Non steroidal Anti-inflammatory drugs
NSAIDs

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Inflammation: is a normal, **protective response** to tissue injury. This means introduction of body to any types of injury (like physical trauma, chemical truma or microbiologic agents) will lead to starting of body **defense** against this abnormal stimuli, leading to **inflammatory** reaction .

Inflammation characterize by the release of **chemical mediators** from injured tissues and **migrating** cells.

The chemical **mediators vary** with the type of inflammatory process , one of these is a **lipid** mediators including **prostaglandins (PG).**

(**PG** responsible for **inflammation**, **pain**, **fever** in addition to its **physiological** action)

Pathway of PG formation :

Arachidonic acid(AA) is **stored** mainly in **phospholipids** of cell membranes. It is **mobilized** largely (from cell membrane) by the action of phospholipase A2 enzyme(see diagram).

Arachidonic acid(AA) then under goes further metabolism by **2 pathways :**

1st pathway : AA metabolised by cyclo-oxygenase (COX) enzyme into :

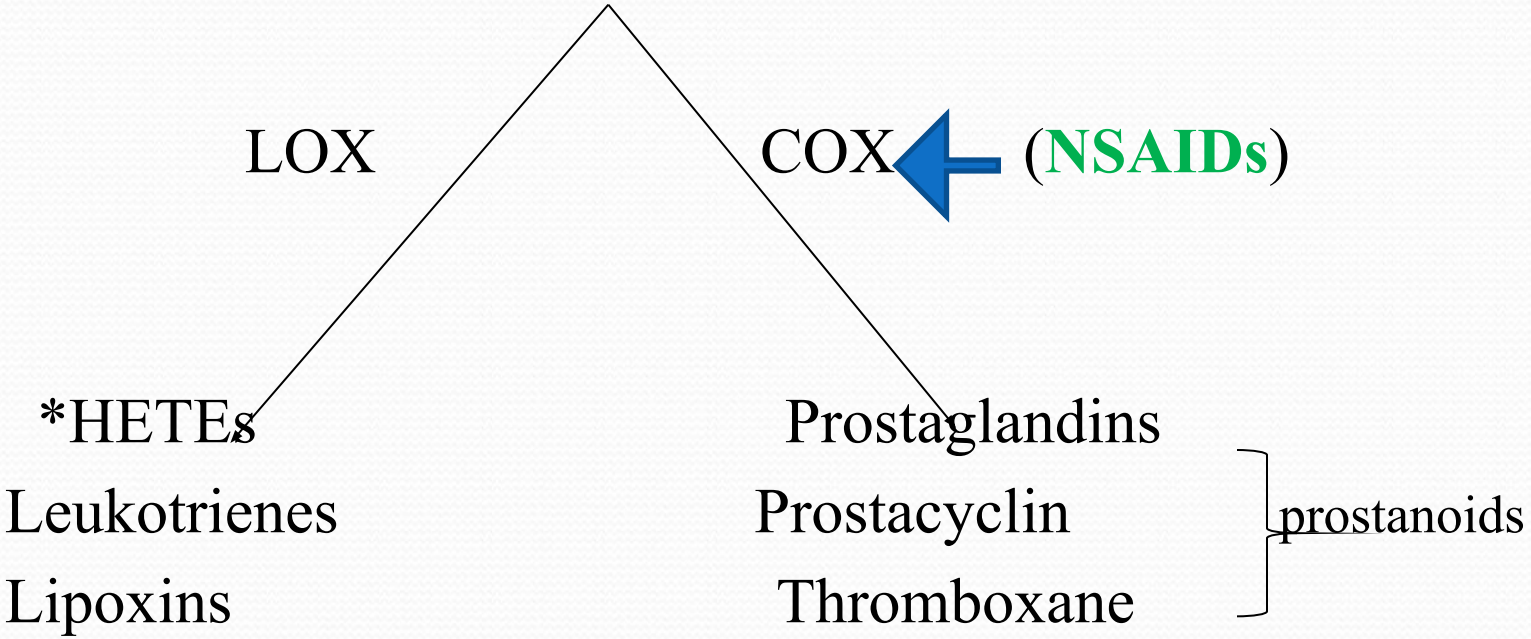
prostaglandins,
prostacyclin and
thromboxan.

AA esterified in cell membrane phospholipids

Physical, chemical, inflammatory And mitogenic stimuli

phospholipase A2

AA



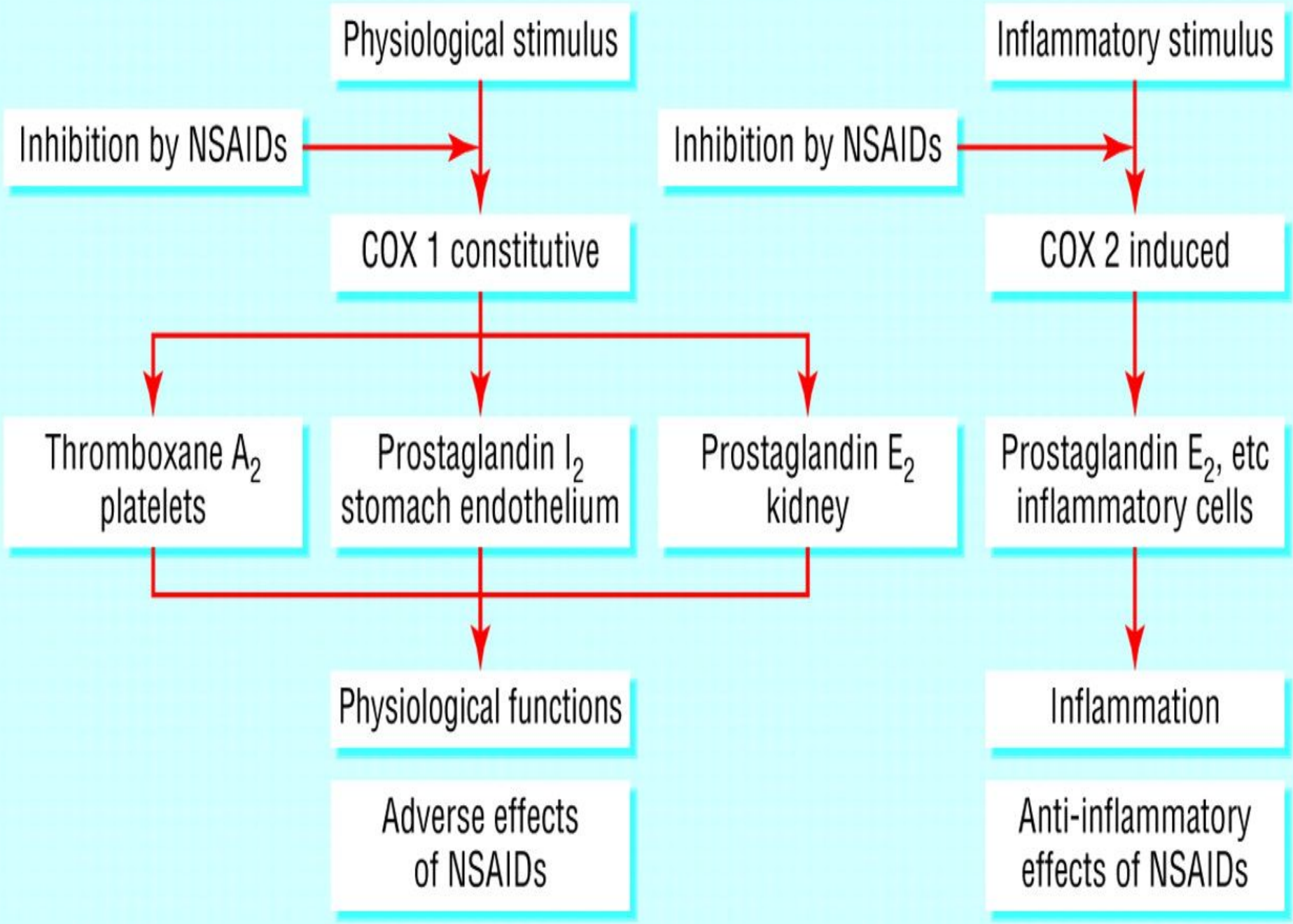
***HETEs** =**hydroxyeicosatetraenoic acids**

COX enzyme **exists as three different types:**
COX-1, COX-2 and COX-3.

COX-1 : is increased by **2-4 folds** in inflammation and present in **most tissues** and responsible for **physiological function** of platelet, stomach and kidney

COX-2 : is increased by **10-20 folds** in inflammation and **present in** macrophages, synoviocytes, chondrocytes and fibroblasts . Less effects on kidney.

COX-3 : in **brain** (newly discovered)


Physiological stimulus
Inhibition by NSAIDs
COX 1 constitutive
Thromboxane A_2 platelets
Prostaglandin I_2 stomach endothelium
Prostaglandin E_2 kidney
Physiological functions
Adverse effects of NSAIDs
Inflammatory stimulus
Inhibition by NSAIDs
COX 2 induced
Prostaglandin E_2, etc inflammatory cells
Inflammation
Anti-inflammatory effects of NSAIDs

2nd pathway: Arachidonic acid is further metabolized by **lipo-oxygenase (LOX) enzyme** to **leukotrienes**, **lipoxin** and **HETE** (Hydroxyeicosatetraenoic acid).

Leukotrienes cause:

1- **Increased** vascular **permeability**

2- **Vasoconstriction**

3- **Bronchoconstriction**

4- **Increase chemotactic activity for leukocytes**

Classification of anti-inflammatory drugs

- Steroid (inhibit phospholipase A2)
- Non steroidal anti-inflammatory drugs (NSAIDs).

In this lecture we talk about **NSAIDs**

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

- They are also **called** ***nonnarcotic***, ***nonopioid*** *or* ***aspirin-like*** analgesics.
- In contrast to morphine they do **not** depress **CNS**, do **not** produce physical **dependence**,
- Have **no abuse** liability
- **Weaker** analgesics (**except** for inflammatory pain).
- Many are over-the-counter drugs.(i.e: these drugs are medicines sold directly to a consumer without a **prescription** from a healthcare)

Mechanism of action of NSAIDs:

The members of this class of drugs, although structurally differs but **all** act by:

1- Inhibiting **COX**.

2- Blocking **prostaglandin** synthesis

3- Reduction of **Thromboxane** (**TXA2**)[[responsible for vasoconstriction and increase platelets aggregation]] **by aspirin**

BUT inhibition of leukotrienes may occur by **Ketoprofen** and ibuprofen.

Pharmacokinetics :-

In general, NSAIDs are

1-Absorbed almost completely from GIT

2- Highly bound to plasma albumin.

3-Most of them are weakly acidic drugs

4- Localized preferentially in the synovial tissue of inflamed joints.

5-Their t1/2 values are differ from short to long

Uses:-

1-Anti-inflammntory effect as in Arthritis, rheumatoid arthritis and other musculoskeletal conditions….

2. Analgesic effect

A. The analgesic effect of NSAIDs is thought to be related to:
   - the peripheral inhibition of prostaglandin production
   - may also be due to the inhibition of pain stimuli at a subcortical site.

B. NSAIDs prevent the potentiating action of prostaglandins on endogenous mediators of peripheral nerve stimulation (e.g., bradykinin).

NSAIDs are **effective** for **mild** to **moderate** pain like musculoskeletal and postoperative pain.

3. Antipyretic effect

- The antipyretic effect of NSAIDs is believed to be related to:
  - inhibition of production of prostaglandins induced by interleukin-1 (IL-1) and interleukin-6 (IL-6) in the hypothalamus
  - the "resetting" of the thermoregulatory system, leading to vasodilatation and increased heat loss.

4-Antiplatelet function : they decrease platelet aggregation, thus NSAIDs are useful in treatment and or prevention of MI and embolic strocks (like aspirin).

It reduces the level of platelet **TXA_2**, and as thromboxan responsible for platelet aggregation, thus NSAIDs resulting in **inhibition** of **platelet aggregation** and a **prolonged bleeding** time. For this reason, aspirin should not be taken for at least 1 week prior to surgery with careful monitoring

- Aspirin is the only antiplatelet agent that **irreversibly** inhibits platelet function.

❖The **recommended** dose of aspirin ranges from **50 to 325** mg.

❖ Complete **inactivation** of platelets occurs with **75 mg** of aspirin given **daily**.

5- Prolongation of gestation and labour:- PG causes uterine contraction , thus inhibition of PG formation by NSAIDs will decrease uterine contractility leading to prolongation of labour.

6-Patency of the ductus arteriosus : as **PG** maintain the ductus arteriosus **opend** (maintain patency), thus NSAIDs **Indomethcin** given to a newborn child with a patent ductus arteriosus can result in closure. Thus NSAID should **never administered before 34 week** of gestation(to avoid early closure of ductus arteriosus) .

7- Primary dysmenorrhea **Mefenamic** acid is used to reduce the production of PGs by uterus (bs PG cause uterine hyper contractility and pain).

Note (information): The **ductus arteriosus** is a blood vessel in the developing fetus connecting the trunk of the **pulmonary artery** to the proximal descending **aorta**. It allows most of the blood from the right ventricle to bypass the fetus's fluid-filled non-functioning **lungs**.

Adverse Effects:

A-**Gastrointestinal effects** : the **commonest** adverse effect of NSAID which occur either by

1- **Direct damage** to gastric and intestinal mucosa.

2- **Indirect effects**: by **Reduction of PG**.:

The **physiological** function of mucosal PG is **cytoprotective**

Because **PGs action** :

a-Increase muocus and bicarbonate secretion

b-Decrease acid secretion

c-Increase blood flow of mucosa

d-Increase capacity for repairing of damaged epith.

thus reduction of PG leads to reduction of protective measures of mucosa and damage to mucosa resulting in gastro- intestinal upset , erosions and peptic ulcer……

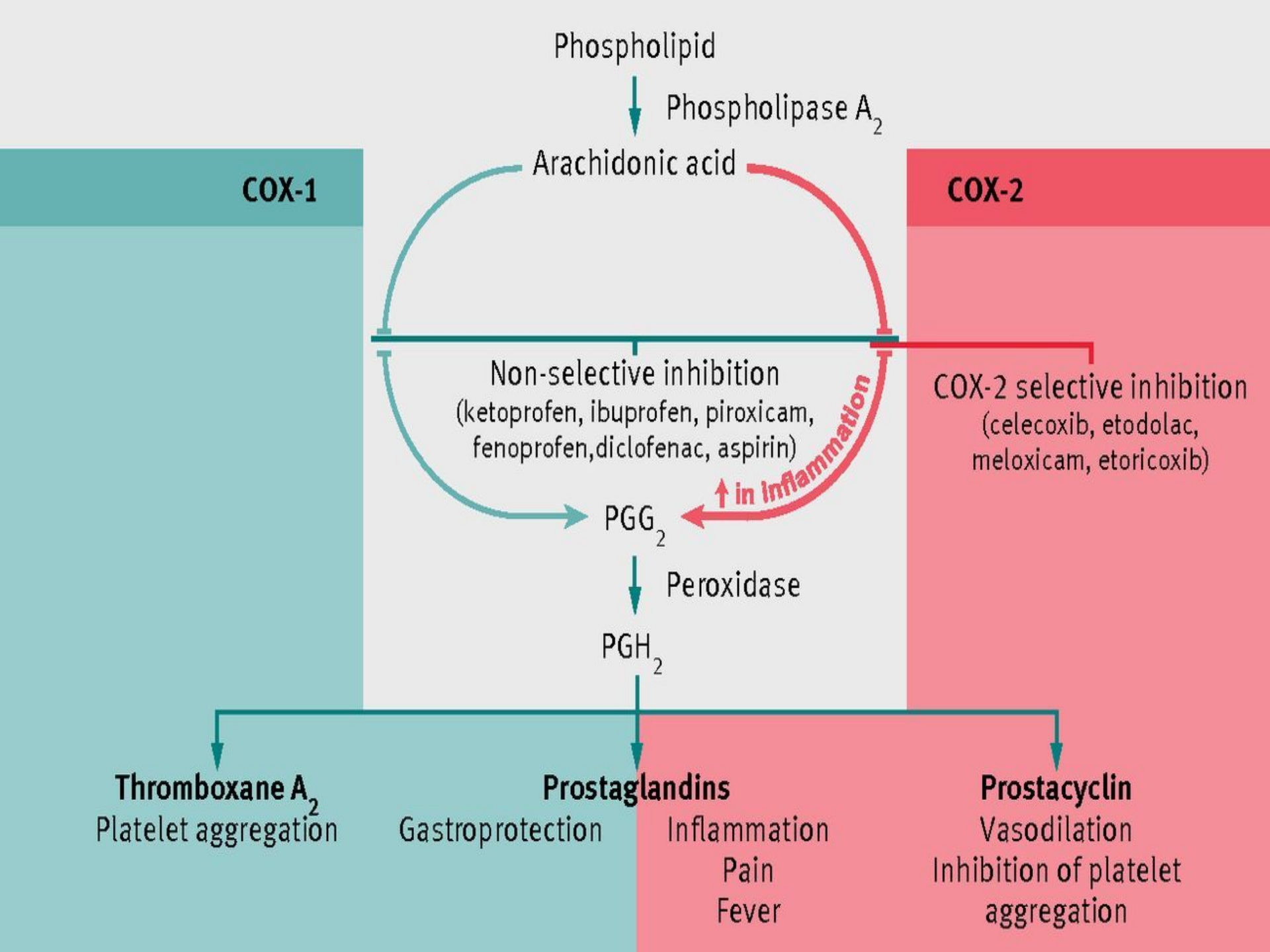
Selective COX-2 inhibitors have **fewer** GIT **adverse effects** than **non COX2** selective compounds (bs COX1 responsible for physiological protection function of mucosa).

in some patients receiving NSAIDs we need an **administration** of one or more **drugs that decrease gastric acid** secretion and protect mucosa like:

1- a proton pump inhibitor

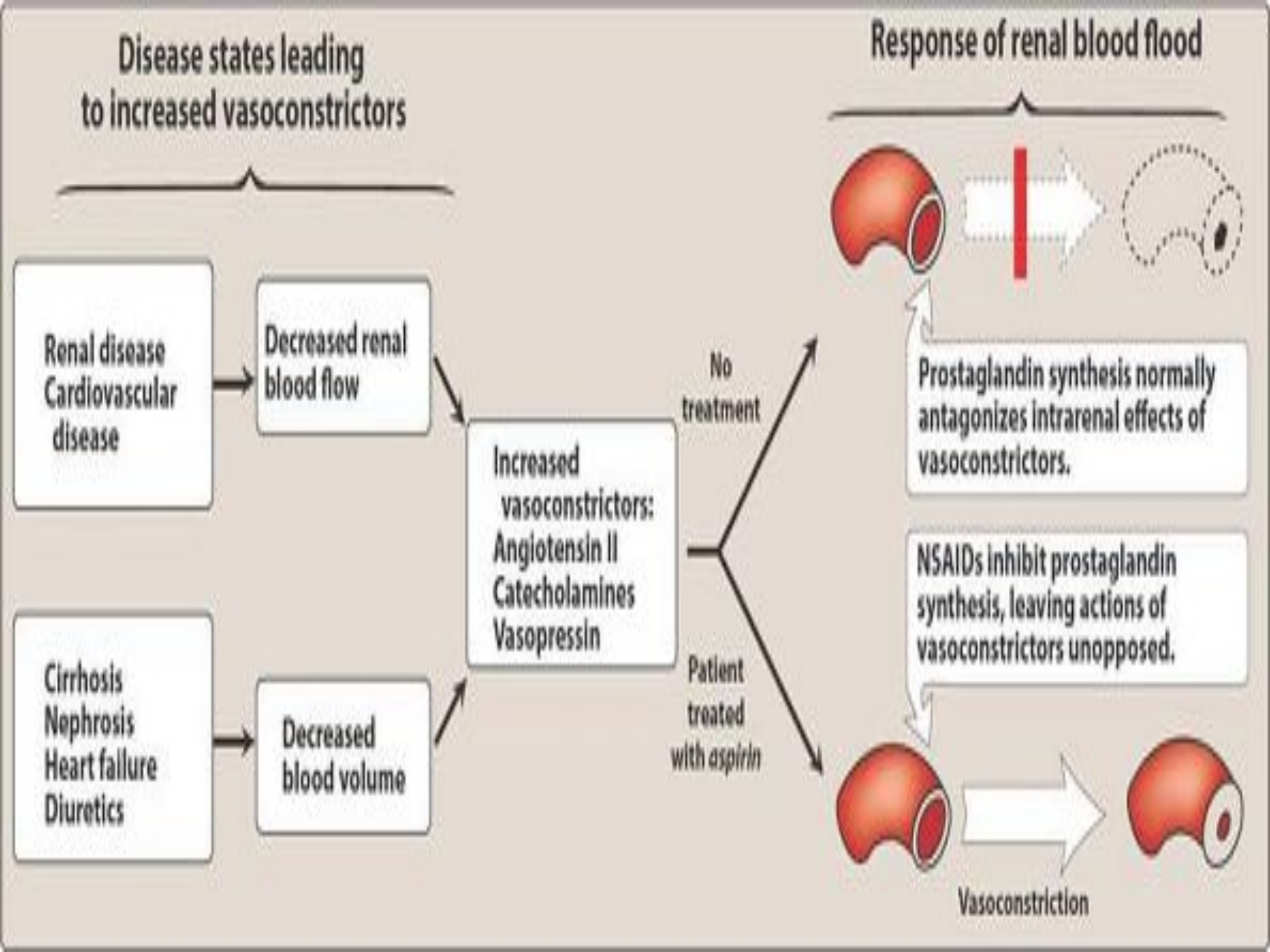
2- H2 receptor blocker

3- PG analogue


Phospholipid
Phospholipase A2
Arachidonic acid
COX-1
COX-2
Non-selective inhibition
(ketoprofen, ibuprofen, piroxicam, fenoprofen,diclofenac, aspirin)
COX-2 selective inhibition
(celecoxib, etodolac, meloxicam, etoricoxib)
↑ in inflammation
PGG2
Peroxidase
PGH2
Thromboxane A2
Platelet aggregation
Prostaglandins
Gastroprotection
Inflammation
Pain
Fever
Prostacyclin
Vasodilation
Inhibition of platelet aggregation

B-Renal effects:

Renal blood **flow** is **reduced because** PG causes vasodilatation of renal blood vessele, so when patient receive NSAID this will decrease synthesis of PG, i.e: the synthesis of vasodilator renal **PGs** is inhibited leading to vasoconstriction which **result in Na and H2O** retention and **hypertension**.


Disease states leading to increased vasoconstrictors
Response of renal blood flood
Renal disease
Cardiovascular disease
Decreased renal blood flow
Cirrhosis
Nephrosis
Heart fallure
Diuretics
Decreased blood volume
Increased vasoconstrictors:
Angiotensin II
Catecholamines
Vasopressin
No treatment
Patient treated with aspirin
Prostaglandin synthesis normally antagonizes intrarenal effects of vasoconstrictors.
NSAIDs inhibit prostaglandin synthesis, leaving actions of vasoconstrictors unopposed.
Vasoconstriction

C- Cutaneous effects include urticaria, photosensitivity and erythema multiform

D- Uncommon effects

hypersensitivity, hepatocellular toxicity , neutropenia and hemolytic anemia.

Ovulation may be reduced or delayed (reversible).

Interactions: with:

1- Angiotensin converting enzyme inhibitors and angiotensin receptor blockers : as this increase the risk of hyperkalemia and renal impairment.

2- Antiplatelets and anticoagulants : as this increase risk of bleeding.

3- Quinolone antimicrobials : as this may causes convulsion.

4- Oral hypoglycemic drugs : NSAID inhibit their metabolism lead to increase their actions (hypoglycemia)

5- Antiepileptics : **inhibit** their **metabolism** lead to increase drug **toxicity**.

6- Antihypertensive drugs: their effect is decrease by Na retention.

7- Cytotoxic drugs excretion is reduced.

8- Lithium excretion is reduced.

General contraindications of NSAIDs

- 1- hypersensitivity
- 2- urticaria and asthma in hypersensetive ptient.
- 3- GIT bleeding or peptic ulcer or heart burn
- 4- heart failure bs NSAIDs induce Na and water retention which lead to inhibition to the action of ACE inhibitors and diuretics (**naproxem** has the **lowest effect** on heart).
- 5- high blood pressure
- 6- liver cirrhosis
- 7- kidney disease.
- 8- bleeding tendency(hemophilia).

CLASSIFICATION:

A. Nonselective COX inhibitors (**traditional NSAIDs**)

1. Salicylates: Aspirin, diflunisal.

2. Propionic acid derivatives: Ibuprofen, Naproxen, Ketoprofen, Flurbiprofen.

3. Fenamate: Mefenamic acid, medofenamate

4. Enolic acid derivatives: Piroxicam, Tenoxicam.

5. Acetic acid derivatives: Ketorolac, Indomethacin, Nabumetone.

6. Pyrazolone derivatives: Phenylbutazone, Oxyphenbutazone.

B. Preferential COX-2 inhibitors: Nimesulide, Diclofenac, Aceclofenac, Meloxicam, Etodolac.

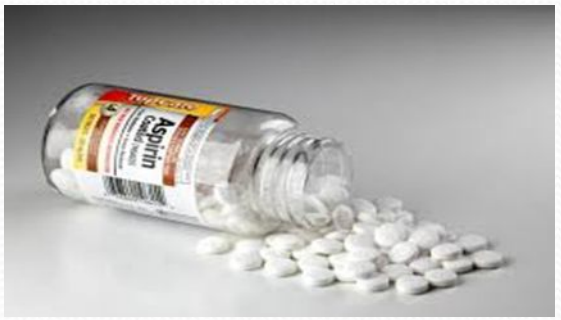
C. Selective COX-2 inhibitors: Celecoxib, Etoricoxib, Parecoxib.

D. Analgesic-antipyretics with poor anti-inflammatory action:

1. COX 3 inhibitors: Para-aminophenol derivative like Paracetamol (=Acetaminophen)(bs it cross BBB).

2. Pyrazolone derivatives: Metamizol (Dipyrone) , Propiphenazone.

3. Benzoxazocine derivative: Nefopam .



Thank you

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