Al-Mustaqbal University
College of Pharmacy
4th stage
Pharmacology III
Lecture: 1

Anti-inflammatory Drugs

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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**.
- However, **inappropriate** activation of the immune system can result in **inflammation** and **immune-mediated diseases** such as rheumatoid arthritis (**RA**).

Anti-inflammatory drugs

In **RA**, white blood cells (**WBCs**) initiate an **inflammatory attack**.

WBC activation leads to stimulation of **T lymphocytes**, which recruit and **activate monocytes and macrophages**.

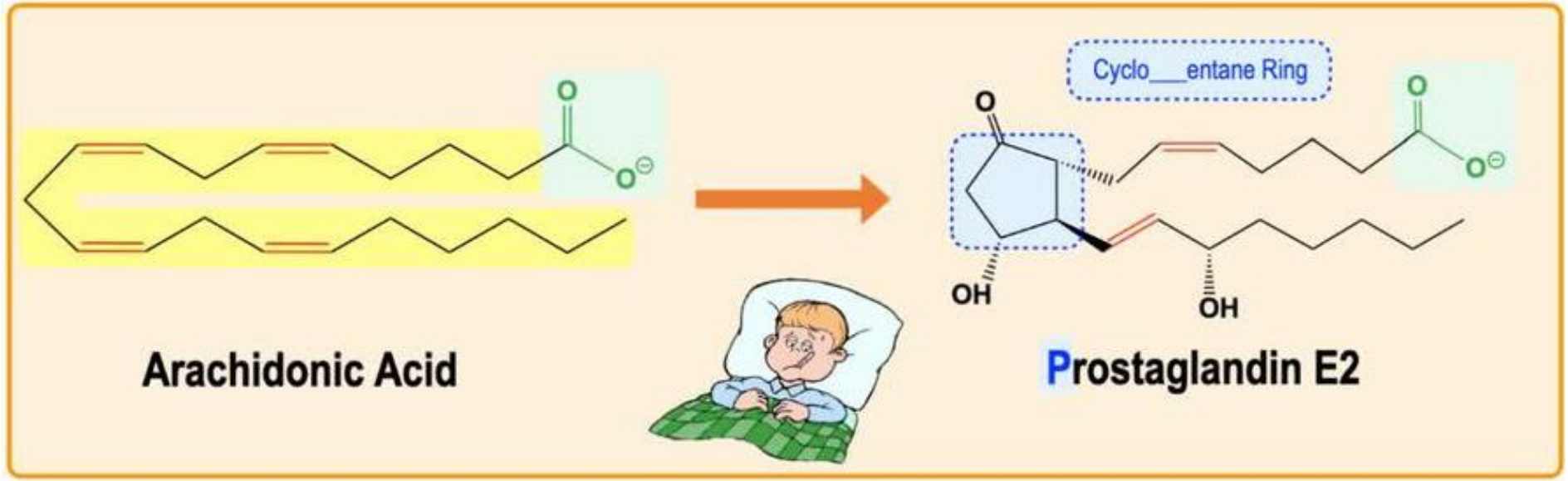
These cells **secrete proinflammatory cytokines**, including TNF-α and IL-β, into the **synovial cavity**, ultimately leading to **joint destruction** and other **systemic abnormalities** characteristic of RA.

In addition to T lymphocyte activation, the **B lymphocytes** are also involved and produce **rheumatoid factor** and other **autoantibodies** to maintain inflammation.

Pharmacotherapy for RA includes **anti-inflammatory and/or immunosuppressive** agents that **modulate/reduce** the inflammatory process, with the **goals** of reducing inflammation and pain, and halting or slowing disease progression.

Prostaglandins

- **Prostaglandins** are **unsaturated fatty acid** derivatives containing **20 carbons** that include a **cyclic ring structure**.
- These compounds are sometimes referred to as **eicosanoids**.
- **Thromboxanes**, **leukotrienes**, and the **hydroperoxyeicosatetraenoic** and **hydroeicosatetraenoic** acids (**HPETEs** and **HETEs**, respectively) are related lipids, synthesized from the **same precursors** as the prostaglandins, and use interrelated pathways.



Synthesis of Prostaglandins

- **Arachidonic acid**, a **20-carbon** fatty acid, is the **primary precursor** of the prostaglandins and related compounds.
- There are **two major pathways** in the synthesis of the **eicosanoids** from **arachidonic acid**.

1. Cyclooxygenase pathway:

- **All** eicosanoids with **ring structures** that is, the **prostaglandins**, **thromboxanes**, and **prostacyclins** are synthesized via the cyclooxygenase pathway.

2. Lipoxygenase pathway:

- Alternatively, several **lipoxygenases** can act on arachidonic acid to form **leukotrienes or lipoxins**, depending on the **tissue**.

Synthesis of Prostaglandins

- **Two related isoforms** of the **cyclooxygenase** enzymes have been described.

1. Cyclooxygenase-1 (COX-1):

- It is responsible for the **physiologic** production of prostanoids, COX-1 is described as a **housekeeping enzyme** that **regulates normal cellular processes**, such as gastric cytoprotection, vascular homeostasis, platelet aggregation, and kidney function.

2. Cyclooxygenase-2 (COX-2):

- It causes the **elevated production of prostanoids** that occurs in **sites** of **disease** and **inflammation**.
- COX-2 is **constitutively expressed** in tissues such as the **brain, kidney, and bone**.
- Its expression at **other** sites is increased during states of **inflammation**.

Functions of prostaglandins in the body

Prostaglandins and their metabolites **produced endogenously** in tissues.

They **control** many **physiological functions**, such as **acid secretion and mucus production** in the GIT, **uterine contractions**, and **renal blood flow**.

Prostaglandins are also among the **chemical mediators** that are released in **allergic** and **inflammatory** processes.

Intradermal, intravenous, or intra-arterial **injections** of small amounts of prostaglandins **mimic** many components of **inflammation**.

Non-steroidal anti-inflammatory drugs (NSAIDs)

- **All NSAIDs**, including the traditional **nonselective** drugs and the subclass of **selective** cyclooxygenase-2 (COX-2) inhibitors, have the following actions:

✓**Anti-inflammatory**

✓**Analgesic**

✓**Antipyretic**

- **NSAIDs** are a chemically heterogeneous group of **organic acids** that **share** certain **therapeutic** actions and **adverse** effects.
- **All** of the NSAIDs act by **inhibiting the cyclooxygenase enzymes** that **catalyze** the **first step** in prostanoid biosynthesis.
- This leads to **decreased prostaglandin** synthesis with **both** beneficial and unwanted effects.

Aspirin and other NSAIDs

- **Aspirin** can be thought of as a **traditional** NSAID, but it exhibits **anti-inflammatory** activity **only** at relatively **high doses** that are **rarely** used.
- It is **used more frequently** at lower doses to **prevent cardiovascular events** such as **stroke** and myocardial infarction (**MI**).
- Aspirin is often **differentiated** from other NSAIDs since it is an **irreversible** inhibitor of cyclooxygenase activity.

Aspirin and other NSAIDs

Mechanism of action:

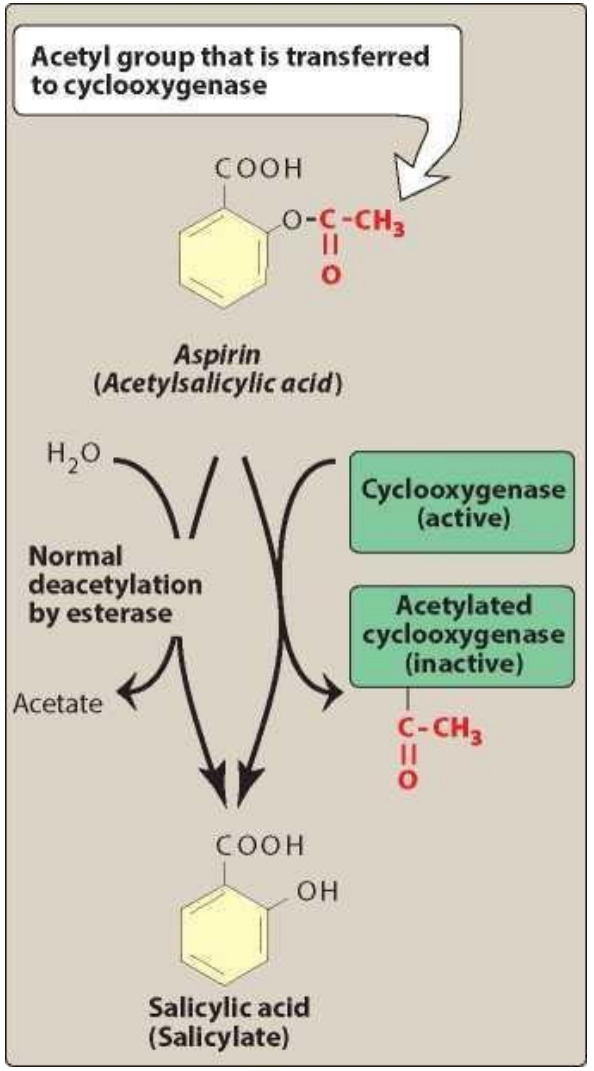
- Aspirin is a **weak organic acid** that **irreversibly** acetylates and, thus, inactivates **cyclooxygenase**.
- The **other** NSAIDs are **reversible inhibitors** of cyclooxygenase.
- The NSAIDs, including aspirin, have **three** major **therapeutic** actions they **reduce**:

✓**Inflammation (anti-inflammatory)**

✓**Pain (analgesic effect)**

✓**Fever (antipyretic effect)**

- However, **not all** NSAIDs are **equally** effective in each of these actions.



Actions of Aspirin and other NSAIDs:

1- Anti-inflammatory effect:

- **Inhibition** of cyclooxygenase **diminishes** the formation of **prostaglandins.**
- Since **PGE2 induce** acute **inflammation** through **mast cell activation via the EP3 receptors**.
- Aspirin **inhibits inflammation in arthritis**, **but** it **neither arrests** the progress of the disease **nor induces** remission.

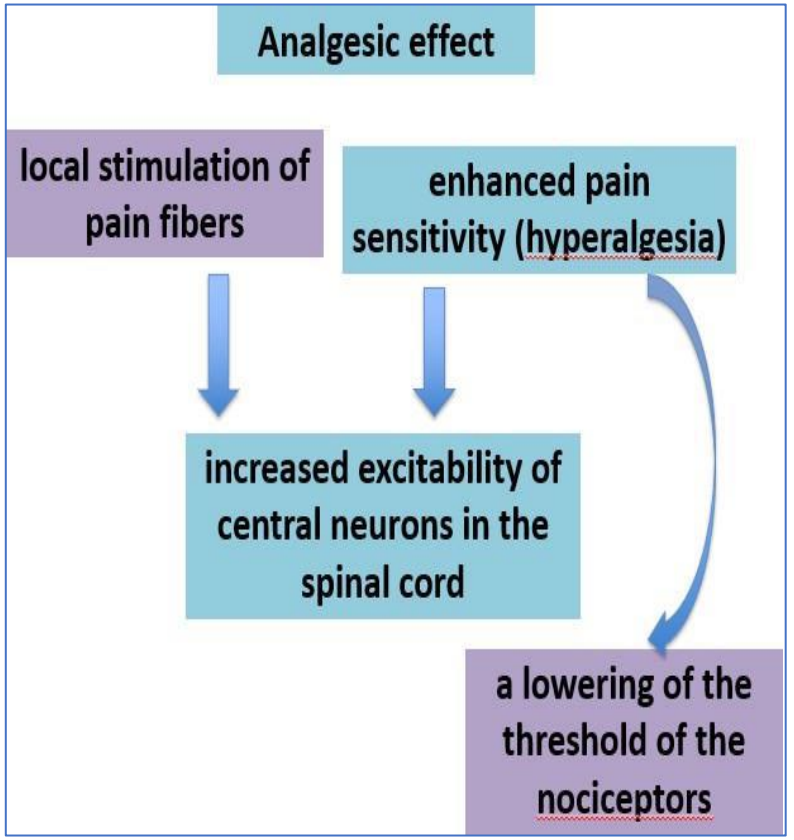
Actions of Aspirin and other NSAIDs:

2- Analgesic action:

- **PGE2** 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 PGE2 synthesis**, the **sensation** of pain can be **decreased**.
- As **COX-2 is expressed** during times of **inflammation and injury**, it is thought that **inhibition** of this enzyme is **responsible** for the analgesic activity of NSAIDs.

Actions of Aspirin and other NSAIDs:

- **No single NSAID** has demonstrated **superior efficacy** over another, and they are generally considered to have **equivalent analgesic efficacy**.
- The NSAIDs are used mainly for the management of **mild to moderate** pain arising from musculoskeletal disorders.
- One exception is **ketorolac**, which can be used for **more severe pain**, but for only a **short duration**.



Actions of Aspirin and other NSAIDs:

3- Antipyretic action:

- **Fever** occurs when the **set-point** of the anterior hypothalamic **thermoregulatory center** is **elevated**.
- This can be caused by **PGE2 synthesis**, which is **stimulated** when endogenous fever-producing agents (**pyrogens**), such as **cytokines**, are released from **WBCs** that are **activated by infection**, **hypersensitivity**, **malignancy**, or **inflammation**.
- The **NSAIDs lower body temperature** in patients with fever by **impeding PGE2** synthesis and release, **resetting** the "**thermostat**" back toward **normal**.
- This **rapidly lowers** the body temperature of **febrile patients** by increasing heat dissipation through peripheral **vasodilation** and **sweating**.
- NSAIDs have **no effect** on **normal** body temperature.

Therapeutic uses of NSAIDs

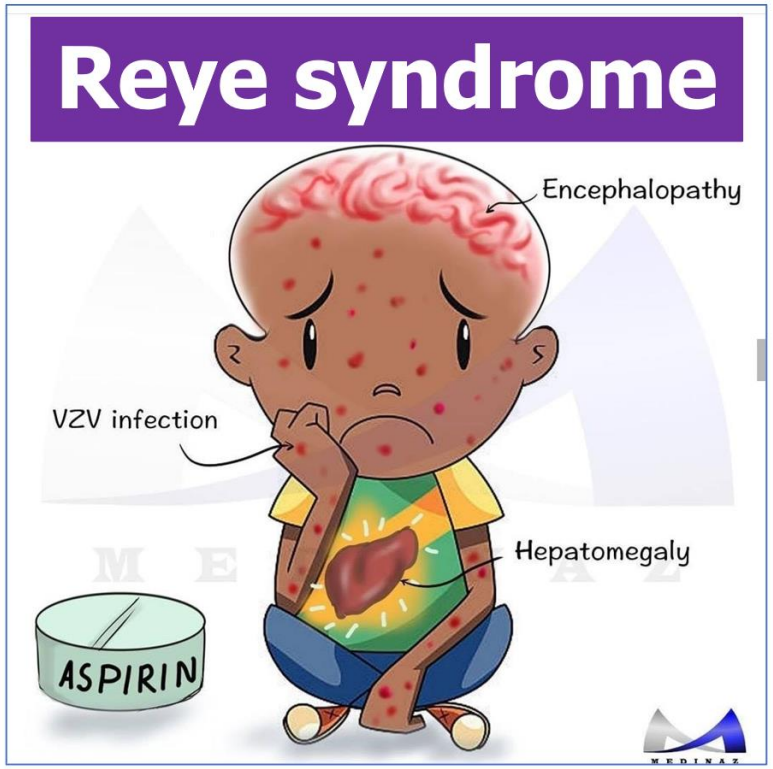
1. Anti-inflammatory and analgesic uses:

- NSAIDs are used in the **treatment** of **osteoarthritis, gout, RA**, and common **conditions** requiring analgesia (for example, **headache, arthralgia, myalgia, and dysmenorrhea**).
- **Combinations** of opioids and NSAIDs may be **effective** in treating **pain caused** by **malignancy**.
- **Furthermore**, the addition of NSAIDs may lead to an **opioid-sparing effect**, allowing **for lower doses of opioids** to be utilized.
- The **salicylates** exhibit **analgesic** activity at **lower doses**.
- Only at **higher doses** do these drugs show **anti-inflammatory activity**.
- For example, **two 325-mg aspirin tablets** administered **four times daily** produce **analgesia**, whereas **12 to 20 tablets per day** produce both **analgesic and anti-inflammatory activity**.

Therapeutic uses of NSAIDs

2. Antipyretic uses:

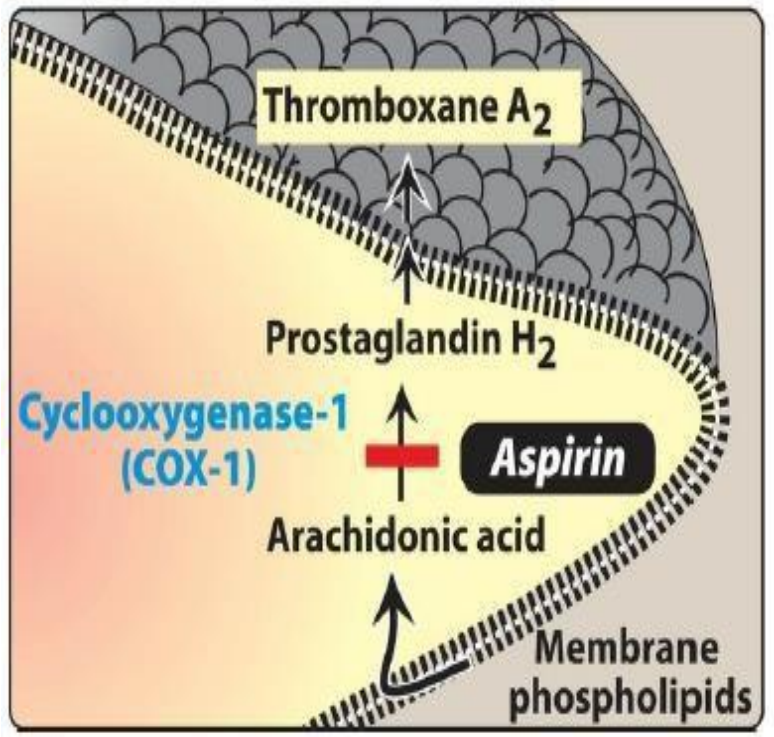
- **Aspirin, ibuprofen, and naproxen** may be used to treat **fever**.
- **Note:**
- **Aspirin** should be **avoided** in patients **less than 19 years** old with **viral infections**, such as varicella (chickenpox) or influenza, to **prevent Reye syndrome** "a syndrome that can **cause fulminating hepatitis with cerebral edema**, often leading to **death**".



Therapeutic uses of NSAIDs

3. Cardiovascular applications:

- Aspirin **irreversibly inhibits** COX-1–mediated production of **TXA2**, thereby **reducing** TXA2-mediated **vasoconstriction** and **platelet aggregation** and the subsequent **risk** of **cardiovascular events**.
- The **antiplatelet effects** persist for the **life of the platelet**.
- **Low doses** of aspirin (75 to 162 mg—commonly 81 mg) are used **prophylactically** to **reduce** the risk of recurrent cardiovascular events, transient ischemic attacks (TIAs), stroke, and death in patients with a **history of previous** MI, TIA, or stroke.



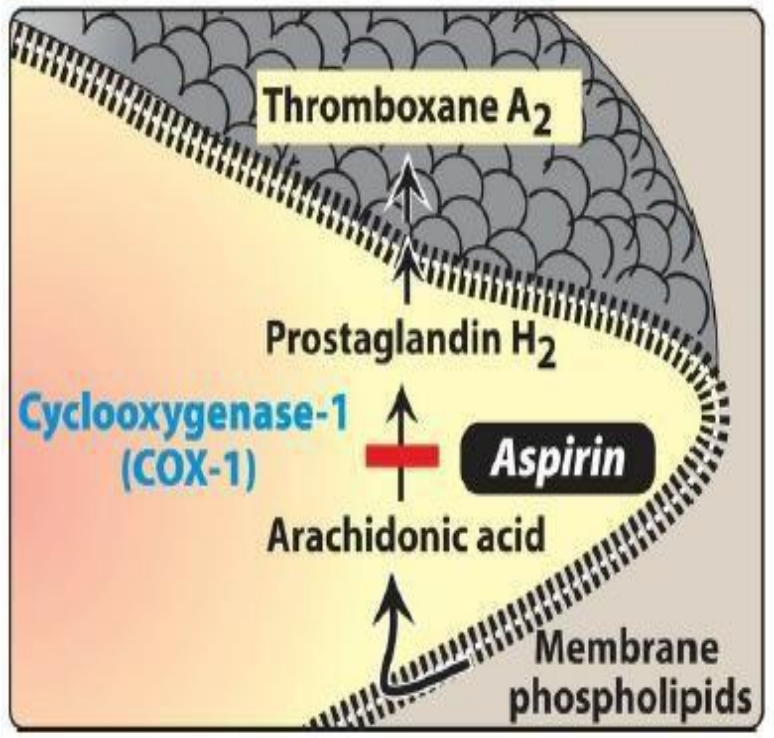
Therapeutic uses of NSAIDs

3. Cardiovascular applications:

- **Chronic use** of aspirin allows for **continued inhibition** as new platelets are generated.
- Aspirin is also **used acutely** to **reduce the risk of death in:**

✓**Acute MI patients**

✓**Patients** undergoing certain **revascularization procedures**.



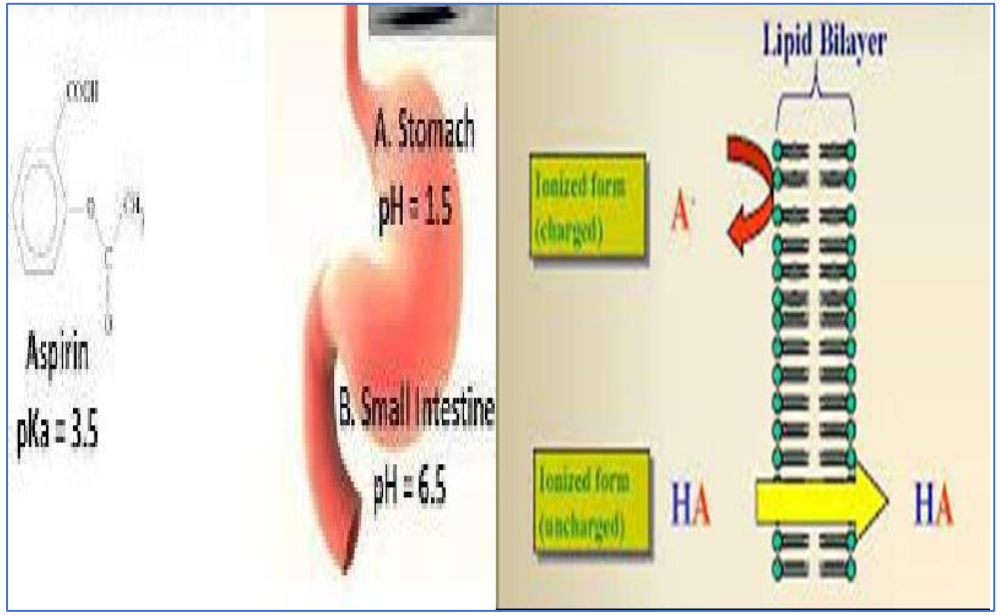
Therapeutic uses of NSAIDs

4. External applications:

- **Salicylic acid** is used topically to **treat corns, calluses, and warts**.
- **Methyl salicylate** is used **externally** as a cutaneous **counterirritant** in **liniments**, such as **arthritis creams** and **sports rubs**.
- **Diclofenac** is available in **topical** formulations (**gel or solution**) for treatment of **osteoarthritis** in the knees or hands.
- In addition, **ocular formulations** of **ketorolac** are approved for management of **seasonal allergic conjunctivitis** and **inflammation** and **pain** related to **ocular surgery**.

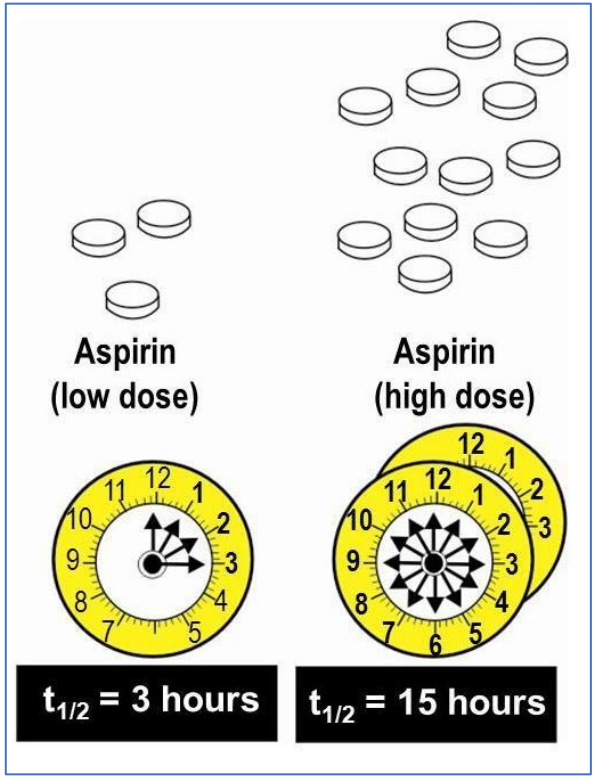
a. Aspirin:

- After **oral** administration, aspirin is **rapidly deacetylated by esterases** in the body to produce **salicylate**.
- **Unionized** salicylates are **passively absorbed** mainly from the **upper small intestine**.
- Salicylates (**except for diflunisal**) **cross** both the blood–brain barrier (**BBB**) and the **placenta** and are **absorbed** through **intact skin** (especially methyl salicylate).



A. Aspirin:

- Salicylate is **converted** by the **liver** to **water-soluble** conjugates that are **rapidly cleared** by the **kidney**, resulting in **first-order elimination** and a serum **half-life of 3.5 hours**.
- At **anti-inflammatory dosages** of aspirin (more than **4 g/day**), the hepatic metabolic pathway becomes **saturated**, and **zero-order kinetics** are observed, leading to a half-life of **15 hours or more** .
- Salicylate is **secreted** into the **urine** and can affect **uric acid excretion**.
- Therefore, aspirin should **be avoided in gout**, if possible, or in patients taking **probenecid**.



B. Other NSAIDs:

- Most NSAIDs are **well absorbed** after oral administration and circulate highly **bound** to **plasma proteins**.
- The **majority** are **metabolized** by the **liver**, mostly to **inactivate** metabolites.
- **Few** (for example, **nabumetone** and **sulindac**) have **active metabolites**.
- **Excretion** of active drug and metabolites is primarily **via the urine**.

Adverse effects of NSAIDs

Because of the **adverse event profile**, it is preferable to use NSAIDs at the **lowest effective dose** for the **shortest duration possible**.

Adverse effects of NSAIDs

a) Gastrointestinal:

- These are the **most common** adverse effects of NSAIDs, **ranging** from **dyspepsia** to **bleeding**.
- Normally, production of prostacyclin (**PGI2**) **inhibits gastric acid secretion**, and **PGE2 and PGF2α stimulate synthesis of protective mucus** in both the **stomach** and **small intestine**.
- Agents that **inhibit COX-1 reduce beneficial levels** of these prostaglandins, resulting in **increased gastric acid secretion**, **diminished mucus protection**, and **increased risk** for GI bleeding and ulceration.

Adverse effects of NSAIDs

a) Gastrointestinal:

- Agents with a **higher relative selectivity for COX-1** may have a **higher risk** for GI events compared to those with a **lower relative selectivity for COX-1** (that is, higher COX-2 selectivity).
- NSAIDs **should be taken with food or fluids** to diminish GI upset.
- If NSAIDs are used in **patients at high risk** for GI events, **proton pump inhibitors or misoprostol** should be used **concomitantly** to prevent NSAID-induced **ulcers**.

Adverse effects of NSAIDs

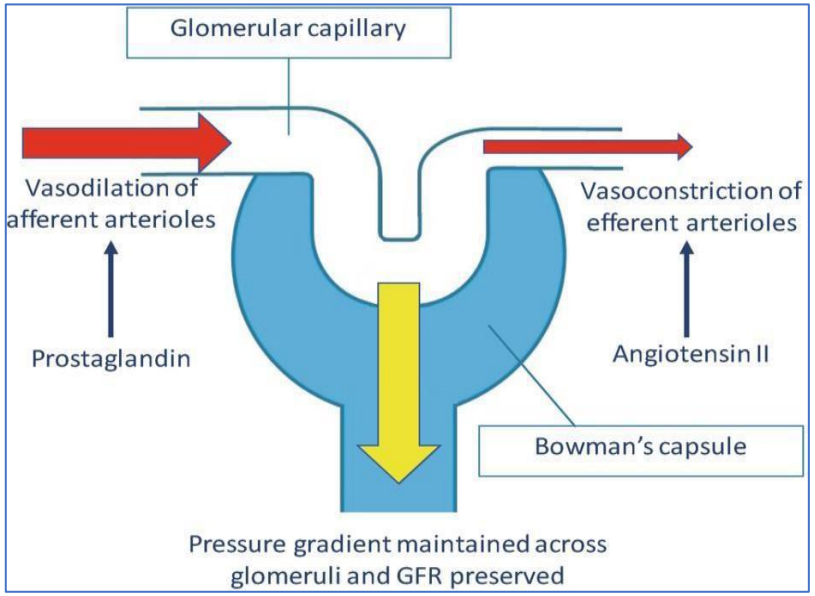
b) Increased risk of bleeding (antiplatelet effect):

- As **aspirin** inhibits COX-1–mediated formation of **TXA2** and **reduces** platelet aggregation for the lifetime of the platelet (3 to 7 days).
- **Platelet aggregation** is the **first step** in thrombus formation, and the antiplatelet effect of **aspirin** results in a **prolonged bleeding time**.
- For **this reason**, aspirin is often **withheld** for at **least 1 week prior to surgery**.
- **NSAIDs** other than aspirin are **not utilized for their antiplatelet effect but** can still **prolong bleeding time**, especially when **combined** with anticoagulants.
- **Concomitant** use of **NSAIDs** and **aspirin** can prevent aspirin from binding to cyclooxygenase.
- Patients who take aspirin for **cardioprotection** should **avoid concomitant NSAID use** if possible **or** take aspirin at least **30 minutes prior** to the NSAID.

Adverse effects of NSAIDs

c) Renal effects:

- NSAIDs **prevent** the **synthesis of PGE2 and PGI2.**
- These prostaglandins that are **responsible** for maintaining **renal blood flow**, that normally **antagonizes** the **intra-renal effect of vasoconstrictors**.
- **NSAIDs leave** the actions of **vasoconstrictors unopposed**.
- **Decreased** synthesis of prostaglandins can result in **retention of sodium and water and may cause edema**.
- Patients with a history of **heart failure or kidney disease** are at particularly **high risk**.



Adverse effects of NSAIDs

c) Renal effects:

- These effects can also **decrease the beneficial effects** of **antihypertensive** medications.
- In **susceptible** patients, NSAIDs have led to **acute kidney injury**.
- **Glomeruli and arterioles** synthesize **not only** the **vasodilatory** prostaglandins PGE2 and PGI2, but also the **vasoconstrictor**, thromboxane A2.
- The primary renal cortical **actions** of these prostaglandins are **renal vasodilatation** and maintenance of GFR (**PGE2 and PGI2**) or **renal vasoconstriction** and reduction of GFR (**thromboxane A2**).

Adverse effects of NSAIDs

c) Renal effects:

- **Vasodilatory** renal prostaglandins are relatively **unimportant under normal circumstances but they** play a modulatory role:

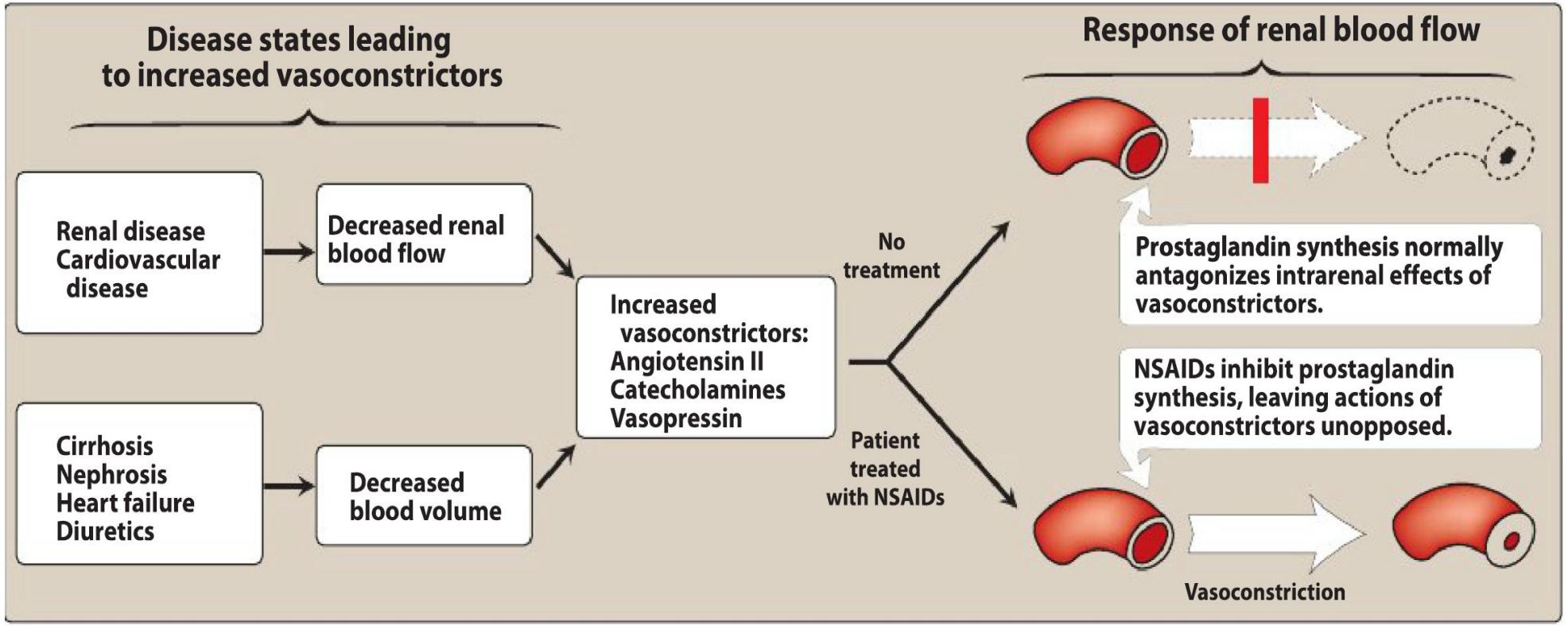
✓after **ischemia**

✓or in the presence of **increased concentrations of vasoconstrictor** substances such as **angiotensin II** (ANG II), **vasopressin** or **norepinephrine**.

- **Conversely**, **arachidonic acid reduces** the glomerular contractile **effect of ANG II**.
- It is, therefore, **concluded that** renal prostaglandins play an important **vasoregulatory role**.

Adverse effects of NSAIDs

c) Renal effects:



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