Nonsteroidal Anti-inflammatory Drugs (NSAIDs) and Analgesics

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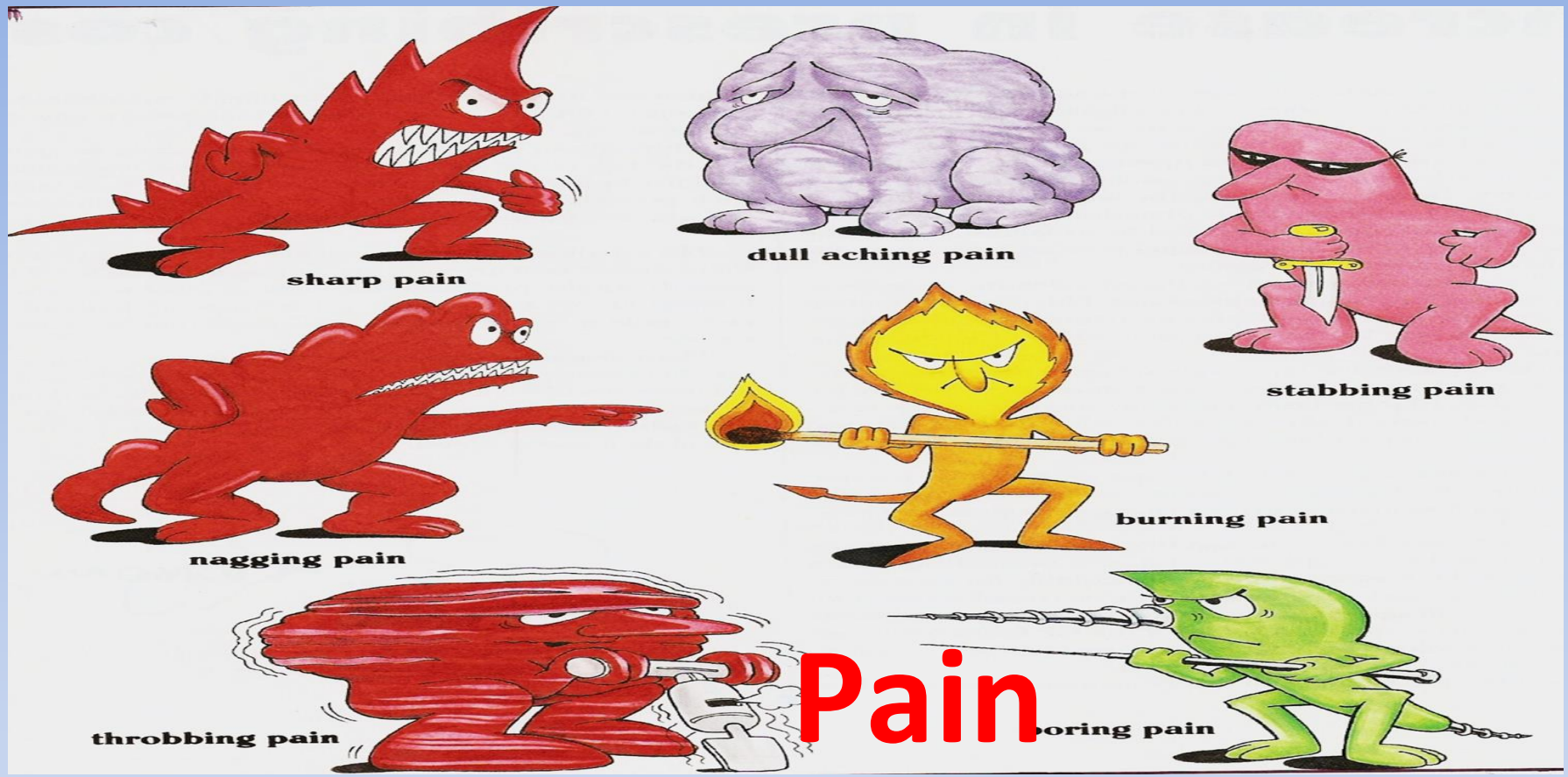


- Universal, Complex, Subjective experience
- No. 1 Reason people take medications
- Generally is related to some type of tissue damage and serves as a warning signal

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

- The non-steroidal anti-inflammatory drugs (NSAIDs (
- Paracetamol = acetaminophen
- Opioid drugs

Comparison of Analgesics

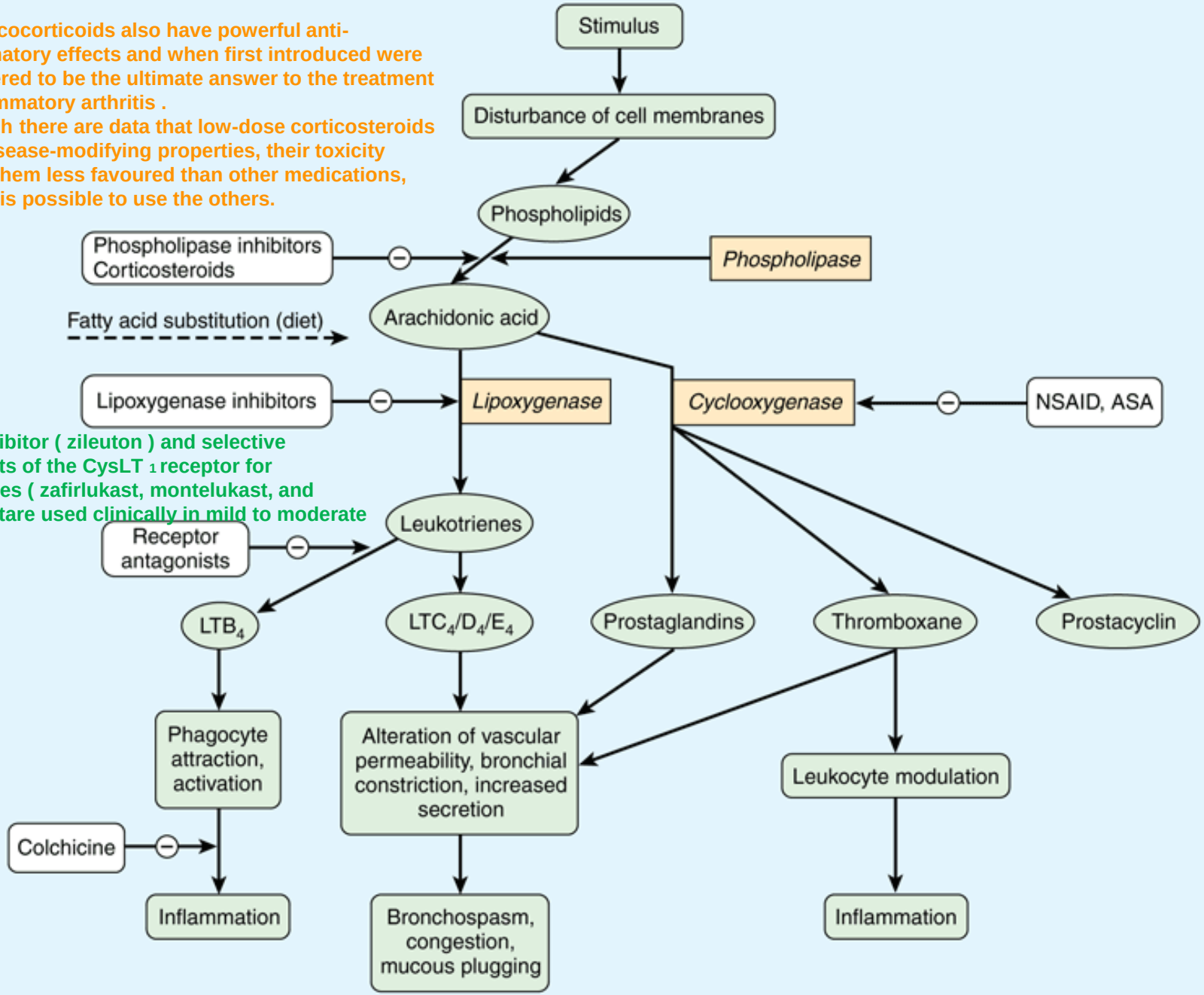
Feature	Narcotic (Opioids (	Nonnarcotic (nonopioid (
Efficacy	Strong	Weak
Prototype	Morphine	Aspirin
Pain Relieved	Any Type	Musculoskeletal
Site of Action	Central	Peripheral and Central
Mechanism	Specific Receptors	PG Synthesis
Danger	Tolerance & Dependence	G.I irritation
Anti-inflammatory	No	Yes
Antipyretic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

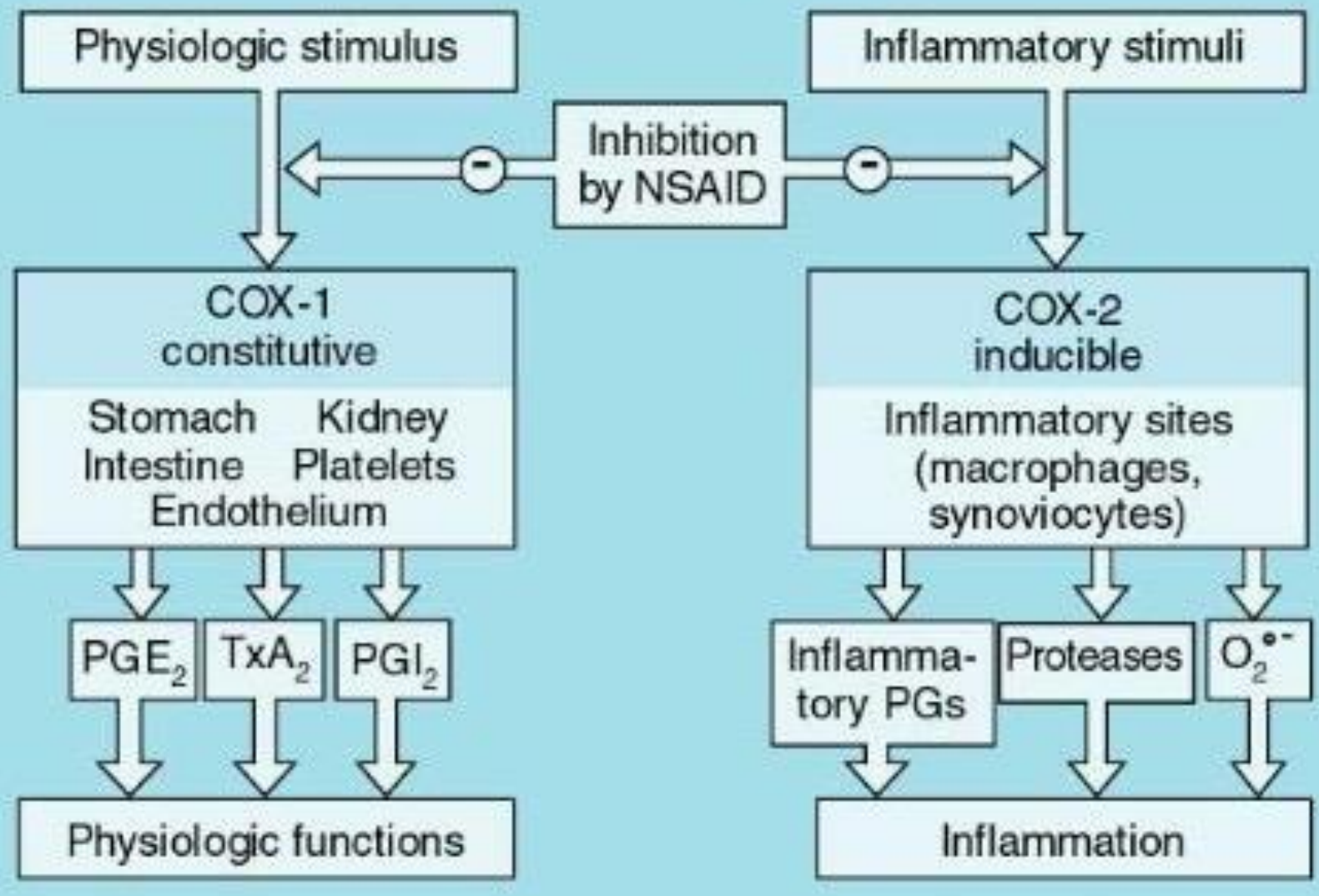
Inflammatory pathways

- 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.

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.




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

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.

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.

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

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:

- Decreased prostaglandin generation means decrease sensitivty of **nociceptive** nerve endings to inflammatory mediators.

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

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.

Antipyretic Effects

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

Antipyretic action:

- 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.

How Infection/Inflammation Causes Fever

Bacteria

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

E. Coli
Klebsiella

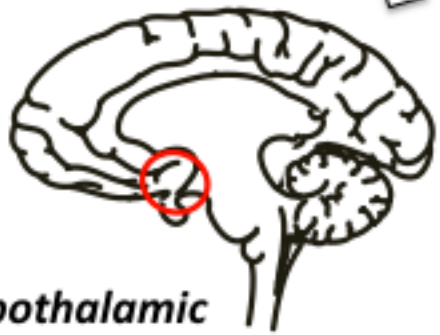
S. aureus
S. pyogenes

Toll-like & MHC receptors

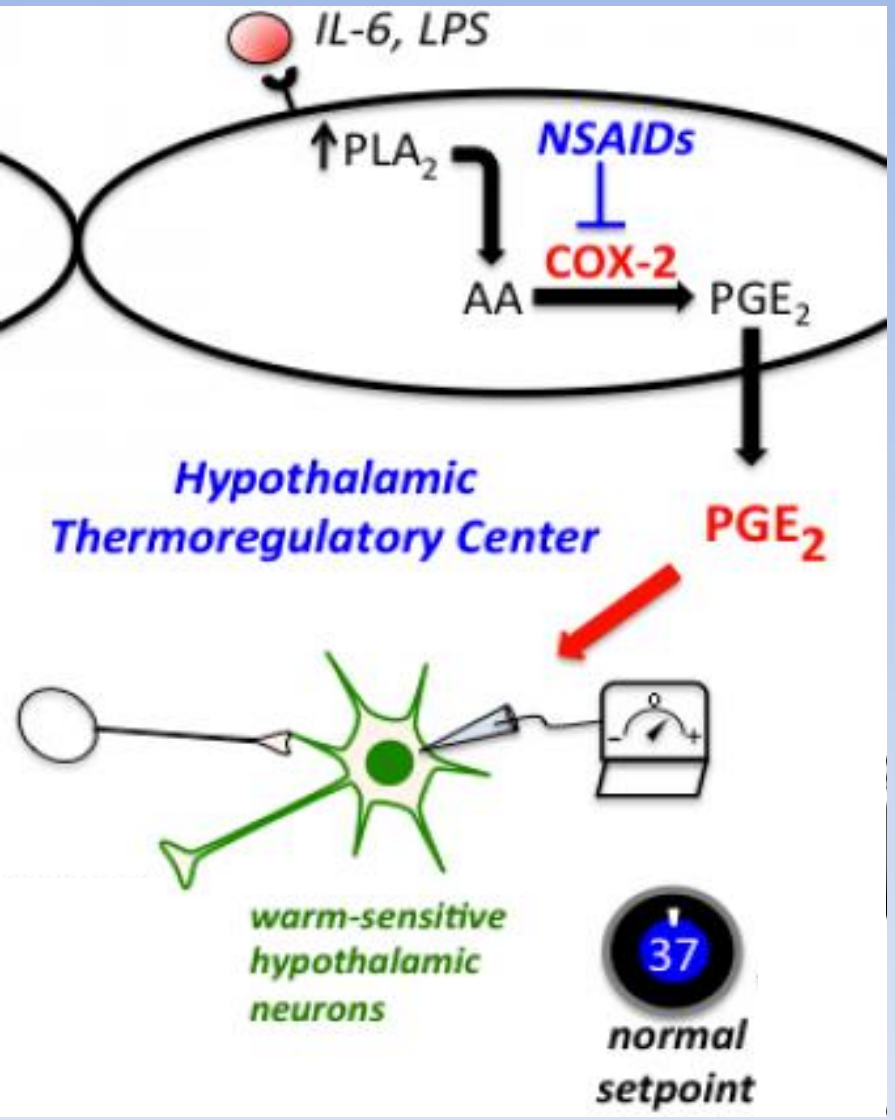
corticosteroids

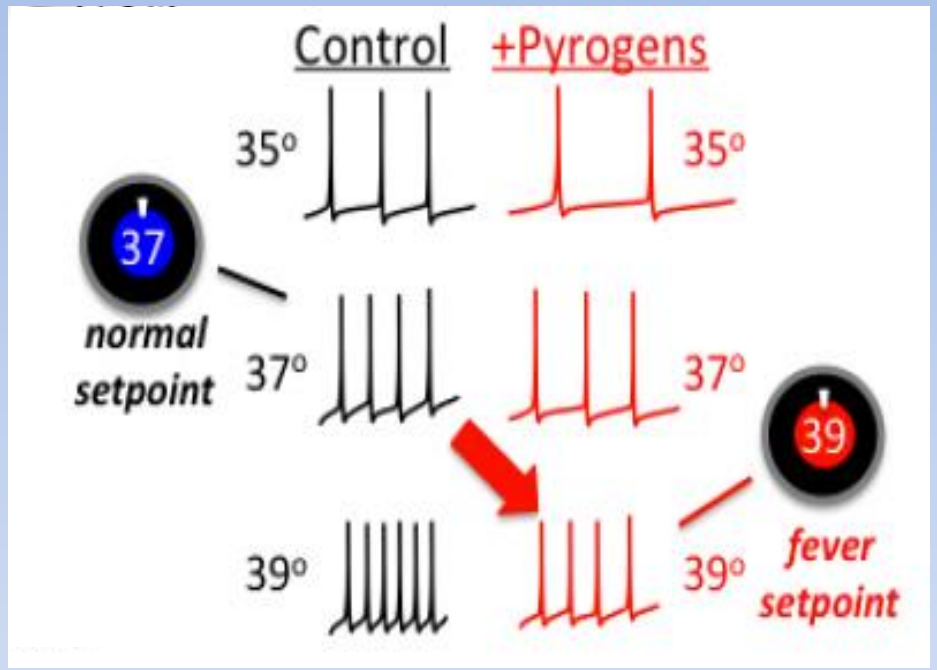
Leukocytes
(monocytes, macrophages)

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



Hypothalamic
Thermoregulatory Center


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


Control
+Pyrogens
35°
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39°
fever
setpoint

Aspirin

- ✦ 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 .

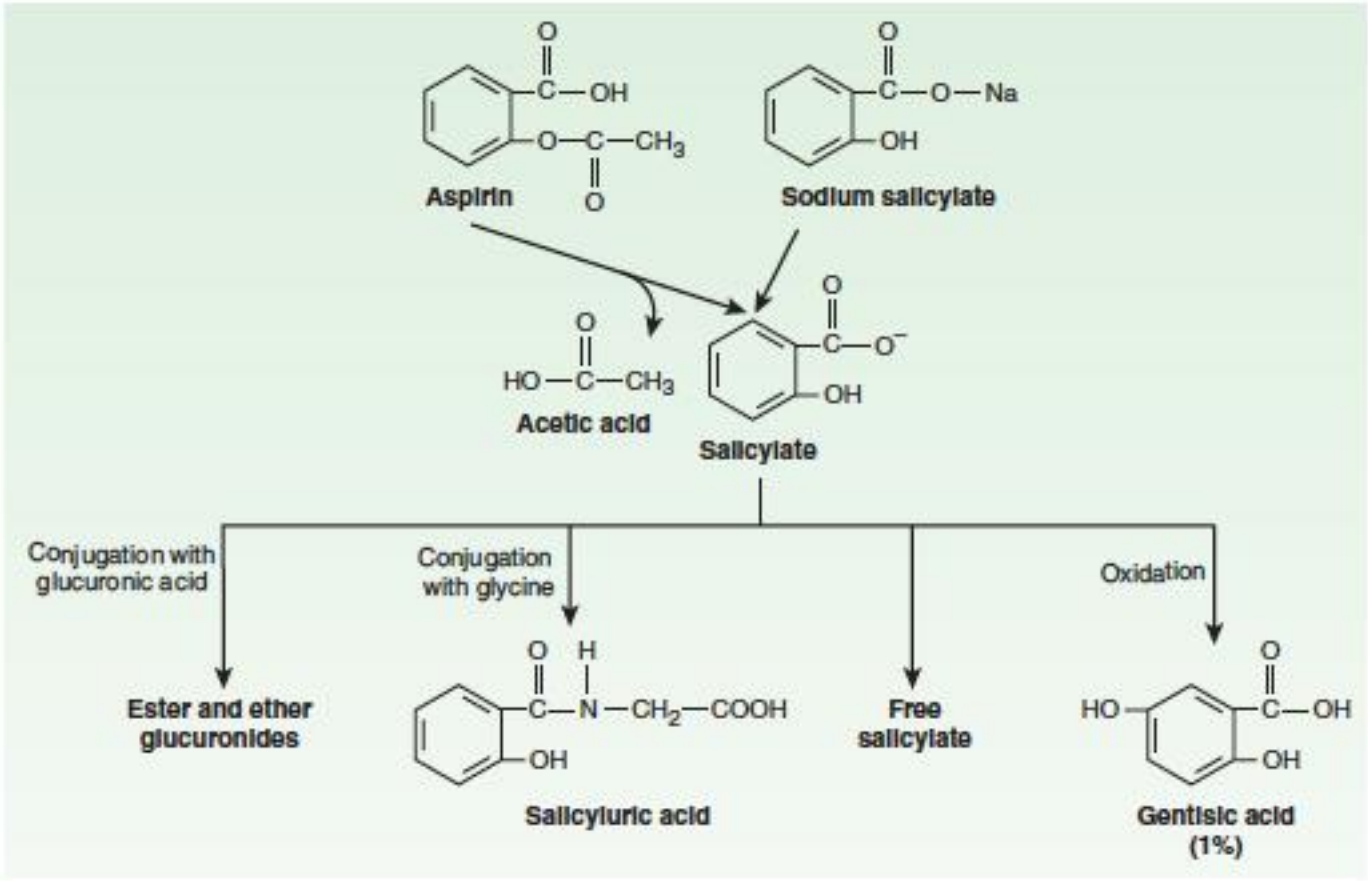


FIGURE 36–3 Structure and metabolism of the salicylates. (Modified and reproduced, with permission, from Meyers FH, Jawetz E, Goldfien A: *Review of Medical Pharmacology*, 7th ed. McGraw-Hill, 1980.)

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.

Gastrointestinal 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 .

- 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.

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

Adverse effects

Gastrointestinal :

- 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.**

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.

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

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.

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 .

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

Toxicity :

The mild form is called salicylism

- nausea, vomiting, marked hyperventilation, 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.

Toxic effects of aspirin on respiratory center

- (1) stimulation of the respiratory center of the brain, leading to hyperpnea and respiratory alkalosis
- (2) uncoupling of oxidative phosphorylation, leading to increased oxygen utilization and glucose demand, increased oxygen utilization and glucose demand, increased glyconeogenesis, and increased heat production
- (3) inhibition of Krebs cycle enzymes, leading to decreased glucose availability and increased organic acids
- (4) alterations in lipid metabolism and amino acid metabolism, enhancing metabolic acidosis
- (5) increased fluid and electrolyte losses, leading to dehydration, sodium depletion, potassium depletion, and loss of buffer capacity.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Drugs	Mechanism of action	Side effect	Other notes
Salicylate • *Aspirin*	• Irreversibly inhibits Cyclooxygenase 1 (COX-1) and COX-2 • Inhibition of COX-2 suppresses prostanoid synthesis providing analgesic, anti-pyretic and anti-inflammatory effects • Aspirin is weakly selective to COX-1	• **Gastrointestinal:** Inhibition of COX-1 causes dyspepsia and if severe gastric bleeding and ulceration • **Rashes:** Morbiliform rash, urticaria, toxic epidermal necrolysis (TEN) • **Acute renal failure** • **Increase blood pressure** • **Reduce effect of anti-hypertensives** (except CCB) • Salicylate poisoning in aspirin overdose (hyperventilation, tinnitus, deafness, vasodilatation)	• Contraindicated in active peptic ulceration, bleeding disorders, children under 16 years (risk of Reye's syndrome), severe cardiac failure
Propionate • *Ibuprofen* • *Naproxen*	• Competitive inhibitors of COX-1 and COX-2 • Both ibuprofen and naproxen are weakly selective to COX-1		• Contraindicated in GI bleed, ulceration, heart failure
Coxibs • *Celecoxib* • *Etoricoxib*	• Competitive inhibitor of COX-2 only at therapeutic dose	• Similar to other NSAIDs • Less gastrointestinal side-effects	• Contraindicated in active GI bleed, ulceration, cerebrovascular disease, inflammatory bowel disease, ischemic heart disease, heart failure, peripheral arterial disease • Monitor blood pressure
Paracetamol	• Exact mechanism unknown but has ability to inhibit COX pathways • Good analgesic and anti-pyretic but poor anti-inflammatory effects	• Paracetamol overdose can cause liver damage • Presents with nausea and vomiting, associated with right subcostal pain and tenderness	

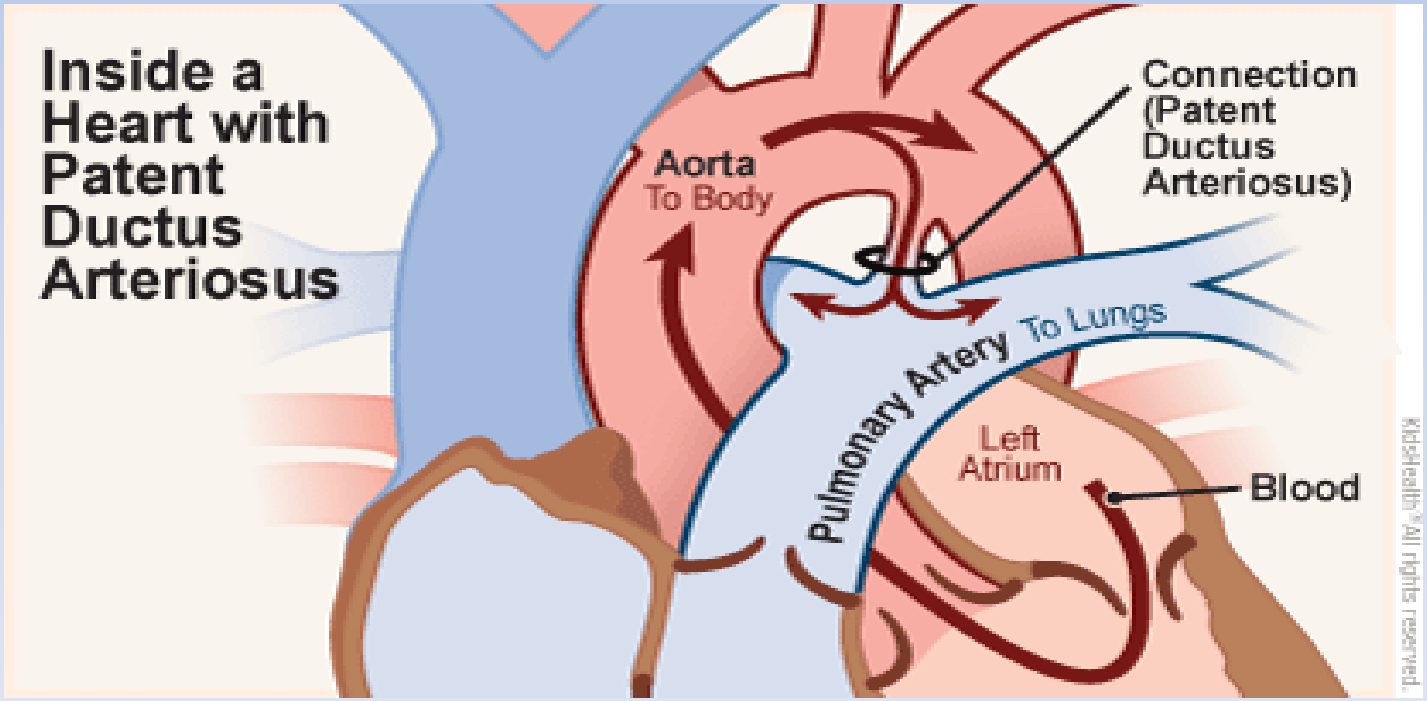
Naproxen and Ibuprofen

- Pregnancy : category C, category D 3rd trimester
- Increase the risk of cardiovascular thrombotic event, MI and stroke.
- 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

- Despite its potency as an anti-inflammatory agent, the **toxicity** of **indomethacin** limits its use to the treatment of acute gouty arthritis, ankylosing spondylitis.



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* .

Diclofenac sodium

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

Acetaminophen

- 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 .
- Acetaminophen does not affect **platelet** function or increase blood clotting time.

Therapeutic uses

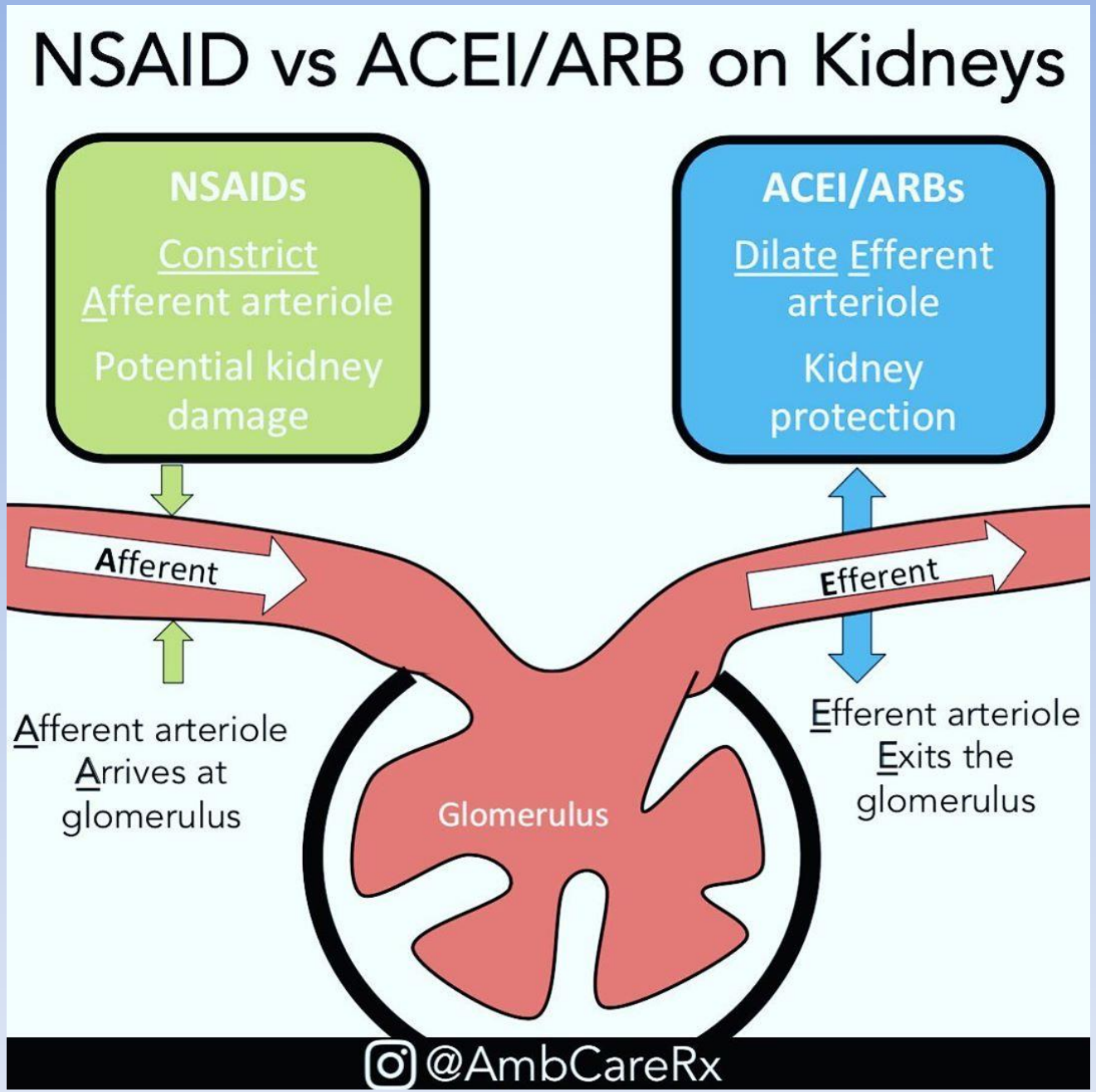
- Acetaminophen is a suitable **substitute** for the analgesic and antipyretic effects of aspirin for those patients with **gastric** complaints, those in whom prolongation of **bleeding** time would be a disadvantage, or those who do not require the anti-inflammatory action of aspirin.

- 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

- With normal therapeutic doses, acetaminophen is virtually free of any significant adverse effects .
- 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.

NSAID vs ACEI/ARB on Kidneys



Paracetamol = Acetaminophen

- **Weak PG synthesis inhibitor**
- **CNS actions:** Paracetamol also modulates the endogenous cannabinoid system
- **<u>Not:</u>**
  - **antiinflammatory**
  - **Platelets inhibitor**
  - **Ulcerogenic**
  - **Teratogenic**

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 .

- 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

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