatic pain (mention the mechanism).

□As antipyretic:

- it should not be used routinely for this purpose because fever may be a normal protective mechanism.

□As anti-inflammatory and anti-rheumatic:

- in rheumatic fever, rheumatoid arthritis, osteoarthritis, etc.

□As antithrombotic:

- in ischemic heart disease, deep vein thrombosis, AF

□As keratolytic & counter-irritant:

- Salicylic acid is used for treatment of warts.
- Methylsalicylic acid is used for local rheumatic pain.

Adverse effects of salicylates

GIT:	<ul style="list-style-type: none">- Epigastric pain, nausea and vomiting.- Acute and chronic gastric ulcers (why?).
Hepatic:	<ul style="list-style-type: none">- Mild reversible hepatic injury in adults.- Severe hepatic injury in children: "Reye's syndrome".
Kidney:	<ul style="list-style-type: none">- Analgesic nephropathy (why?).- Salt and water retention.- ↓ the diuretic effect of loop diuretics and antihypertensive effects of β-blockers (why?).
Blood:	<ul style="list-style-type: none">- Increase bleeding tendency: (why?).- Displacement of other drugs from plasma proteins.
Uterus:	<ul style="list-style-type: none">- Prolongation of pregnancy and delay of labor (why?).
Hypersensitivity reactions:	<ul style="list-style-type: none">- Bronchospasm (aspirin asthma) in patients with history of asthma or allergic rhinitis due to accumulation of LTs.

Quiz

- **The pharmacologic effects of acetylsalicylic acid include:**

A- Reduction of high body temperature

B- Promotion of platelet aggregation

C- Reduction of pain by stimulation of PGs synthesis

D- Less gastric irritation than other NSAIDs

- **Which of the following statements concerning the anti-inflammatory effect of NSAIDs are TRUE?**
- A. Anti-inflammatory effect of NSAIDs results from inhibition of cyclooxygenase
- B. Anti-inflammatory effect of NSAIDs results from inhibition of phospholipase A2 and reducing prostaglandin and leukotriene synthesis
- C. Anti-inflammatory effect of NSAIDs results from induction of cyclooxygenase II expression which results in reducing the amount of an enzyme available to produce prostoglandins
- D. All of the above

• **The following statements concerning aspirin are true, EXCEPT:**

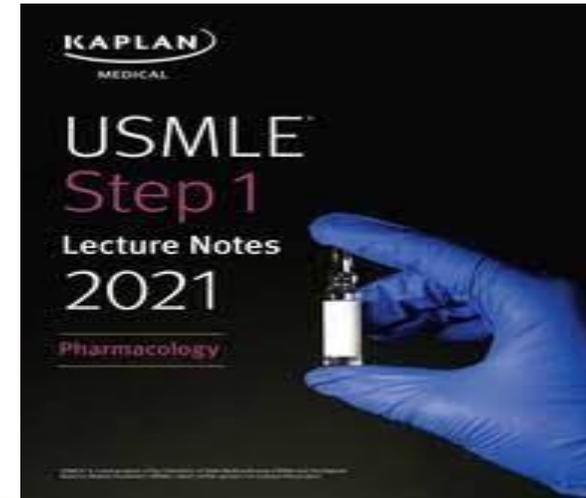
- A. In contrast to most other NSAIDs, aspirin irreversibly inhibits COX
- B. Aspirin interferes with the chemical mediators of the kallikrein system
- C. Aspirin inhibits phospholipase A2
- D. Aspirin inhibits tromboxane A2 formation

• **Indication for aspirin administration are the following, EXCEPT:**

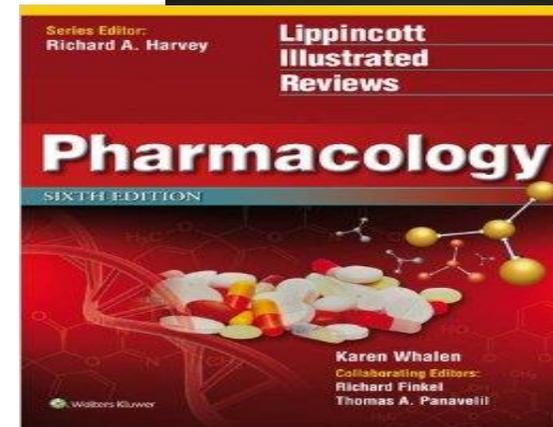
- A. Inflammatory conditions
- B. Decreasing the incidence of transient ischemic attack, unstable angina, coronary artery thrombosis with myocardial infarction, and thrombosis after coronary artery bypass grafting
- C. Relieving severe visceral pain(myocardial infarction, cancer pain condition, renal or biliary colic)
- D. Reducing elevated body temperature

References or further readings

**1) Kaplan USMLE STEP1, lecture notes
Pharmacology latest edition.**



**2) Lippincott's illustrated review:
Pharmacology, latest edition**



Thank you