MSS

Pharmacology

LEC no. 5+6

Writer: Alaa Khader
Hebah Khraisat

Corrector: Layan Alodat

Doctor: Alia Shatanawi

Nonsteroidal Anti-inflammatory Drugs (NSAIDs) and Analgesics

Dr. Alia Shatanawi

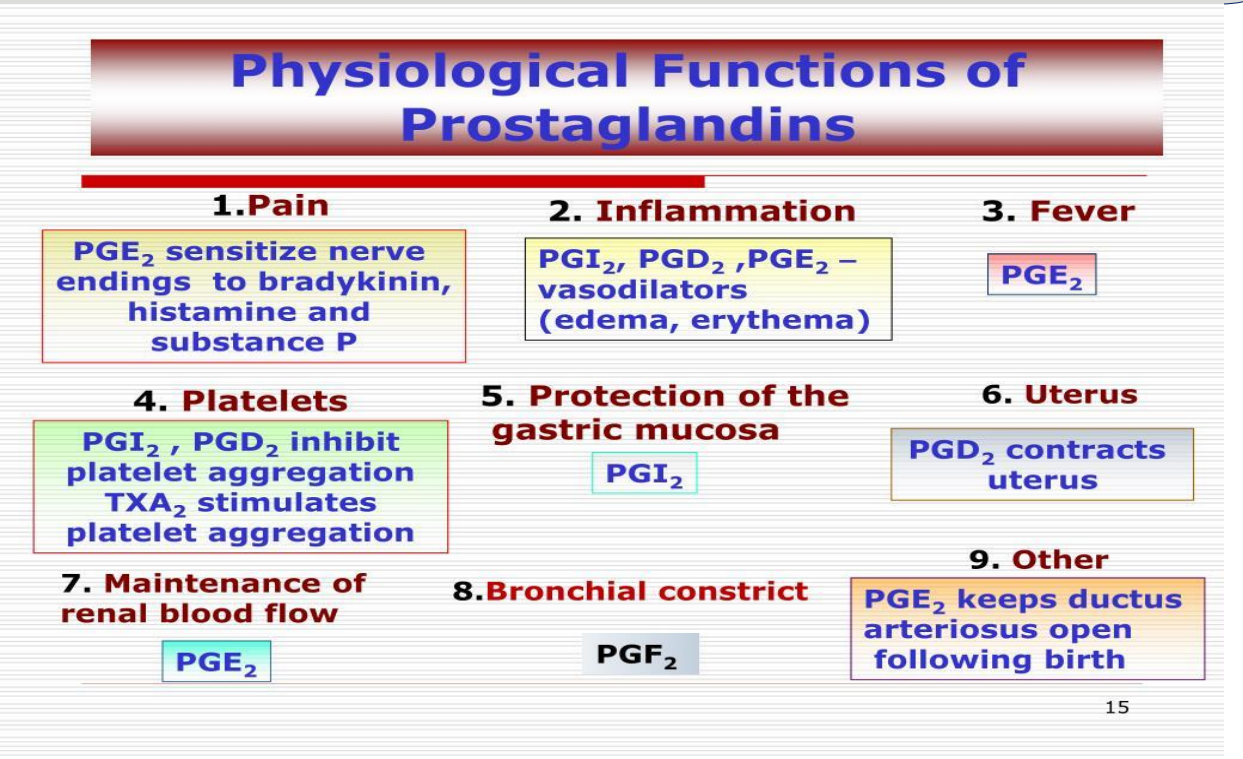
NSAIDs (non-steroidal anti-inflammatory drugs) are a class of medications that reduce inflammation. They act as immunomodulators and are not classified as steroids. Common examples of NSAIDs include aspirin, celecoxib, and ibuprofen. These drugs work by inhibiting the enzymes known as cyclooxygenases (COX), particularly COX-1 and COX-2.

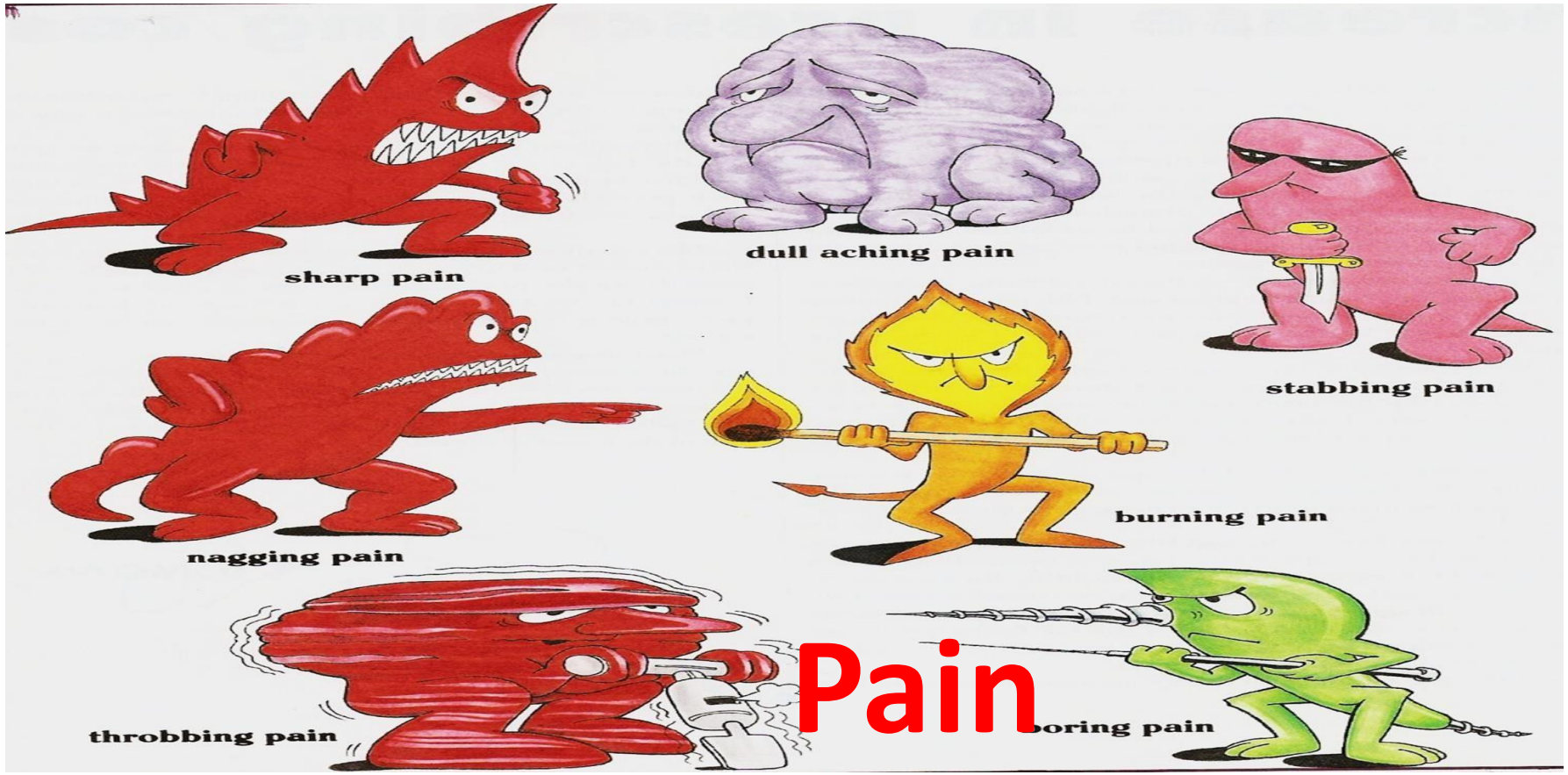
NSAIDs have multiple therapeutic effects, including:

1. analgesic (pain-relieving),
2. antipyretic (fever-reducing)
3. anti-inflammatory properties.

NSAIDs primarily exert their actions in the peripheral system. The major side effect of NSAIDs is causing GI irritation (chronic use) -----> peptic ulcer and bleeding.

Small recap: Remember the physiological effects of Prostaglandins, so that you can understand more.





- Universal, Complex, Subjective experience
- No. 1 Reason people take medications
- Generally is related to some type of tissue damage by prostaglandins and serves as a warning signal

Analgesics

-Pain killers

-Derived from Greek **an**- "without" & -**algia** "pain."

An **analgesic**, or **painkiller**, is any member of the group of drugs used to achieve analgesia — relief from pain.

-Act in various ways on the peripheral and central nervous systems.

Analgesics

There are three groups for pain killers:

- The non-steroidal anti-inflammatory drugs (NSAIDs)

Aspirin, ibuprofen, diclofinic sodium (voltaren), mefenamic acid, indomethacin and more.

- Paracetamol = acetaminophen

Paracetamol and NSAIDs share analgesic and antipyretic properties, but Paracetamol lacks anti-inflammatory effects and acts on the CNS rather than peripherally. Unlike NSAIDs, it doesn't commonly cause gastric irritation or nephrotoxicity but poses a risk of hepatotoxicity instead. These differences classify them into distinct groups.

- Opioid drugs

Comparison of Analgesics

After Surgeries (visceral pain)

Feature	Narcotic (Opioids)	Nonnarcotic (nonopioid) (NSAIDs + Paracetamol)
Efficacy	Strong	Weak
Prototype الجد الأكبر	Morphine	Aspirin
Pain Relieved	Any Type	Musculoskeletal
Site of Action	Central	Peripheral and Central
Mechanism	Specific Receptors	PG Synthesis
Danger	Tolerance & Dependence مسببات الادمان	G.I irritation
Anti-inflammatory	No	Yes
Antipyretic	No	Yes
Antiplatelets	No	Yes

Inflammatory pathways

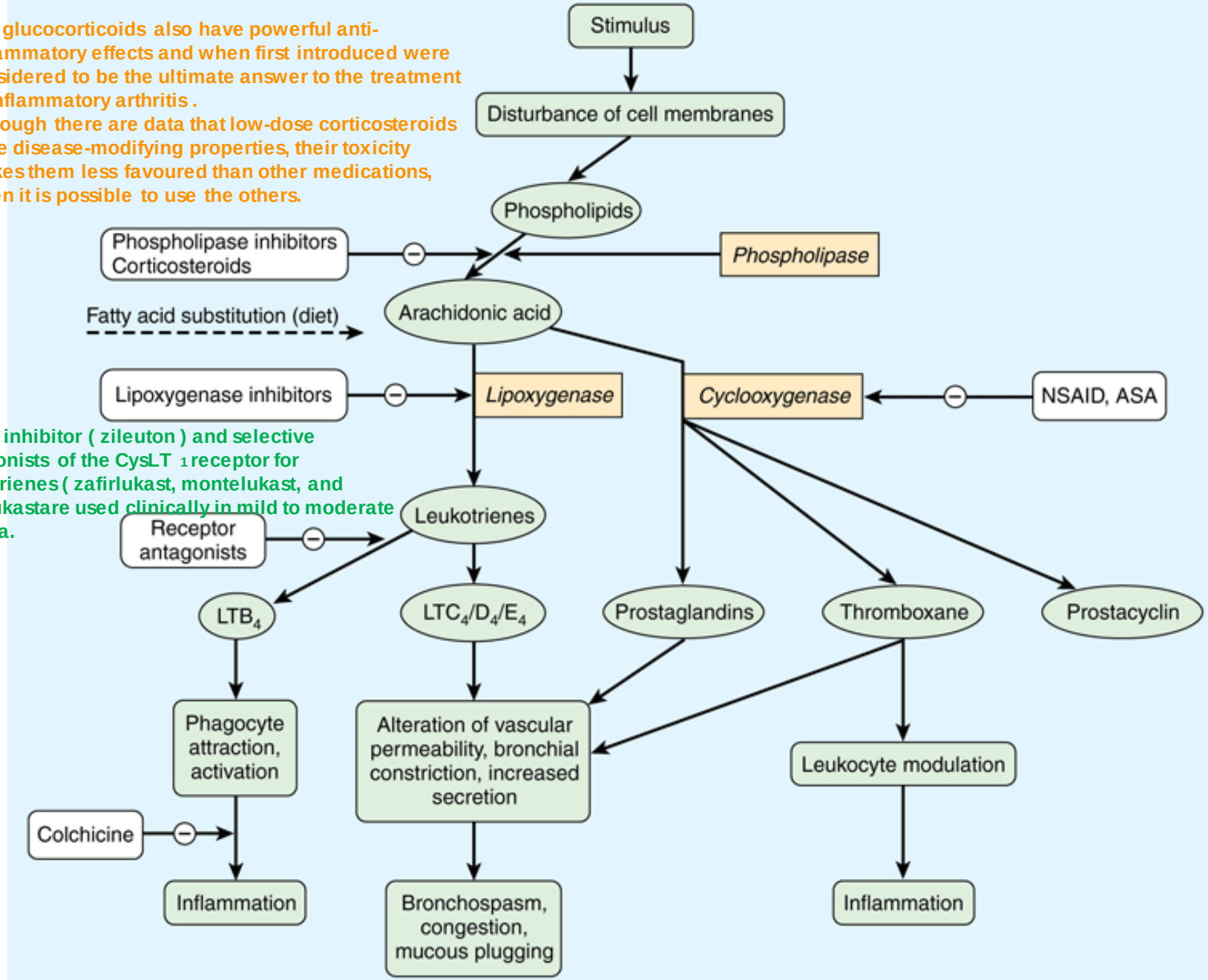
- Cyclooxygenase (COX) pathway of arachidonate metabolism produces prostaglandins
- Effects on blood vessels, on nerve endings, and on cells involved in inflammation .
- The lipoxygenase pathway of arachidonate metabolism yields leukotrienes
- have a powerful chemotactic effect on eosinophils, neutrophils, and macrophages and promote bronchoconstriction and alterations in vascular permeability.

Side effects of NSAIDs:

1) Nephrotoxic: Prostaglandins play a protective role in maintaining normal kidney function, including regulation of renal blood flow and maintaining a balance of salt and water. Inhibition of prostaglandin synthesis by NSAIDs can disrupt these renal functions leading to sodium and water retention, which can strain the kidneys and lead to nephrotoxicity.

2)High BP: prostaglandin E2 plays a role in vasodilation. Inhibition of prostaglandin synthesis by NSAIDs can disrupt this balance and lead to vasoconstriction, which can increase blood pressure.

The glucocorticoids also have powerful anti-inflammatory effects and when first introduced were considered to be the ultimate answer to the treatment of inflammatory arthritis .
Although there are data that low-dose corticosteroids have disease-modifying properties, their toxicity makes them less favoured than other medications, when it is possible to use the others.



-5LOX inhibitor (zileuton) and selective antagonists of the CysLT 1 receptor for leukotrienes (zafirlukast, montelukast, and pranlukastare used clinically in mild to moderate asthma.

Injury causes damage of cell membranes ——--> releases the phospholipids -----> arachidonic acid (AA) by phospholipase. AA is the substrate for these two pathways:

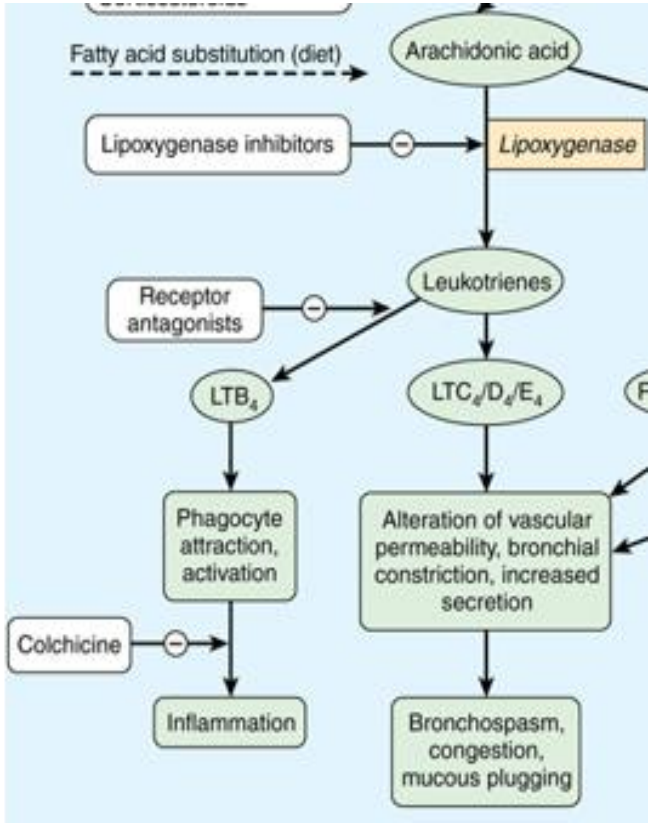
1. Lipoxygenase pathway
2. COX pathway (our topic in this lecture)

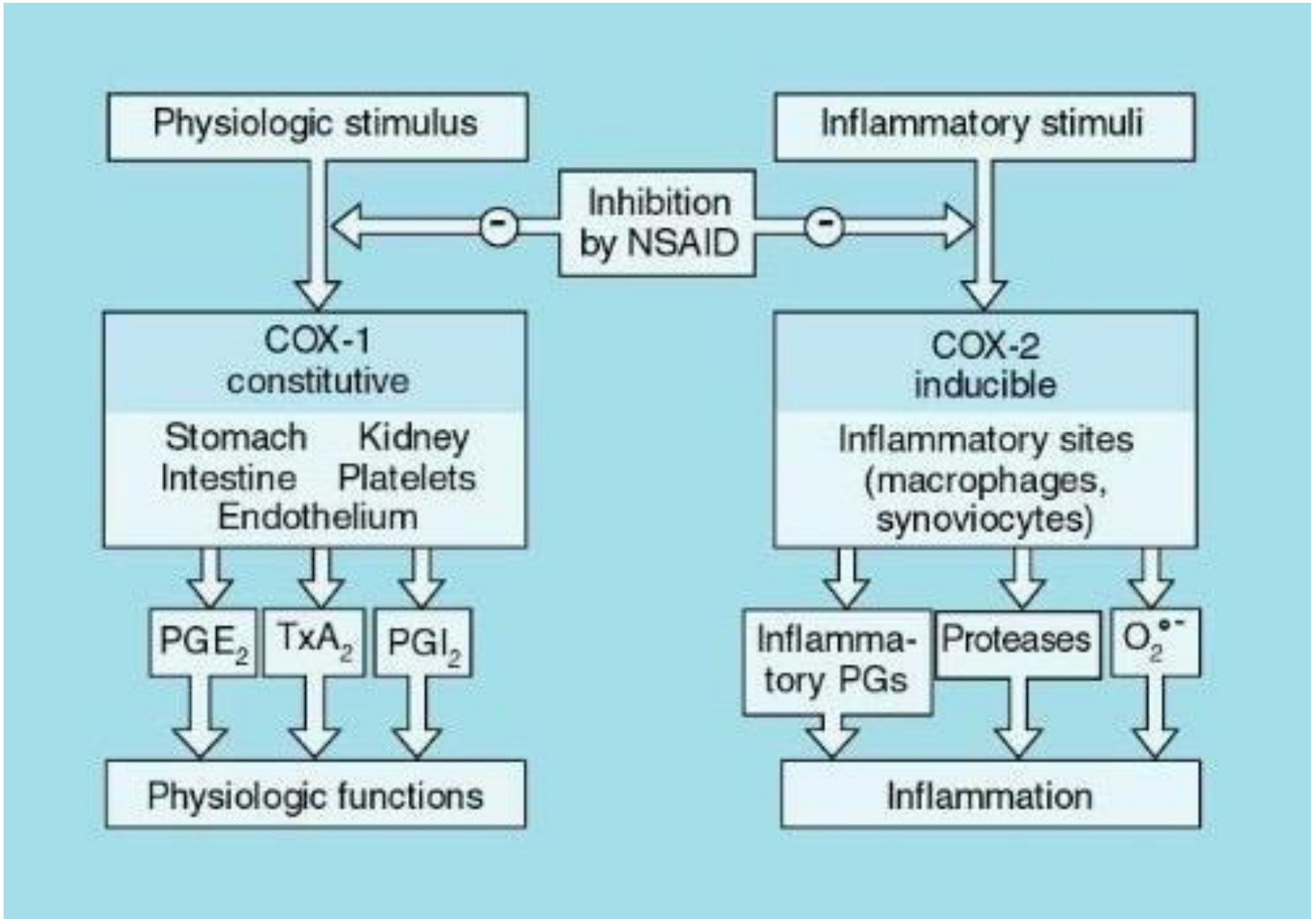
5LOX inhibitor (zileuton) and selective antagonists of the CysLT 1 receptor for leukotrienes (zafirlukast, montelukast, and pranlukastare), also called LT modifiers, **are used clinically in mild to moderate asthma.**

Normally, Leukotrienes cause bronchoconstriction, produce mucus in the bronchi and increase permeability of blood vessels, so controlling this pathway can help in asthma patients.

Zileuton inhibits the enzyme 5-lipoxygenase, which is responsible for the synthesis of leukotrienes from arachidonic acid. By blocking this enzyme, zileuton reduces the production of leukotrienes.
Zafirlukast, montelukast, and pranlukastare are selective antagonists of the CysLT1 receptor. They prevent the binding of leukotrienes. This inhibition reduces the bronchoconstrictive and inflammatory effects.

Colchicine is used in treatment of gout.
Gout: inflammatory disease is caused by hyperuricemia (high uric acid), that will be deposited in the joints in the form of urate crystals, and urate crystals are foreign bodies that attract leukocytes with help of leukotrienes. Colchicine causes inhibition of phagocyte attraction.




Physiologic stimulus
Inflammatory stimuli
Inhibition by NSAID
COX-1 constitutive
Stomach Kidney
Intestine Platelets
Endothelium
COX-2 inducible
Inflammatory sites (macrophages, synoviocytes)
PGE2
TxA2
PGI2
Inflamma-tory PGs
Proteases
O2•-
Physiologic functions
Inflammation

There are two main isoforms of cyclooxygenase - there's a new third form but that isn't our focus for today- COX 1 AND COX 2.
COX1 is the constitutive form, that means it exists throughout different sites of the body and are continuously functional, producing prostaglandins -within certain levels- upon need.

COX 2 is the inducible form, that means it is synthesized and released in the inflammatory sites only during inflammation, enhancing and increasing prostaglandin.
for eg: rheumatoid arthritis causes release of different prostaglandins from synoviocytes / macrophages into the joints

info for you: the dr mentioned here how most medications we buy directly actually should require prescriptions, yet in jordan the only truly monitored medications through prescriptions are controlled substances aka drugs (cns function that may lead to addiction).
بسموها الوصفة الحمرة :D

Constitutively released prostaglandins: PGE/TXA/PGI. Each has a distinct role in the different organs of the body:

- PGE2: vasodilatory
- PGI2 (AKA prostacyclin): vasodilatory

-They increase the blood vessel diameter (vasodilation) which in turn increases the permeability of the blood vessel, which may cause leakage and EDEMA.

- TXA: vasoconstrictor

important for clot formation and platelet aggregation to happen.

Aspirin is an antiplatelet drug, hence elderly may take aspirin AT LOW DOSES prophylactically to avoid strokes (it's used at a low dose only for its antiplatelet effect).
Aspirin was needed in HIGH DOSES for its anti-inflammatory effect, however it isn't as commonly used as before (it has been replaced by various painkillers such as voltarene/ ibuprofen/ etc).

Cyclo-oxygenase (COX)

- Exists in the tissue as constitutive isoform (COX-.)1
- At site of inflammation, cytokines stimulates the induction of the 2nd isoform (COX-.)2
- Inhibition of COX-2 is thought to be due to the anti-inflammatory actions of NSAIDs.
- Inhibition of COX-1 is responsible for their GIT toxicity.
- Most currently used NSAIDs are somewhat selective for COX-1, but selective COX-2 inhibitors are available.

And anti-inflammatory actions of NSAIDs are due to the inhibition of COX-2.

Basically limiting the sites of the drugs activity, inhibiting the inflammatory effect whilst preserving the good effects of COX1.

Drug companies released many selective COX2 inhibitors by the early 2000's such as celecoxib and rofecoxib, which had many adverse effects, including blood clotting, this is due to the over activation of the COX1 in compensation (COX1 arm will take over since the COX2 isn't active anymore) which leads to unopposed action of thromboxane, increasing the chances of thromboembolic diseases (myocardial infarction or a stroke), which lead to the withdrawal of rofecoxib (there's a required percentage of incidences to lead to the drug withdrawal, that's why celecoxib is still available, yet it has a black box warning).
Celecoxib is still used in patients (cautiously) who need the anti-inflammatory effect of inhibiting COX, yet have GIT issues so they cannot use NSAIDS (Not the 1st choice of treatment).

Black box warning is writing the dangerous side effects on the outer box instead of writing it on the leaflet inside (eg isotretenoin warning for pregnant women, celecoxib warning for people with history of thromboembolic diseases).

Celecoxib isn't advised in patients with hypertension/hypercholesterolemia as they're more prone to develop atherosclerotic event, which will lead to thromboatherosclerotic event, hence they are prescribed aspirin instead (it's not absolutely contraindicated though).

Most of the drugs we talked about are nonselective COX inhibitors.
Recent studies have shown that the most currently used drugs are somewhat selective for COX1, which is UNTRUE. It can be said to be true for some drugs in low doses, remember what we said about aspirin, the low doses have an antiplatelet effect and it loses that effect at higher doses, that is related to selectivity loss of the drug as we increase the dose, as it starts activating multiple receptors instead of a single one.

We can say that aspirin at a low dose is more selective to COX1 (thromboxane inhibition), but at higher doses we can see both COX1 and COX2 inhibition (anti-inflammatory effect).

Recently there has been concern surrounding other NSAIDS, including ibuprofen and endomethacin, as, according to some papers, may cause clotting in some patients , which they shouldn't, as they are nonselective, and a side effect of those drugs is actually bleeding! so it has become a controversial topic.

Most of the explanations are of phenomenas we see not things we have actual proof of.

NSAIDs

- The NSAIDs are a group of chemically dissimilar agents that differ in their **antipyretic**, **analgesic**, and **anti-inflammatory** activities.

- **inhibiting** the **cyclooxygenase** enzymes that catalyze the first step in prostanoid biosynthesis .

>>>>decreased prostaglandin synthesis with both **beneficial** and **unwanted** effects.

note that the numbers in the table ARE NOT for memorization the orange highlighted drugs will be covered in future lectures

TABLE 36–1 Properties of aspirin and some other nonsteroidal anti-inflammatory drugs.

Drug	Half-Life (hours)	Urinary Excretion of Unchanged Drug	Recommended Anti-Inflammatory Dosage
Aspirin	0.25	<2%	1200–1500 mg tid
Salicylate[1]	2–19	2–30%	See footnote 2
Celecoxib	11	27%[3]	100–200 mg bid
Diclofenac	1.1	<1%	50–75 mg qid
Diflunisal	13	3–9%	500 mg bid
Etodolac	6.5	<1%	200–300 mg qid
Fenoprofen	2.5	30%	600 mg qid
Flurbiprofen	3.8	<1%	300 mg tid
Ibuprofen	2	<1%	600 mg qid
Indomethacin	4–5	16%	50–70 mg tid
Ketoprofen	1.8	<1%	70 mg tid
Ketorolac	4–10	58%	10 mg qid[4]
Meloxicam	20	Data not found	7.5–15 mg qd
Nabumetone[5]	26	1%	1000–2000 mg qd[6]
Naproxen	14	<1%	375 mg bid
Oxaprozin	58	1–4%	1200–1800 mg qd[6]
Piroxicam	57	4–10%	20 mg qd[6]
Sulindac	8	7%	200 mg bid
Tolmetin	1	7%	400 mg qid

Most are nonselective drugs except celecoxib - Meloxicam have been found to be slightly cox2 selective so it might have less side effects.

Aspirin analgesics tablets are usually 325 mg so the patient ingests at least two at a time for the anti-inflammatory effect,
whereas only 81- 100 mg is needed for the anti-platelet effect.

Because we need a high dose for the anti-inflammatory properties, this high dose will cause GI irritation.

There are other inflammatory mediators that are released by the inducible cox. In addition to the inflammatory prostaglandins
It releases proteases, and super oxide, which have a role in killing pathogens in the site of inflammation.

Non-steroidal anti-inflammatory drugs (NSAIDs)

pain

fever

Inflammation

By inhibition of cyclo-oxygenase enzymes COX1 & COX.2

NSAIDs

An anti-inflammatory action :

(1) decrease Vasodilator PG (PGE_2, PGI_2) leads to less vasodilatation and, indirectly, less edema .

(2) The inhibition of activity of adhesion molecule.

(3) Accumulation of inflammatory cells is also reduced.

NSAIDs

An analgesic effect:

Nociceptors (Pain receptors) which detect physical or chemical damage occurring in the tissues.

- Decreased prostaglandin generation means decrease sensitivty of **nociceptive** nerve endings to inflammatory mediators. (basically it increases the threshold of pain)

- Relief of **headache** is due to decreased prostaglandin-mediated vasodilatation.

PGE2 released from endothelial cells causes strong dilation of cerebral vessels and causing tension on certain arterial receptor

Analgesic action:

- Prostaglandin E2 (PGE2) is thought to **sensitize** nerve endings to the action of bradykinin, histamine, and other chemical mediators released locally by the inflammatory process.

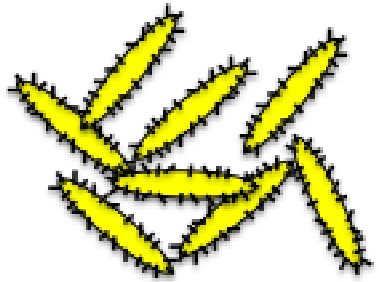
- management of pain of low to moderate intensity arising from musculoskeletal disorders rather than that arising from the viscera (opioids drugs).

Antipyretic Effects

- The antipyretic due primarily to the blockade of **prostaglandin** synthesis at the thermoregulatory centers in the hypothalamus and at peripheral target sites.
- Fever occurs when the set-point of the anterior hypothalamic thermoregulatory center is elevated
- ---->impeding PGE2 synthesis and release ------> resets the hypothalamus toward normal
- Aspirin has no effect on normal body temperature.

effect of PGE2 on temperature –video link

How Infection/Inflammation Causes Fever



Bacteria

1) releases

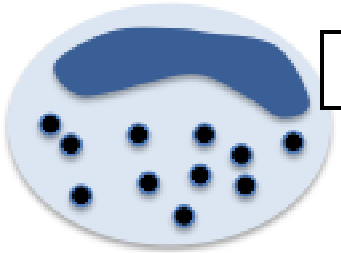
Bacterial toxins
(exogenous pyrogens)
G-: endotoxins (LPS)
G+: enterotoxins

E. Coli
Klebsiella

S. aureus
S. pyogenes

2) activates

Toll-like & MHC receptors



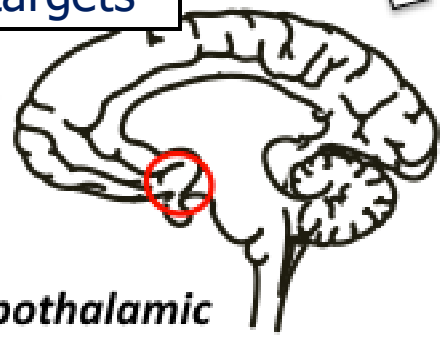
corticosteroids

3) secrete

Leukocytes
(monocytes, macrophages)

Inflammatory cytokines
(endogenous pyrogens)
IL-1β, TNF-α, **IL-6**

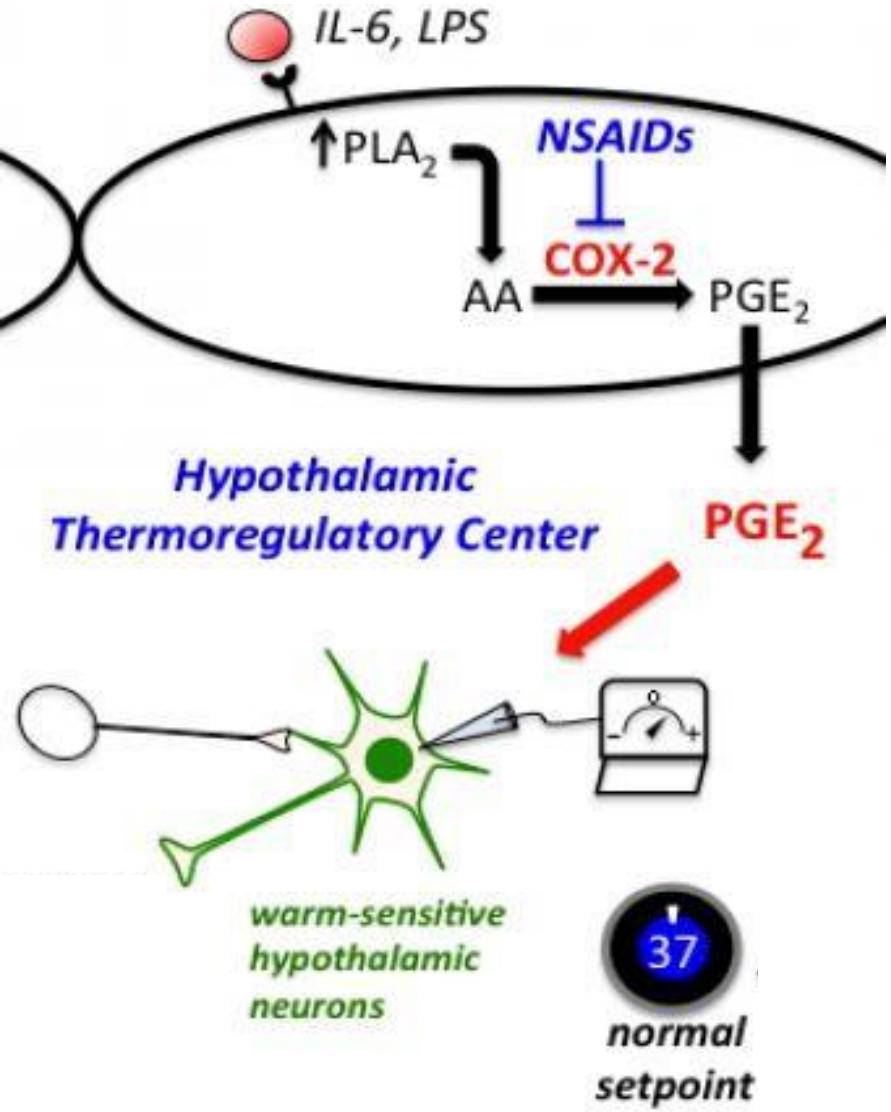
4)targets

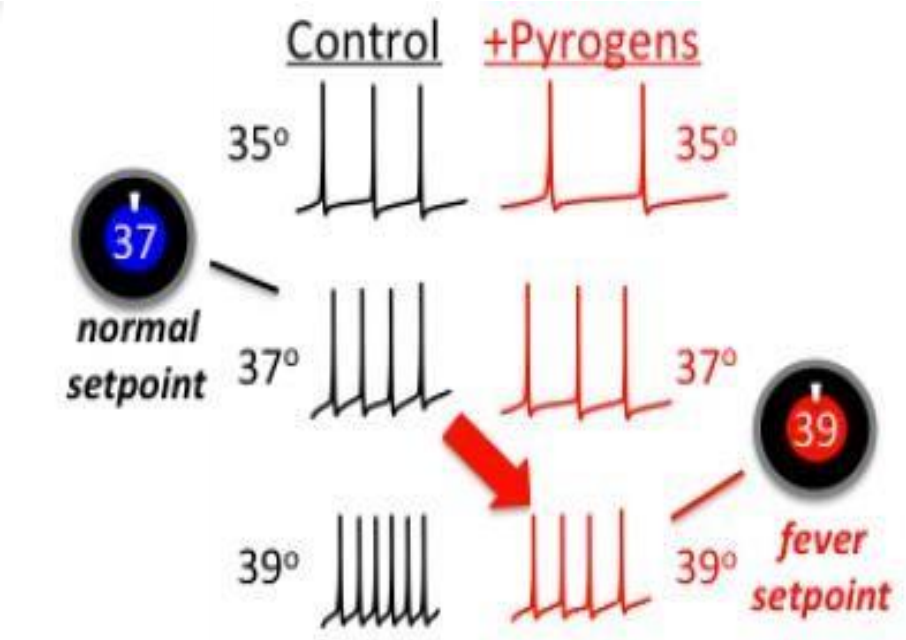


Hypothalamic
Thermoregulatory Center

5) Causes resetting of the temperature

(the most important cytokines involved in elevation of body temperature)
Pyrogens = fever agents


IL-6, LPS
PLA2
NSAIDs
COX-2
AA
PGE2
Hypothalamic
Thermoregulatory Center
PGE2
warm-sensitive
hypothalamic
neurons
37
normal
setpoint


Control
+Pyrogens
35°
35°
37
normal
setpoint
37°
37°
39
39°
39°
fever
setpoint

Aspirin

Acetylsalicylic acid

- It can cause **irreversible** inactivation of COX-1 and COX-.2

- Aspirin is the prototype of **traditional** NSAIDs and was officially approved by the FDA in .1939

Mechanism of action

- Aspirin is a weak organic acid that is unique among the NSAIDs in that it **irreversibly** inactivates cyclooxygenase

- The other NSAIDs are all reversible

- Aspirin is rapidly deacetylated by esterases in the body producing salicylate, which has anti-inflammatory, antipyretic, and analgesic effects .

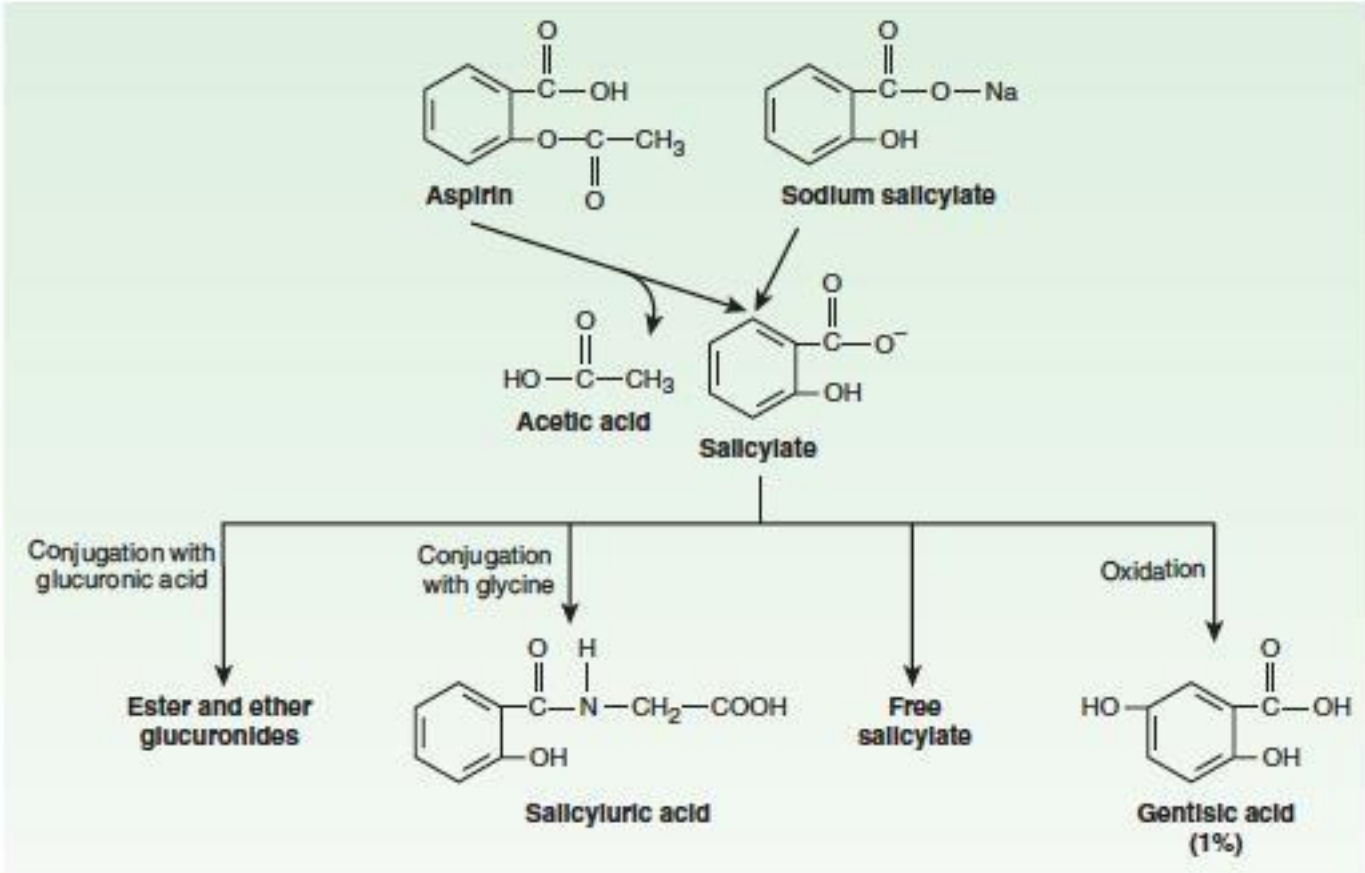


FIGURE 36–3 Structure and metabolism of the salicylates. (Modified and reproduced, with permission, from Meyers FH, Jawetz E, Goldfien A: *Review of Medical Pharmacology*, 7th ed. McGraw-Hill, 1980.)

Respiratory actions:

Aspirin can cause bronchoconstriction in some asthmatic patients through increased production of proinflammatory mediators, particularly leukotrienes.

Clinical Uses

Aspirin decreases the incidence of transient ischemic attacks, unstable angina, coronary artery thrombosis with myocardial infarction, and thrombosis after coronary artery bypass grafting

Epidemiologic studies suggest that long-term use of aspirin at low dosage is associated with a lower incidence of colon cancer, possibly related to its COX-inhibiting effects.

Cox 1 is found in different sites including the stomach, so it's responsible for this side effect ;)

Gastrointestinal effects:

- **PGE2** stimulate synthesis of protective **mucus** in both the stomach and small intestine.

and decreases the acid secretion (HCL), so it can be seen as a protection from the stomachs acidity.

- In the presence of aspirin, these prostanoids are not formed, resulting in increased gastric acid secretion and diminished mucus protection .

which leads to a more powerful effect of acid on the stomach, resulting in GI toxicity/ irritation.

- Agents used for the prevention of gastric and/or duodenal ulcers include proton-pump inhibitors (**PPIs**); esomeprazole, lansoprazole, omeprazol

Effect on platelets:

Aspirin irreversibly inhibits platelet COX so that aspirin's anti platelet effect lasts 8–10 days (the life of the platelet .)
In other tissues, synthesis of new COX replaces the inactivated enzyme so that ordinary doses have a duration of action of 6–12 hours.

Actions on the kidney:

- Cyclooxygenase inhibitors prevent the synthesis of PGE2 and PGI2 that are responsible for maintaining **renal blood flow.**

- Decreased synthesis of prostaglandins can result in **retention of sodium and water** and may cause **edema** and **hyperkalemia** in some patients.

NSAIDs have the potential to elevate blood pressure by opposing the vasodilatory actions of prostaglandins. Kidneys receive blood through the afferent arteriole, and NSAIDs can cause constriction of this arteriole, resulting in reduced blood flow to the kidneys. In response, the kidneys attempt to maintain blood volume by enhancing the reabsorption of electrolytes and sodium, consequently promoting water retention and leading to elevated blood pressure and the development of edema.

Common Adverse Effects

- Platelet Dysfunction
- Gastritis and peptic ulceration with bleeding (inhibition of PG + other effects)
- Acute Renal Failure in susceptible
- Sodium+ water retention and edema
- Analgesic nephropathy
- Prolongation of gestation and inhibition of labor.
- GIT bleeding and perforation

اللهم انصر إخواننا في فلسطين

اللهم ثبت أقدامهم، اللهم قوي عزائمهم، اللهم صبرهم على مصيبتهم، اللهم تقبل شهداءهم، وفرج كربتهم، اللهم كن معهم ولا تكن عليهم واعنهم ولا تعن عليهم وانصرهم ولا تنصر عليهم، اللهم ردّ كيد المحتل إلى نحورهم