Pharmacology - 3rd year - college of Dentist Medicine.

Anti-inflammatory drugs:

- Inflammation is a normal, protective response to tissue injury caused by physical trauma, noxious chemicals, or microbiologic agents.
- Inflammation is the body's effort to inactivate or destroy invading organisms, remove irritants, and set the stage for tissue repair.
- When healing is complete, the inflammatory process usually subsides.

Prostaglandins:-

All of the NSAIDs act by inhibiting the synthesis of prostaglandins. Thus, an understanding of NSAIDs requires comprehension of the actions and biosynthesis of prostaglandins-(unsaturated fatty acid derivatives containing 20 carbons that include a cyclic ring structure).

Role of prostaglandins as local mediators:-

- Prostaglandins and related compounds are produced in minute quantities by virtually all tissues.
- They generally act locally on the tissues in which they are synthesized, and they are rapidly metabolized to inactive products at their sites of action.
- Therefore, the prostaglandins do not circulate in the blood in significant concentrations.
- Thromboxanes and leukotrienes synthesized from the same precursors as the prostaglandins, and use interrelated pathways.

Synthesis of prostaglandins:-

Arachidonic acid is the primary precursor of the prostaglandins and related compounds. Arachidonic acid is present as a component of the phospholipids of cell. Free arachidonic acid is released from tissue phospholipids by the action of phospholipase A_2 via a process controlled by hormones and other stimuli.

Cyclooxygenase pathway:

- All prostaglandins, thromboxanes, and prostacyclins - are synthesized via the cyclooxygenase pathway.
- Two related isoforms of the cyclooxygenase enzymes have been described. Cyclooxygenase-1 (COX-1) is responsible for the physiologic production of prostaglandins

- Whereas cyclooxygenase-2 (COX-2) causes the elevated production of prostaglandins that occurs in sites of disease and inflammation.

Nonsteroidal Anti-Inflammatory Drugs:- NSAID

- The NSAIDs are a group of chemically dissimilar agents that differ in their antipyretic, analgesic, and anti-inflammatory activities.
- They act primarily by inhibiting the cyclooxygenase enzymes that catalyse the first step in prostaglandins biosynthesis.
- This leads to decreased prostaglandin synthesis with both beneficial and unwanted effects.

Aspirin and other salicylic acid derivatives:-

Aspirin is the prototype of traditional NSAIDs and was officially approved by the FDA in 1939. It is the most commonly used and is the drug to which all other anti-inflammatory agents are compared.

Mechanism of action:

- Aspirin is a weak organic acid that is unique among the NSAIDs in that it irreversibly inactivates cyclooxygenase .
- Aspirin is rapidly deacetylated by esterases in the body producing salicylate, which has anti-inflammatory, antipyretic, and analgesic effects.
- The antipyretic and anti-inflammatory effects of salicylate are due primarily to the blockade of prostaglandin synthesis at the thermoregulatory centres in the hypothalamus and at peripheral target sites.
- Furthermore, by decreasing prostaglandin synthesis, salicylate also prevents the sensitization of pain receptors to both mechanical and chemical stimuli.

Actions: The NSAIDs, including aspirin, have three major therapeutic actions , they reduce inflammation **(anti-inflammation**), pain **(analgesia**), and fever (**antipyrexia)**.

Anti-inflammatory actions: Because aspirin inhibits cyclooxygenase activity, it diminishes the formation of prostaglandins and, thus, modulates those aspects of inflammation in which prostaglandins act as mediators. Aspirin inhibits inflammation in arthritis.

Analgesic action: Prostaglandin E_2 (PGE_2) is thought to sensitize nerve endings to the action of bradykinin, histamine, and other chemical

mediators released locally by the inflammatory process. Thus, by decreasing PGE_2 synthesis, aspirin and other NSAIDs repress the sensation of pain.

Antipyretic action: Fever occurs when the set-point of the anterior hypothalamic thermoregulatory center is elevated. This can be caused by PGE_2 synthesis, which is stimulated when an endogenous fever-producing agent (pyrogen), is released from white cells that are activated by infection, hypersensitivity, malignancy, or inflammation.

The salicylates lower body temperature in patients with fever by impeding PGE_2 synthesis and release. Aspirin resets the thermostat toward normal, and it rapidly lowers the body temperature of febrile patients by increasing heat dissipation as a result of peripheral vasodilation and sweating.

Gastrointestinal effects: PGE_2 and $PGF_{2\alpha}$ stimulate synthesis of protective mucus in both the stomach and small intestine. In the presence of aspirin, these prostaglandins are not formed, resulting in increased gastric acid secretion and diminished mucus protection. This may cause epigastric distress, ulceration, haemorrhage.

Buffered and enteric-coated preparations are only marginally helpful in dealing with this problem. Agents used for the prevention of gastric and/or duodenal ulcers include the PGE_1-derivative **misoprostol** and the proton-pump inhibitors (PPIs); **esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole);** Also H_2-antihistamines (**cimetidine, famotidine, nizatidine, and ranitidine**) relieve dyspepsia due to NSAIDS.

Effect on platelets: TXA_2 enhances platelet aggregation, whereas PGI_2 decreases it.

As a result of the decrease in TXA_2, platelet aggregation (the first step in thrombus formation) is reduced, producing an anticoagulant effect with a prolonged bleeding time.

Therapeutic uses:

Anti-inflammatory, antipyretic, and analgesic uses: The salicylic acid derivatives are used in the treatment of gout, rheumatic fever, osteoarthritis, and Rheumatoid arthritis. Commonly treated conditions requiring analgesia include headache, arthralgia, and myalgia.

External applications: Salicylic acid is used topically to treat corns, calluses, and warts. Methyl salicylate is used externally.

Cardiovascular applications: Aspirin is used to inhibit platelet aggregation. Low doses are used prophylactically to **1)** reduce the risk of transient ischemic attacks (TIAs) and stroke or death in those who have had single or multiple episodes of TIA or stroke; **2)** reduce the risk of death in those having an acute myocardial infarction; **3)** reduce the risk of myocardial infarction and sudden death in patients with chronic stable angina pectoris;

Pharmacokinetics:

Salicylates must be avoided in children and teenagers (<15 years old) with varicella (chickenpox) or influenza to prevent Reye's syndrome.

Salicylates cross both the blood-brain barrier and the placenta.

Adverse effects:

Gastrointestinal: The most common GI effects of the salicylates are epigastric distress, nausea, and vomiting. Aspirin should be taken with food and large volumes of fluids to diminish dyspepsia.

Reye's syndrome: Aspirin and other salicylates given during viral infections has been associated with an increased incidence of Reye's syndrome, which is an often fatal, fulminating hepatitis with cerebral edema. This is especially encountered in children, who therefore should be given acetaminophen instead of aspirin when such medication is required to reduce fever. Ibuprofen is also appropriate.

Drug interactions: Aspirin could displace other highly protein-bound drugs, such as warfarin, phenytoin, or valproic acid, resulting in higher free concentrations of the other agent.

In pregnancy: Because salicylates are excreted in breast milk, aspirin should be avoided during pregnancy and while breast-feeding.

Propionic acid derivatives:-

Ibuprofen was the first in this class . It has been joined by **naproxen , fenoprofen , ketoprofen , flurbiprofen , and oxaprozin .** All these drugs possess anti-inflammatory, analgesic, and antipyretic activity; also, they can alter platelet function and prolong bleeding time. They have gained wide acceptance in the chronic treatment of RA and osteoarthritis, **because their GI effects are generally less intense than those of aspirin.**

Acetic acid derivatives:-

This group of drugs includes **indomethacin , sulindac** , and **etodolac** . All have anti-inflammatory, analgesic, and antipyretic activity. They act by reversibly inhibiting cyclooxygenase.

They are generally not used to lower fever. Despite its potency as an anti-inflammatory agent, the toxicity of indomethacin limits its use to the treatment of acute gouty arthritis, ankylosing spondylitis, and osteoarthritis of the hip.

Sulindac: It is closely related to indomethacin. Although the drug is less potent than indomethacin, it is useful in the treatment of RA, ankylosing spondylitis, osteoarthritis, and acute gout.

Oxicam derivatives:-

Piroxicam and **meloxicam** are used to treat RA, ankylosing spondylitis, and osteoarthritis. **They have long half-lives, which permit once-daily administration**.

Meloxicam inhibits both COX-1 and COX-2, with preferential binding for COX-2.

Fenamates:-

Mefenamic acid and **meclofenamate** have no advantages over other NSAIDs as anti-inflammatory agents. Their side effects, such as diarrhea, can be severe, and they are associated with inflammation of the bowel.

Heteroaryl acetic acids:-

Diclofenac and **tolmetin** are approved for long-term use in the treatment of RA, osteoarthritis, and ankylosing spondylitis.

Diclofenac is more potent than **indomethacin** or **naproxen**.

Diclofenac accumulates in synovial fluid, and the primary route of excretion for the drug and its metabolites is the kidney.

Tolmetin is an effective anti-inflammatory, antipyretic, and analgesic agent with a half-life of 5 hours. It is 99 percent bound to plasma proteins.

Ketorolac

- is a potent analgesic but has moderate anti-inflammatory effects.
- It is available for oral administration, for intramuscular use in the treatment of postoperative pain, and for topical use for allergic conjunctivitis.
- Ketorolac is indicated for short-term relief of moderate to severe pain for up to 5 days.

- Ketorolac can cause fatal peptic ulcers as well as GI bleeding and/or perforation of the stomach or intestines.

Nabumetone:-

Nabumetone is indicated for the treatment of RA and osteoarthritis and is associated with a low incidence of adverse effects.

Celecoxib

- Celecoxib is significantly more selective for inhibition of COX-2 than of COX-1 .
- Celecoxib is approved for treatment of RA, osteoarthritis, and pain.

Adverse effects: Headache, dyspepsia, diarrhea, and abdominal pain are the most common adverse effects. As with other NSAIDs, kidney toxicity may occur. Celecoxib should be avoided in patients with chronic renal insufficiency, severe heart disease, and/or hepatic failure. Celecoxib has the ability to inhibit CYP2D6 and, thus, could lead to elevated levels of some β-blockers, antidepressants, and antipsychotic drugs.

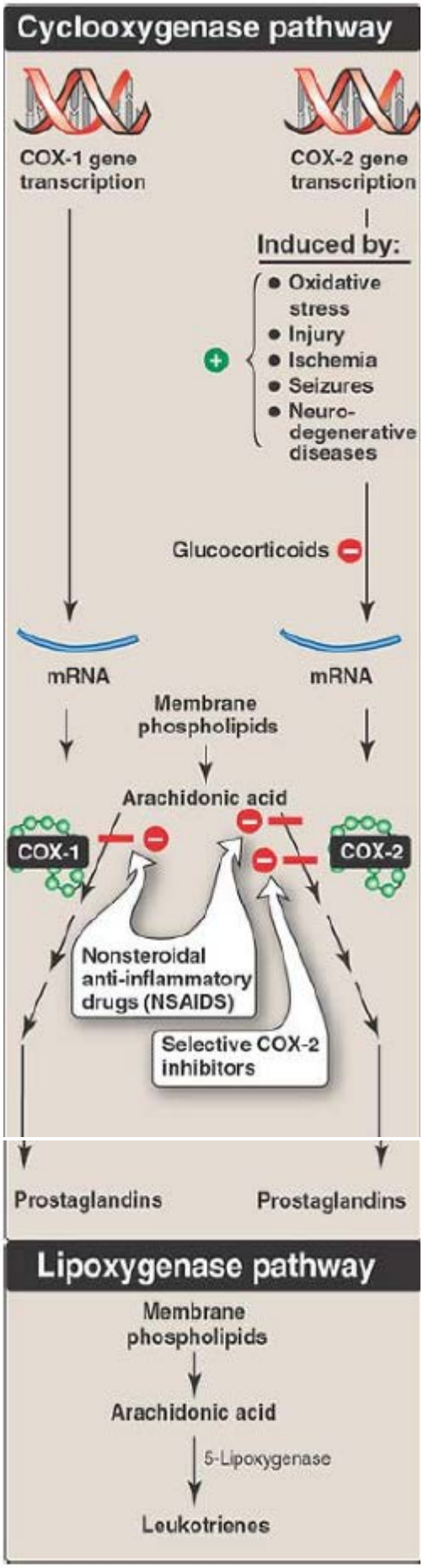
Acetaminophen:-

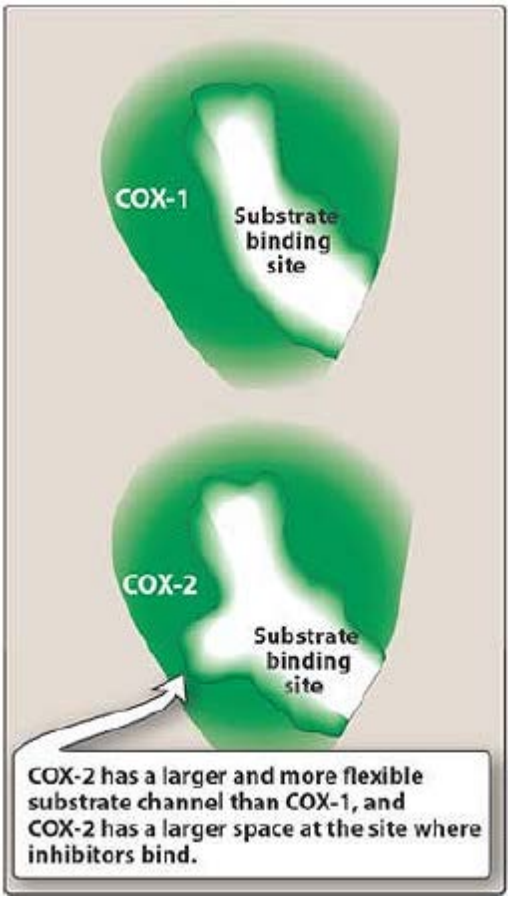
Acetaminophen inhibits prostaglandin synthesis in the CNS. **This explains its antipyretic and analgesic properties.** Acetaminophen does not affect platelet function or increase blood clotting time.

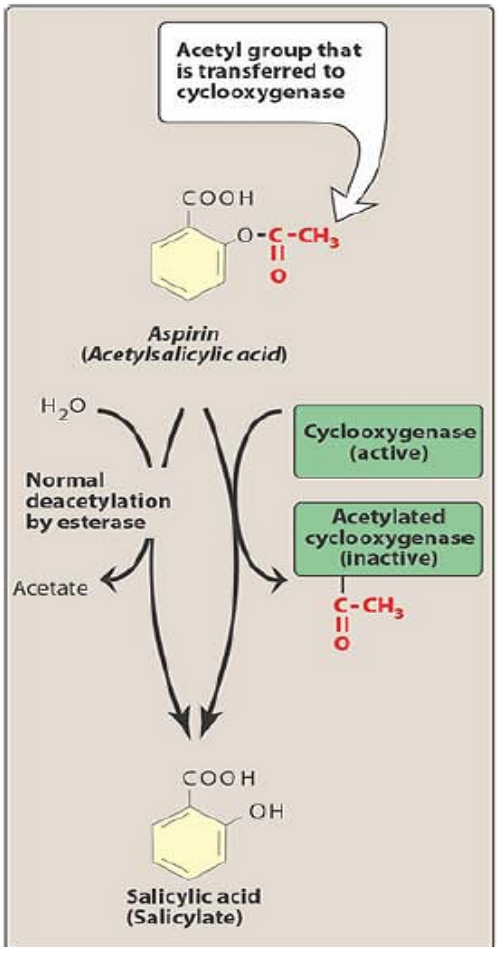
Therapeutic uses:-

Acetaminophen is a suitable substitute for the analgesic and antipyretic effects of aspirin for those patients with **1-** gastric complaints **2-** those in whom prolongation of bleeding time would be a disadvantage **3-** those who do not require the anti-inflammatory action of aspirin.

Acetaminophen is the analgesic/antipyretic of choice for children with viral infections or chickenpox.


Cyclooxygenase pathway
COX-1 gene transcription
COX-2 gene transcription
Induced by:
Oxidative stress
Injury
Ischemia
Seizures
Neuro-degenerative diseases
Glucocorticoids
mRNA
mRNA
Membrane phospholipids
Arachidonic acid
COX-1
COX-2
Nonsteroidal anti-inflammatory drugs (NSAIDS)
Selective COX-2 inhibitors
Prostaglandins
Prostaglandins
Lipoxygenase pathway
Membrane phospholipids
Arachidonic acid
5-Lipoxygenase
Leukotrienes


COX-1
Substrate binding site
COX-2
Substrate binding site
COX-2 has a larger and more flexible substrate channel than COX-1, and COX-2 has a larger space at the site where inhibitors bind.


Acetyl group that is transferred to cyclooxygenase
COOH
O-C-CH3
O
Aspirin
(Acetylsalicylic acid)
H2O
Normal deacetylation by esterase
Acetate
Cyclooxygenase (active)
Acetylated cyclooxygenase (inactive)
C-CH3
O
COOH
OH
Salicylic acid
(Salicylate)