# Nonsteroidal Anti-inflammatory Drugs (NSAIDs) and Analgesics

Dr. Alia Shatanawi

Modified by Dima Rafaiah

# Pain

- Universal, Complex, Subjective experience

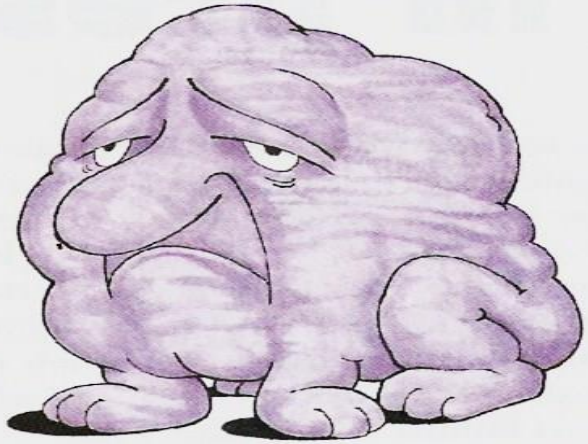
same kind of pain can be different between individuals depending on many factors like your pain tolerance.

- No. 1 Reason people take medications

pain is an alarming sign to take action against an underlaying issue that caused certain mediators to be secreted and produce pain. (like bradykinins)

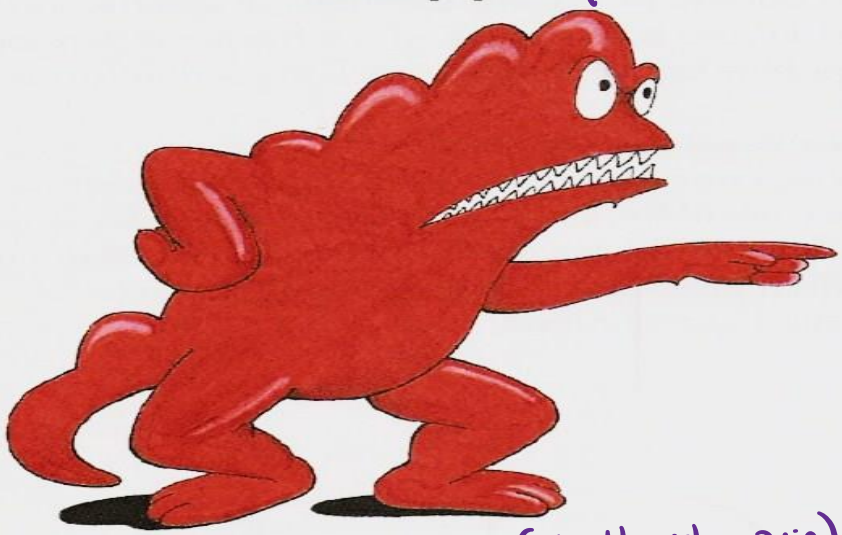
- Generally is related to some type of tissue damage and serves as a warning signal

sharp pain ( wound, incision)

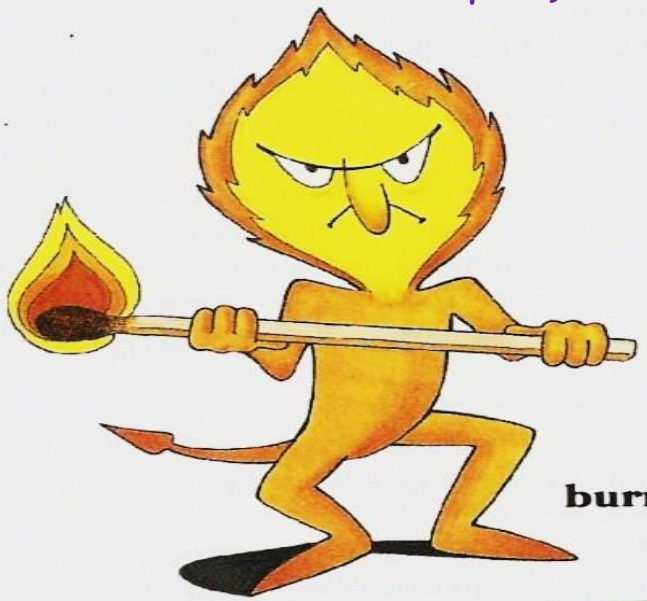


dull aching pain (chronic back pain)

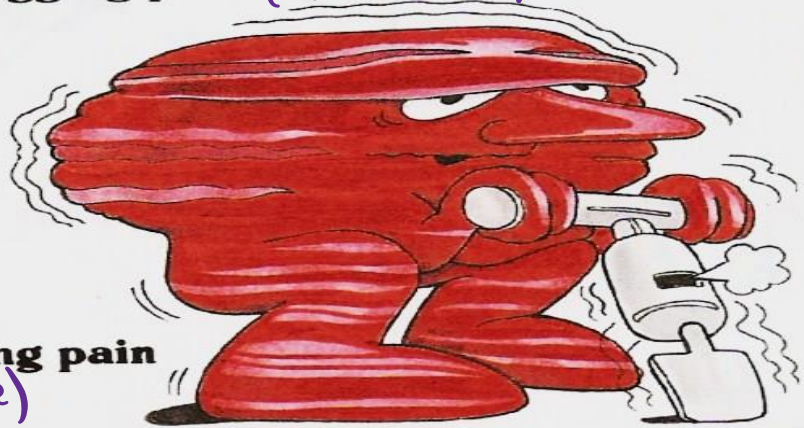
stabbing pain



nagging pain ( tooth ache pain)



burning pain



throbbing pain
( headache)

boring pain

# 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.

↳ opioid drugs (Discussed next year)

# Analgesics

* Can be classified into:

- The non-steroidal anti-inflammatory drugs (NSAIDs)
  - Aspirin is the prototype
- Paracetamol = acetaminophen
  - British name
  - American name
  - it has very weak anti-inflammatory properties
- Opioid drugs (morphine is the prototype)

paracetamol resembles NSAIDs in alot of features with minor differences

# Comparison of Analgesics

Their efficacy is very high with serious side effects so they're used in major conditions (surgery, visceral pain)

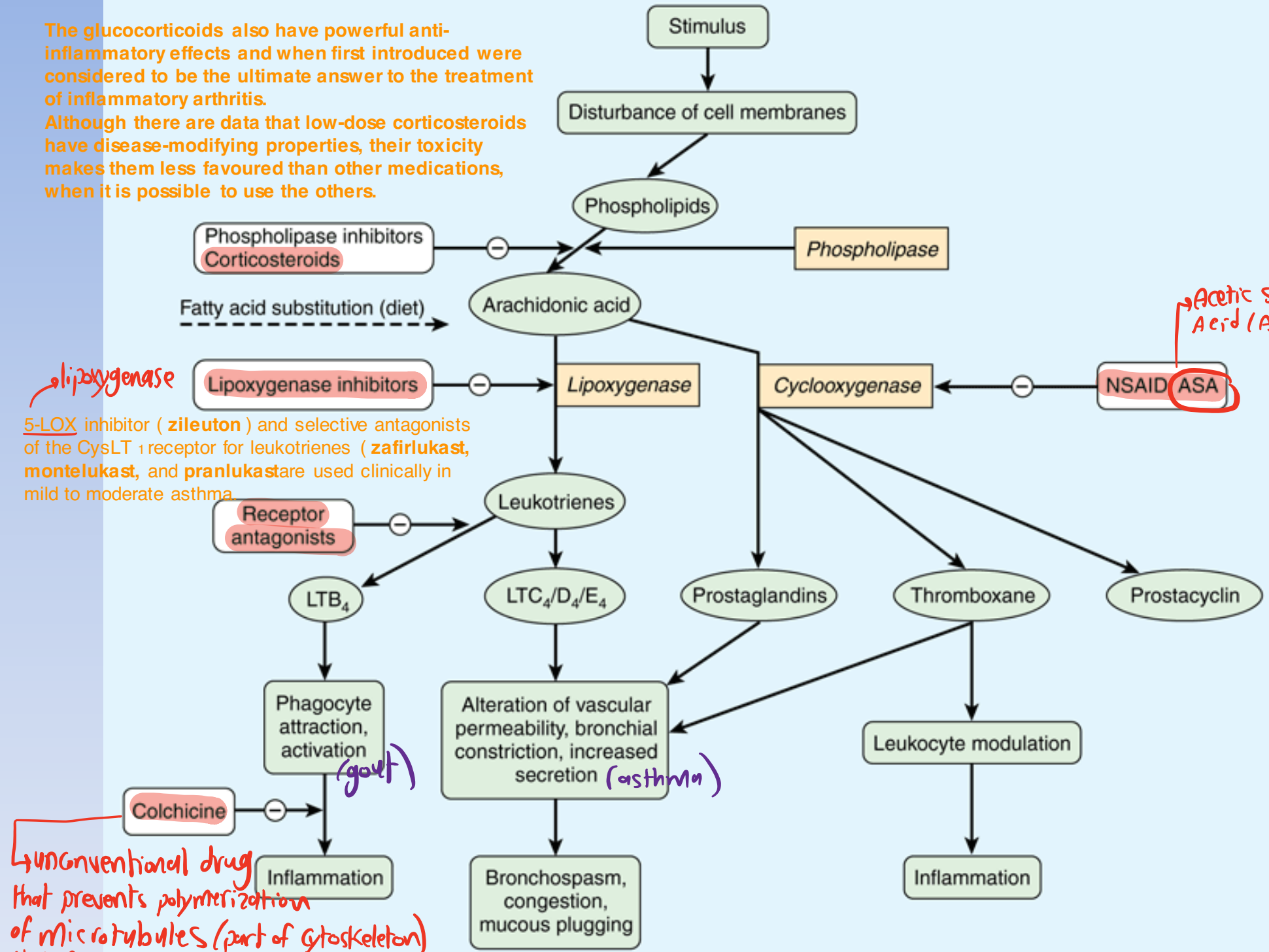
| Feature | Narcotic (Opioids) | Nonnarcotic (nonopioid) |
|---|---|---|
| Efficacy | Strong | Weak (But good enough to relief pain) |
| Prototype | Morphine | Aspirin |
| Pain Relieved | Any Type | Musculoskeletal (Muscles, joints) |
| Site of Action | Central | Peripheral and Central (at the site of inflammation) |
| Mechanism | Specific Receptors (opioid receptors) | PG Synthesis (by targetting COX enzymes) |
| Danger (Side effects) | Tolerance & Dependence (have to be prescribed by a doctor) | G.I irritation (can cause peptic ulcer or only a little discomfort according to how much you tolerate this drug, or how you use it) |
| Anti-inflammatory | No | Yes |
| Antipyretic خافض حرارة | No | Yes |
| Antiplatelets مضاد للتخثر | 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.

producing edema

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.



[1] A stimulus like dust in the air works as an antigen that interacts with certain proteins on the surface of our immune cells causing

[2] Disturbance of cell membranes, this cell membrane releases

[3] phospholipids, action site for an enzyme called phospholipase A2 that converts it into

[4] Arachidonic acid goes into 2 pathways

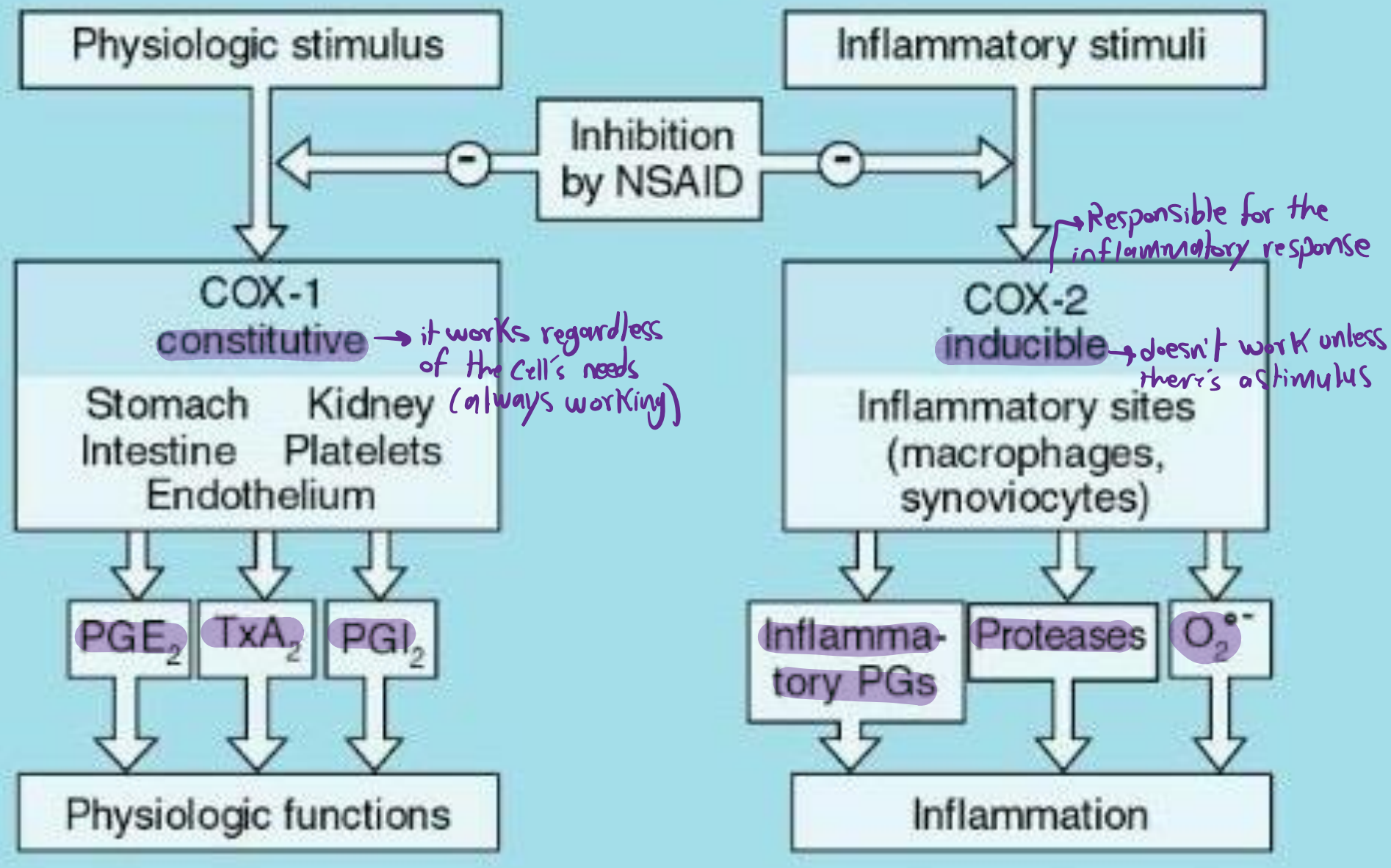
inhibited by Corticosteroids
- They inhibit the production of Arachidonic acid
- They thought to be the ultimate treatment for chronic inflammatory conditions
- They have lot of side effects as they cause immuno suppression increasing risk of infection, and they cause pituitary adrenal axis suppression.
- They also have side effects on metabolism as they cause increase in the fat deposition (Moon face, buffalo hump)

(A) lipoxygenase pathway produces leukotrienes that are important in asthma and gout pathogenesis (look at their effects in the previous slide)

inhibited by 5-LOX inhibitors (zileuton) OR CysLT blockers (the lukasts)

(B) Cyclooxygenase pathway produces PG, Thromboxane, $PGI_2$ that have a role in inflammation by leukocyte modulation

inhibited by NSAIDs mainly aspirin


Physiologic stimulus
Inflammatory stimuli
Inhibition by NSAID
COX-1
constitutive
it works regardless of the cell's needs (always working)
Stomach
Kidney
Intestine
Platelets
Endothelium
COX-2
inducible
doesn't work unless there's a stimulus
Responsible for the inflammatory response
Inflammatory sites (macrophages, synoviocytes)
$PGE_2$
$TxA_2$
$PGI_2$
Inflamma-tory PGs
Proteases
$O_2^{\bullet -}$
Physiologic functions
Inflammation

# 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. (Aspirin has higher selectivity for COX-1)

# NSAIDs

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

in the degree of these activities, that's why we need different doses of each

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

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

**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 |

NOT required

just notice the different doses required that indicate how their efficacy differ

Must be taken every 4 hours ← Ibuprofen

Must be taken once a day (More convenient) ← Piroxicam

## Non-steroidal anti-inflammatory drugs (NSAIDs)

pain

fever

Inflammation

**By inhibition of cyclo-oxygenase enzymes COX1 & COX2.**

How do they prevent inflammation?

# 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.
(which are important in chemotactic action)

(3) Accumulation of inflammatory cells is also reduced.

# NSAIDs

How do they relief pain?

**An analgesic effect:**

- Decreased prostaglandin generation means decrease sensitivty of **nociceptive** nerve endings to inflammatory mediators. (So basically it increases threshold of pain)
  - relating to the perception or sensation of pain
  - bradykinin, histamine
- Relief of **headache** is due to decreased prostaglandin-mediated vasodilatation.
  - stimulate headache by causing tension on certain arterial receptors

## **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

# Antipyretic Effects

- The antipyretic due primarily to the blockade of **prostaglandin** synthesis at the thermoregulatory centers in the hypothalamus and at peripheral target sites.

where they elevate the set-point

**Antipyretic action:**

- Fever occurs when the set-point of the anterior hypothalamic thermoregulatory center is elevated by PG
- > impeding PGE2 synthesis and release > resets the hypothalamus toward normal
- it rapidly lowers the body temperature of febrile patients by increasing heat dissipation as a result of peripheral vasodilation and sweating.
- Aspirin has no effect on normal body temperature.

# How Infection/Inflammation Causes Fever

***Bacteria***

releases

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

E. Coli
Klebsiella

S. aureus
S. pyogenes

activates

Toll-like & MHC receptors

***corticosteroids***

***Leukocytes***
***(monocytes, macrophages)***

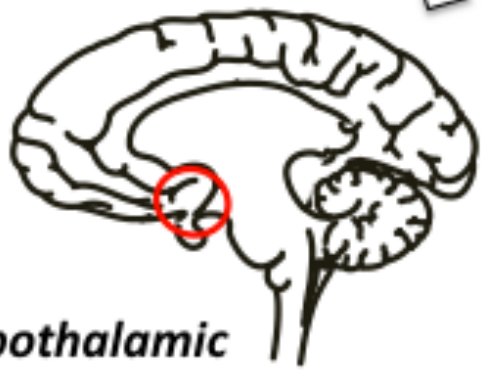
releases

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

(The most important cytokines involved in elevation of body temp)

pyrogens = agents that produces fever

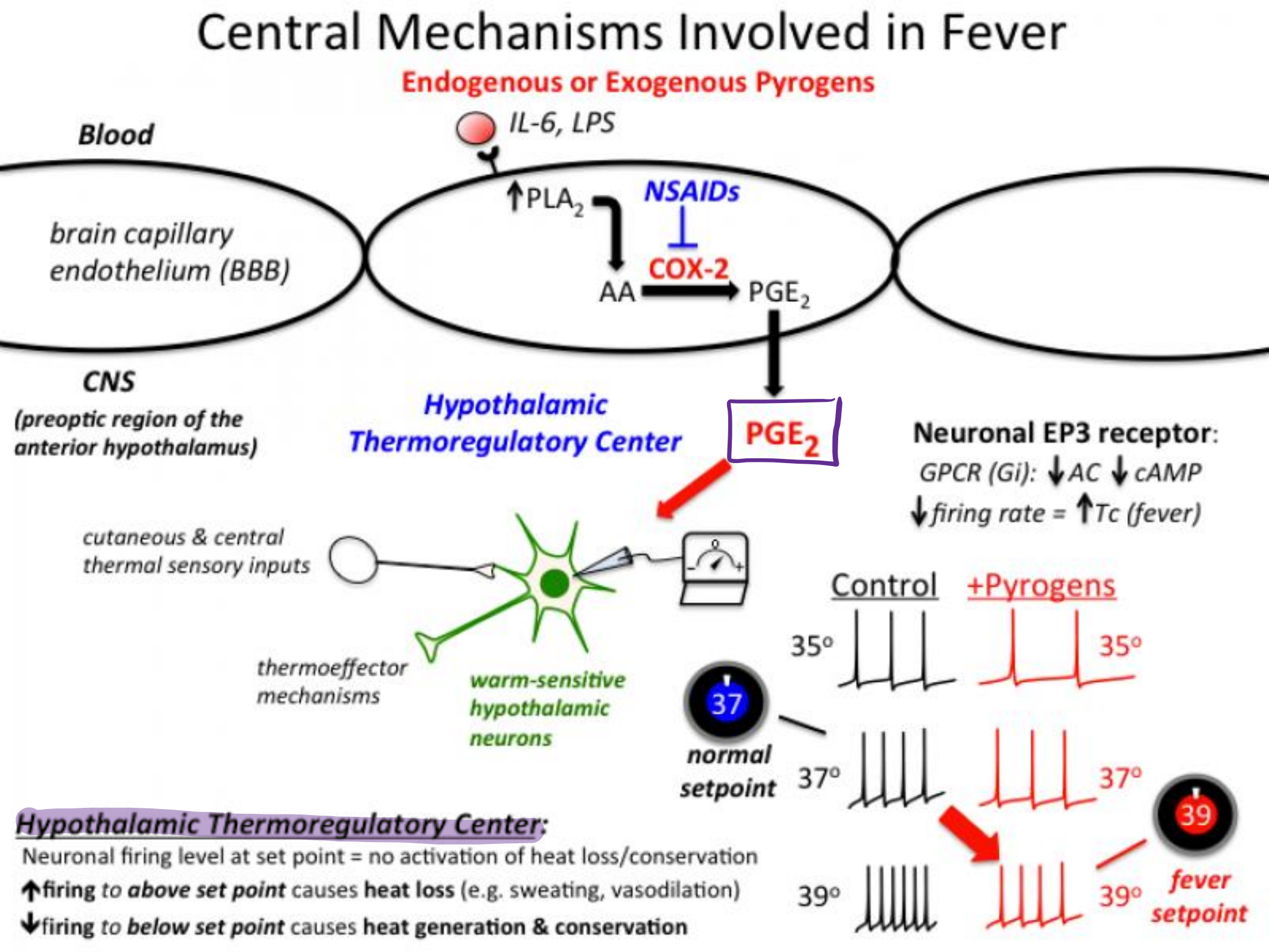
target



***Hypothalamic Thermoregulatory Center***

causing resetting of the body temp

# Central Mechanisms Involved in Fever




**Hypothalamic Thermoregulatory Center:**

Neuronal firing level at set point = no activation of heat loss/conservation

↑**firing** *to* ***above set point*** causes **heat loss** (e.g. sweating, vasodilation)

↓**firing** *to* ***below set point*** causes **heat generation & conservation**

# Aspirin (its chemical name is Salicylic 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

  → it binds to the enzyme until the body synthesize another one

- 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. + antiplatelet effect Since it's a selective inhibitor of COX-1 that prevents the production of TXA which is responsible for platelet agregation

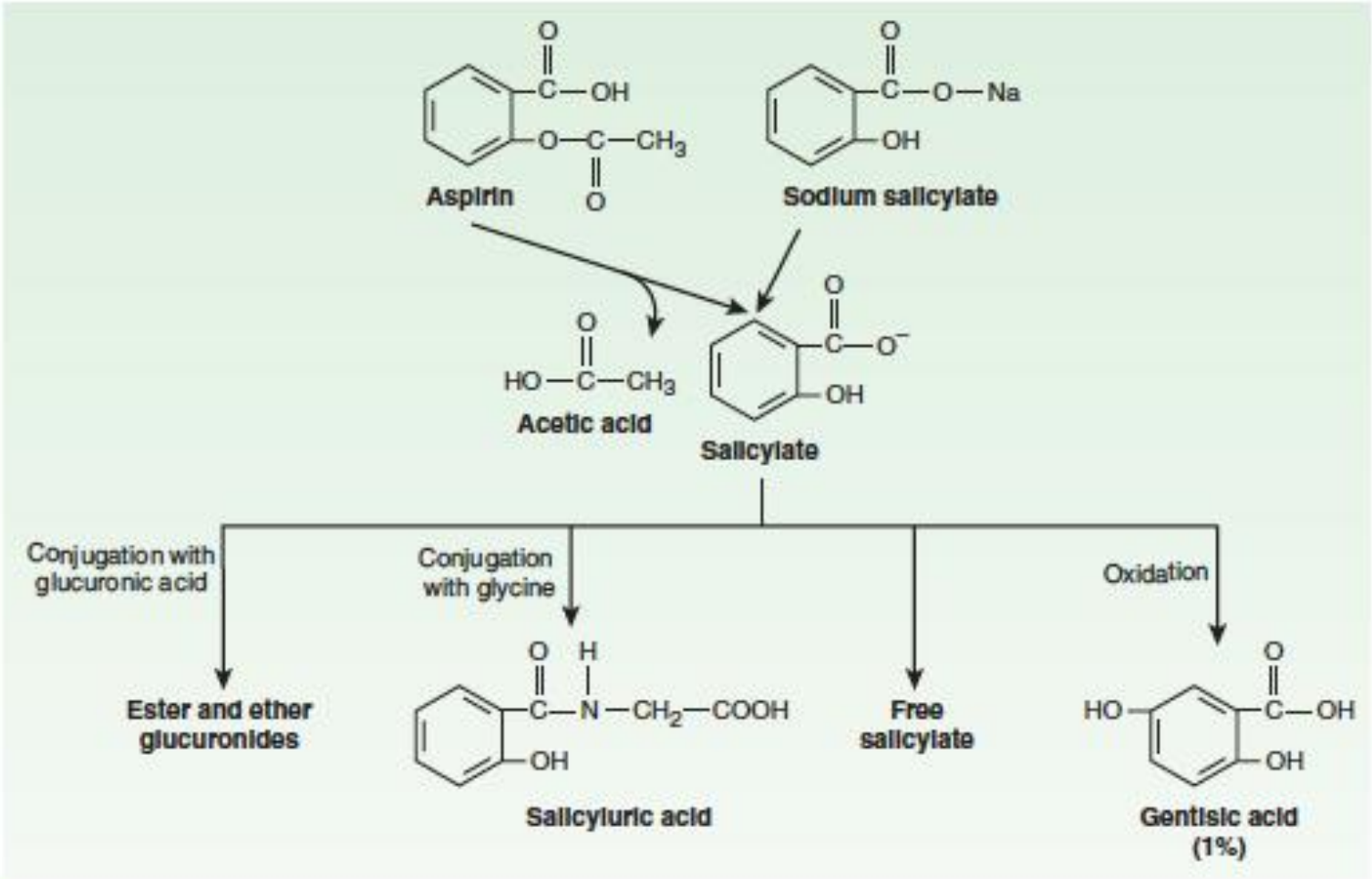



**FIGURE 36–3** Structure and metabolism of the salicylates. (Modified and reproduced, with permission, from Meyers FH, Jawetz E, Goldfien A: *Review of Medical Pharmacology*, 7th ed. McGraw-Hill, 1980.)

**Respiratory actions:**

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

So why NSAIDs are not recommended for asthmatic patients ?

inhibition of COX pathway of AA metabolism ⟶ Shift to LOX pathway

⟶ increased production of leukotrienes ⟶ increased asthmatic manifestations.

# 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.

**Gastrointestinal effects:** (Side effects)

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

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

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

given in combination with aspirin

prototype

This pump mediate gastric acid secretion

**Effect on platelets:** they're not real cells, they don't have a nucleus

The plasma half-life of aspirin is only 20 minutes; however, because platelets cannot generate new COX, the effects of aspirin last for the duration of the life of the platelet

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.

low dose of aspirin is needed for the anti-platelet effect, because it's highly selective for COX-1

(Recently, there's cautions on the use of high doses of NSAIDs because they might cause thrombosis)

**Actions on the kidney:** (Side effects)

Can cause permenant kidney damage if taken chronically, or if taken by susceptible patients

- 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.

# 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

Because PG causes contraction of the uterus

# Adverse effects

1. **Gastrointestinal**:

Discomfort in the upper abdomen, can progress to an ulcer

- The most common GI effects of the salicylates are **epigastric distress**, nausea, and vomiting.
- Microscopic **GI bleeding** is almost universal in patients treated with salicylates.
- At stomach pH, aspirin is uncharged; consequently, it readily crosses into mucosal cells, where it ionizes (becomes negatively charged) and becomes trapped, thus potentially causing **direct damage to the cells.**

② **Hypersensitivity: Approximately 15 percent of patients taking *aspirin experience hypersensitivity reactions.***

- Symptoms of true allergy include urticaria, bronchoconstriction, or angioedema. Fatal anaphylactic shock is rare.

③ **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.
  → NOT A Causative
- This is especially encountered in children, who therefore should be given acetaminophen instead of aspirin

# Reye's syndrome

- Reye's syndrome is a potentially fatal disease that has numerous detrimental effects to many organs, especially the brain and liver, as well as causing a lower than usual level of blood sugar (hypoglycemia) The classic features are a rash, vomiting, and liver damage. The exact cause is unknown and, while it has been associated with aspirin consumption by children with viral illness, it also occurs in the absence of aspirin use.

specifically with salicylate ingestion

That's why we usually give children with viral illness paracetamol rather than aspirin or salicylate-containing drugs

# Drug interactions:

- Salicylate is 90 to 95 percent protein bound and can be displaced from its protein-binding sites, resulting in increased concentration of free salicylate

- alternatively, aspirin could displace other highly protein-bound drugs, such as **warfarin**, **phenytoin**, or **valproic** acid, resulting in higher free concentrations of the other agent .

  → Can cause toxicity of those drugs

- Concomitant use of **ketorolac** and aspirin is contraindicated because of increased risk of GI bleeding and platelet aggregation inhibition.

  The use of them at the same time

# Toxicity: (overdoes or oversusceptability)

**The mild form is called salicylism**

- nausea, vomiting, marked hyperventilation (→ rapid or deep breathing ⇒ low levels of $CO_2$ and $HCO_3$), headache, mental confusion, dizziness, and tinnitus (ringing or roaring in the ears).

Aspirin has a direct effect on the respiratory center in the brain leading to hyperventilation. The body responds to hyperventilation by having the kidneys produce more bicarbonate and excrete more potassium which leads to an elevated anion gap metabolic acidosis.

In serious cases, mandatory measures include the intravenous administration of **fluid**, **dialysis** correction of **acid-base** and electrolyte balances.

# *Propionic acid derivatives*

(Don't memorize chemical groups, just the name of the drug)

**Ibuprofen , naproxen, fenoprofe, ketoprofen , flurbiprofen**

- All these drugs possess anti-inflammatory, analgesic, and antipyretic activity
- their **GI** effects are generally less intense than those of aspirin.
- These drugs are **reversible** inhibitors of the cyclooxygenases

- All are well **absorbed** on oral administration and are almost totally bound to serum **albumin**.
- They undergo **hepatic** metabolism and are excreted by the **kidney**.
- The most common adverse effects are **GI**, ranging from dyspepsia to bleeding.
- Side effects involving the central nervous system (**CNS**), such as headache, tinnitus, and dizziness, have also been reported.

# Naproxen and Ibuprofen

- Pregnancy : category C, category D 3rd trimester

Category C : Risk of this drug can't be ruled out because there's no satisfactory studies on human

during 1st and second trimester

(So it's better to use paracetamol)

- Increase the risk of cardiovascular thrombotic event, MI and stroke.

Category D : positive evidence of human fetal risk

- Increase risk of GI bleeding.

- Ibuprofen not exceed 3200mg/day., and take with food or with water to avoid GI effect.

# *Acetic acid derivatives*

**indomethacin , sulindac , Etodolac**

- Despite its potency as an anti-inflammatory agent, the **toxicity** of **indomethacin** limits its use to the treatment of acute gouty arthritis, ankylosing spondylitis .
- The adverse reactions caused by **sulindac** are similar to, but less severe than, those of the other NSAIDs, including indomethacin.
- **Etodolac** has effects similar to those of the other NSAIDs

# *Oxicam derivatives*

***Piroxicam*** *and* ***meloxicam***

- *are used to treat RA, ankylosing spondylitis, and* osteoarthritis.
- They have **long half-lives**, which permit once-daily administration, and the parent drug as well as its metabolites are renally excreted in the urine.
- ***Meloxicam*** *inhibits both COX-1 and COX-2, with preferential binding for COX-2,* and at low to moderate doses shows less GI irritation than *piroxicam.*

# *Fenamates*

Just know it causes hemolytic anemia

***Mefenamic***

- *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.
- Cases of hemolytic anemia have been reported

# *Heteroaryl acetic acids*

voltaren, volt fast

- ***Diclofenac and tolmetin , ketorlac***
- *are approved for long-term use in the treatment of RA,* osteoarthritis.
- ***Diclofenac*** *is more potent than indomethacin or naproxen.*
- *An* ***ophthalmic*** preparation is also available.
- *Diclofenac accumulates in synovial fluid, and the primary route of excretion for the* drug and its metabolites is the **kidney**.

# Diclofenac sodium (Voltaren)

- Used PO 50mg after food, I.M. inj 75mg
- (Diclofenac potassium) (volt fast) is prompt release and has quicker onset where as the Diclofenac sodium is delayed release.
- Toxicity similar to others

# Acetaminophen

- works centrally
- inhibits PG synthesis
- less anti-inflammatory effect

- Acetaminophen inhibits prostaglandin synthesis in the **CNS**.
- This explains its antipyretic and analgesic properties.
- Acetaminophen has less effect on cyclooxygenase in peripheral tissues, which accounts for its **weak** anti-inflammatory activity. (That's why it's not an NSAID)
- 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 **gastric** complaints, those in whom prolongation of **bleeding** time would be a disadvantage, or those who do not require the anti-inflammatory action of aspirin.

  caused by aspirin

  - it's also used during pregnancy (category A)

- Acetaminophen is the analgesic/antipyretic of **choice** for **children** with viral infections or chickenpox (recall that aspirin increases the risk of **Reye's** syndrome).

## Adverse effects (an overdose can cause liver toxicity)

- With normal therapeutic doses, acetaminophen is virtually free of any significant adverse effects. Maximum dose is 4g (8 pills) per day
- Renal tubular necrosis and hypoglycemic coma are rare complications of prolonged, large-dose therapy.
- large doses Hepatic necrosis, a very serious and potentially life-threatening condition can result.
- Renal tubular necrosis may also occur.
- Periodic monitoring of liver enzymes tests is recommended for those on high-dose acetaminophen.

# Paracetamol = Acetaminophen

- **Weak PG synthesis inhibitor**
- **CNS actions:** Paracetamol also modulates the endogenous cannabinoid system
- **<u>Not:</u>**
  - **antiinflammatory** doesn't work peripherally
  - **Platelets inhibitor**
  - **Ulcerogenic** suitable for patient with gastric complaints
  - **Teratogenic** suitable during pregnancy "category A"

## Pharmacokinetics

- Acetaminophen is rapidly **absorbed** from the GI tract. A significant first-pass metabolism occurs in the **luminal** cells of the intestine and in the **hepatocytes**.

- Under normal circumstances, acetaminophen is conjugated in the **liver** to form inactive metabolites.

- A portion of acetaminophen is hydroxylated to form **N-acetylbenzoiminoquinone** a highly reactive and potentially dangerous metabolite .

→ which causes hepatic necrosis if accumulated

- At normal doses of acetaminophen, the N-acetylbenzoiminoquinone reacts with the sulfhydryl group of **glutathione**, forming a nontoxic substance .

- Acetaminophen and its metabolites are excreted in the urine.

# Paracetamol

- **Toxicity**
  - **Severe hepatotoxicity with high doses**
  - **N- acetylcysteine is the antidote when given in the first 24hours.**

## Cyclooxygenase II Inhibitors: Celocoxib

- Inhibit prostaglandin synthesis by the COX-2 isozyme induced at sites of inflammation without affecting the action of the constitutively active “housekeeping” COX-1 isozyme found in the GI tract, kidneys, and platelets.

- COX-2 is constitutively active within the kidney, recommended doses of COX-2 inhibitors cause renal toxicities similar to those associated with traditional NSAIDs

Because COX-1 (that produces TXA) takes over after inhibiting COX-2 pathway

Clinical data have suggested a higher incidence of cardiovascular thrombotic events associated with COX-2 inhibitors such as rofecoxib and valdecoxib,
resulting in their withdrawal from the market.

# Celecoxib

a selective COX-2 inhibitor—about 10–20 times more selective for COX-2 than for COX-1.

It interacts occasionally with warfarin—as would be expected of a drug metabolized via CYP2C9