Terms and Definitions

- **Analgesics:**

drugs used to relieve pain. This derives from Greek *an-, "without",* and *-algia, "pain".*

***Analgesic drugs act in various ways on the peripheral* and central nervous systems; they include the nonsteroidal antiinflammatory drugs (NSAIDs) and opioids.**

- **Anti-inflammatory:**

property of a substance or treatment that reduces inflammation

- **Anti-pyretic:**

prevents or reduces fever by lowering the body temperature from a raised state by acting on the hypothalamus. Will not affect the normal body temperature.

- **Addiction:**

dependence on a substance (alcohol, drugs) to the point that stopping is very difficult and causes severe physical and mental reactions.

Nonsteroidal anti-inflammatory drugs

- Widely used therapeutic agents (Rx and non-Rx forms)
- Inhibit arachidonate cyclooxygenase and thus inhibit production of prostaglandins (PG) and thromboxanes (TX)

– 3 types of cyclooxygenase enzymes:

COX-1: wide spread, constitutive enzyme and important in tissue homeostasis

COX-2: induced in inflammatory cells by inflammatory mediators

COX-3: a splice variant of COX-1 (also referred to as COX-1b or -1v)

– NSAIDS generally inhibit both COX-1 and -2, thus :

COX-1 inhibition: GI distress

COX-2 inhibition: anti-inflammatory effect

– Goal is to develop NSAIDS with a selective action on COX-2

3 main pharmacologic effects of NSAIDS

1. Antipyretic: (lowering of an elevated temperature)

-NSAIDs inhibit PG production in hypothalamus (contains center for normal body temperature regulation) & “reset” temp

-During inflammation IL-1 increase PGE $\rightarrow\uparrow$set point temp.

-COX-2: induced by IL-1 in hypothalamus and $\uparrow$PGE

2. Analgesic effect: (reduction of pain associated with inflammation)

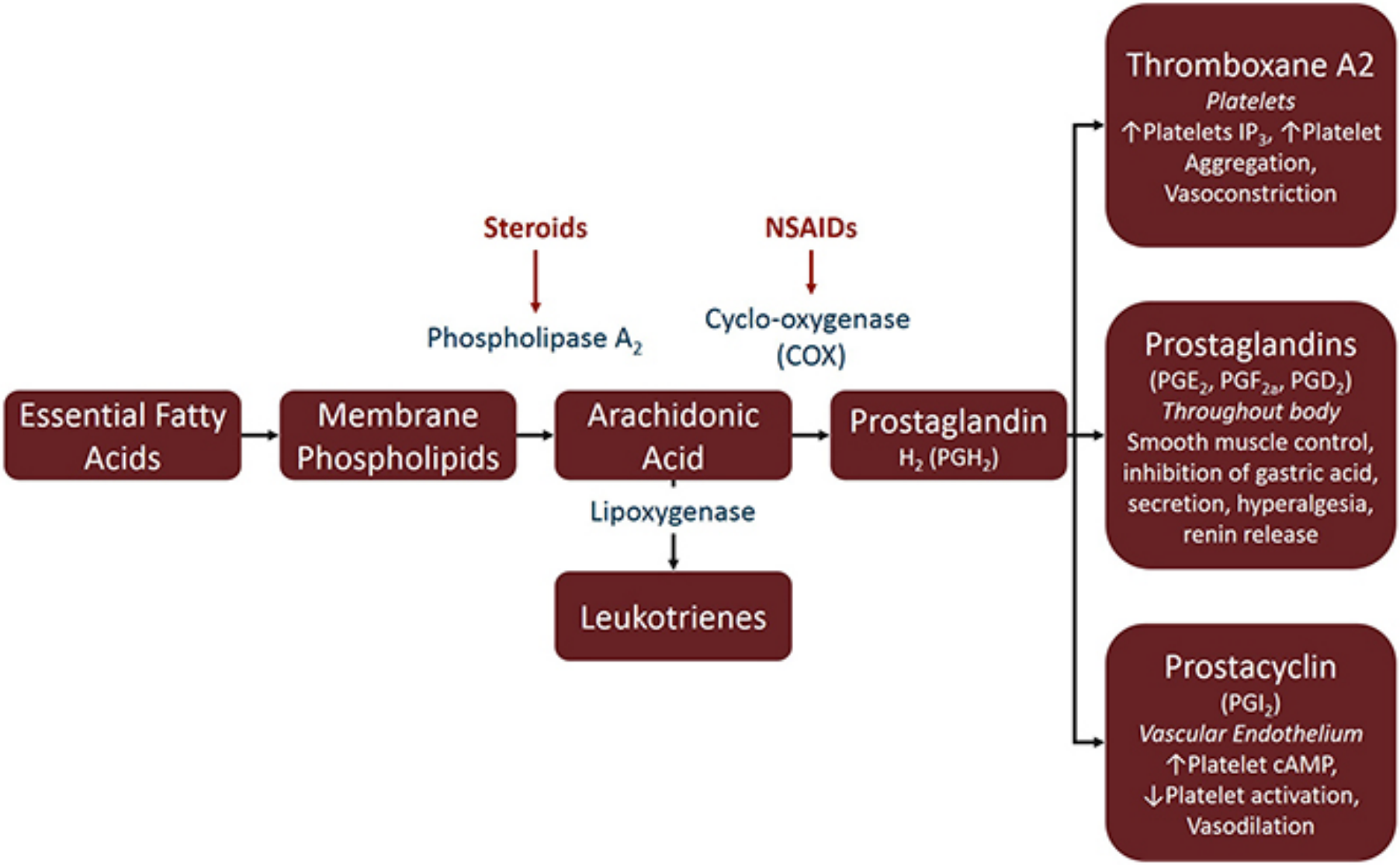
-"PGs that sensitize pain receptors to inflammation mediators

3. Anti-inflammatory: (modification of the reaction)

-Due to action of COX-2 (NSAIDs "PGs and TX syn in inflam.cells)

a. Decrease "vasodilation, cell adhesion & migration, stablizes lysosomes

b. Decrease "vascular permeability and thus "edema


Thromboxane A2
Platelets
↑Platelets IP3, ↑Platelet Aggregation, Vasoconstriction
Steroids
NSAIDs
Phospholipase A2
Cyclo-oxygenase (COX)
Prostaglandins
(PGE2, PGF2a, PGD2)
Throughout body
Smooth muscle control, inhibition of gastric acid, secretion, hyperalgesia, renin release
Essential Fatty Acids
Membrane Phospholipids
Arachidonic Acid
Prostaglandin H2 (PGH2)
Lipoxygenase
Leukotrienes
Prostacyclin
(PGI2)
Vascular Endothelium
↑Platelet cAMP, ↓Platelet activation, Vasodilation

NSAID Classification

Nonselective COX inhibitors

Acetic acid
Diclofenac
Etodolac
Indomethacin
Sulindac
Tolmetin

Fenamate
Meclofenamate
Meclofenamic acid

Naphthylalkanone
Nabumetone

Oxicam
Piroxicam
Meloxicam

Propionic acid
Fenoprofen
Flurbiprofen
Ibuprofen
Ketoprofen
Naproxen
Oxaprozin

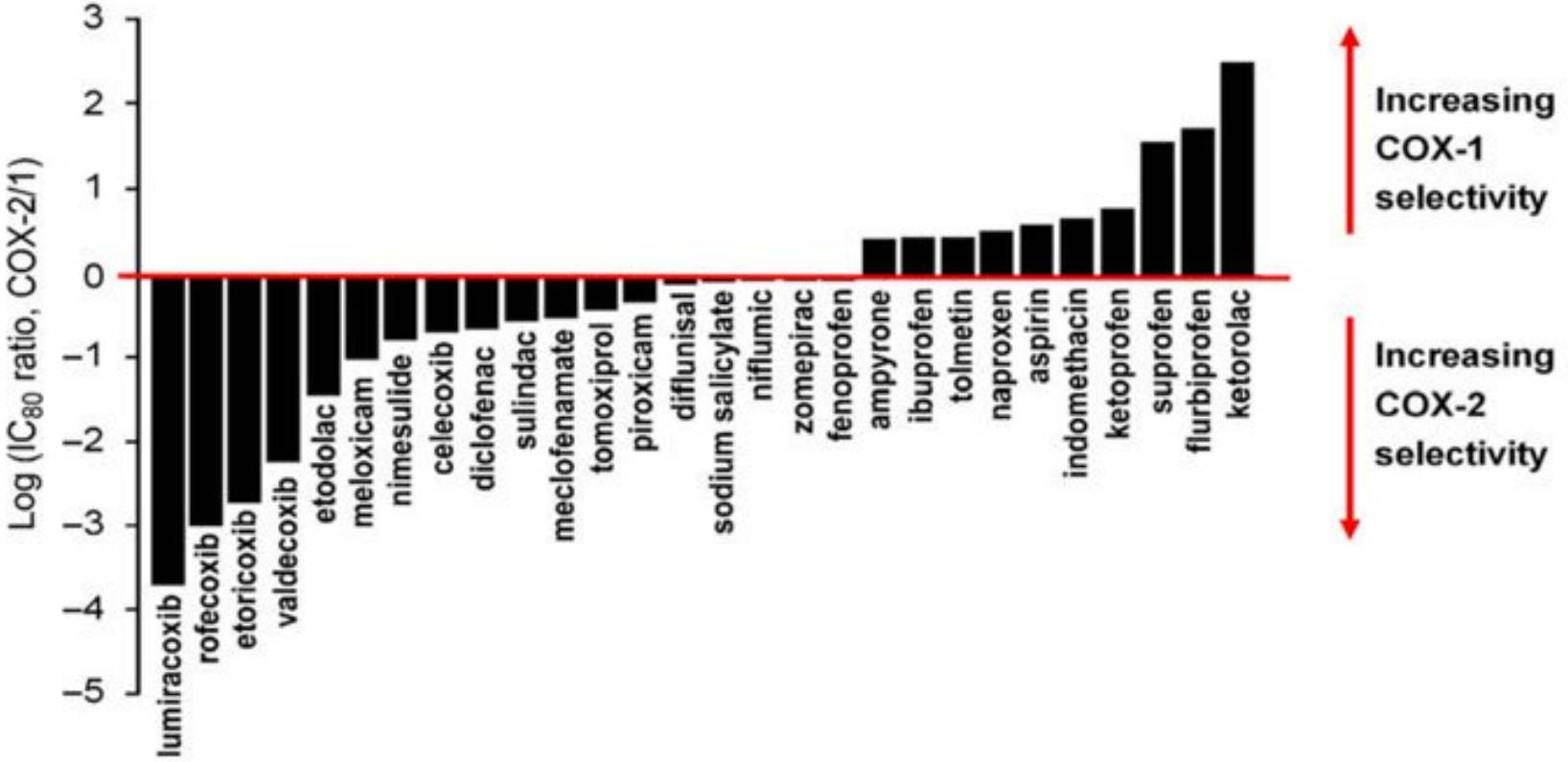
Salicylate
Aspirin
Diflunisal

Choline magnesium trisalicylate
Salsalate

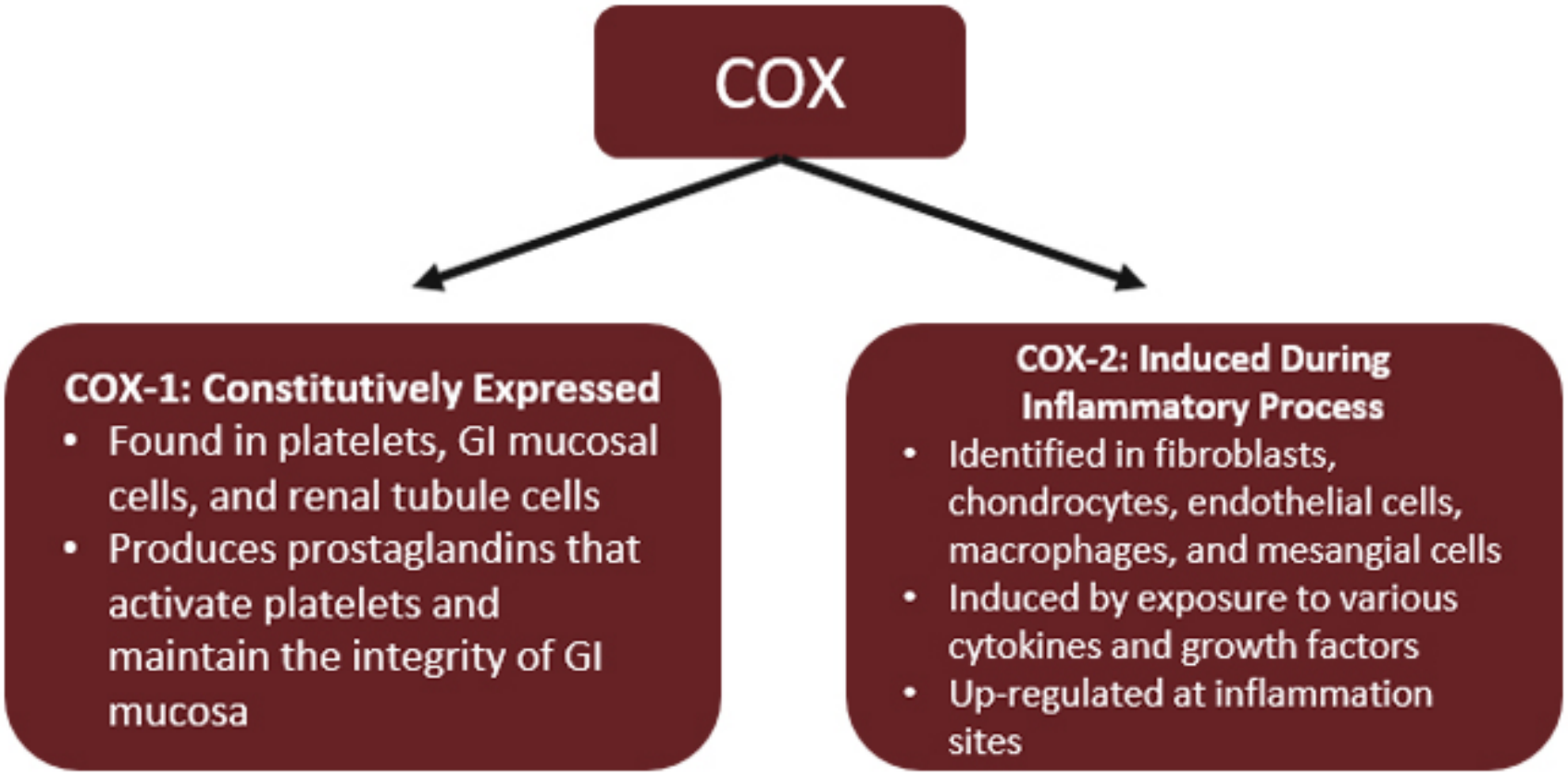
Selective COX-2 inhibitors

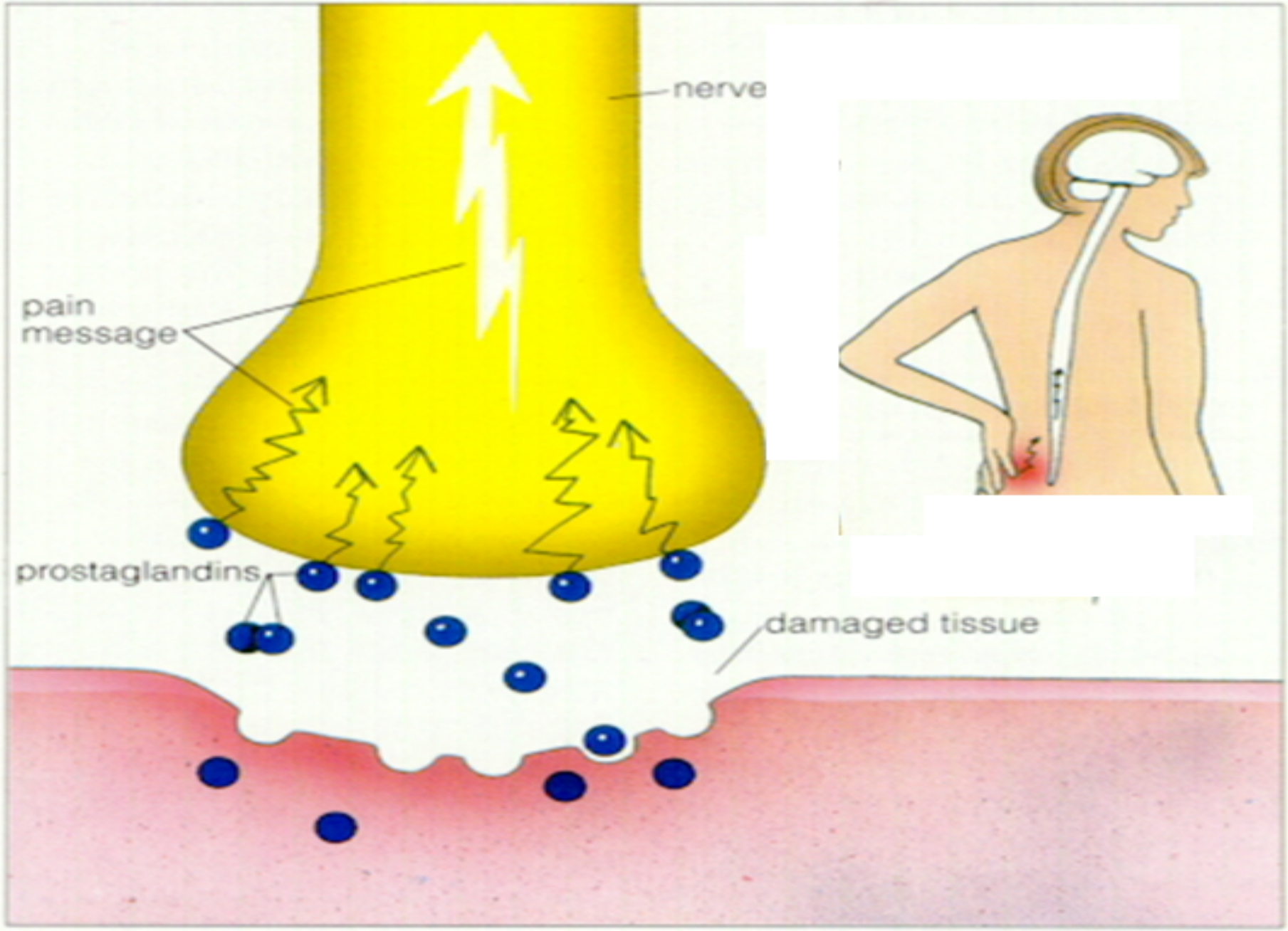
Celecoxib
Rofecoxib

igure 2. Relative COX Selectivity of Non-steroidal Anti-inflammatory Drugs Displayed by the Concentration of the Drugs (IC80) Required to Inhibit COX-1 and COX-2 Activity by 80%[12]

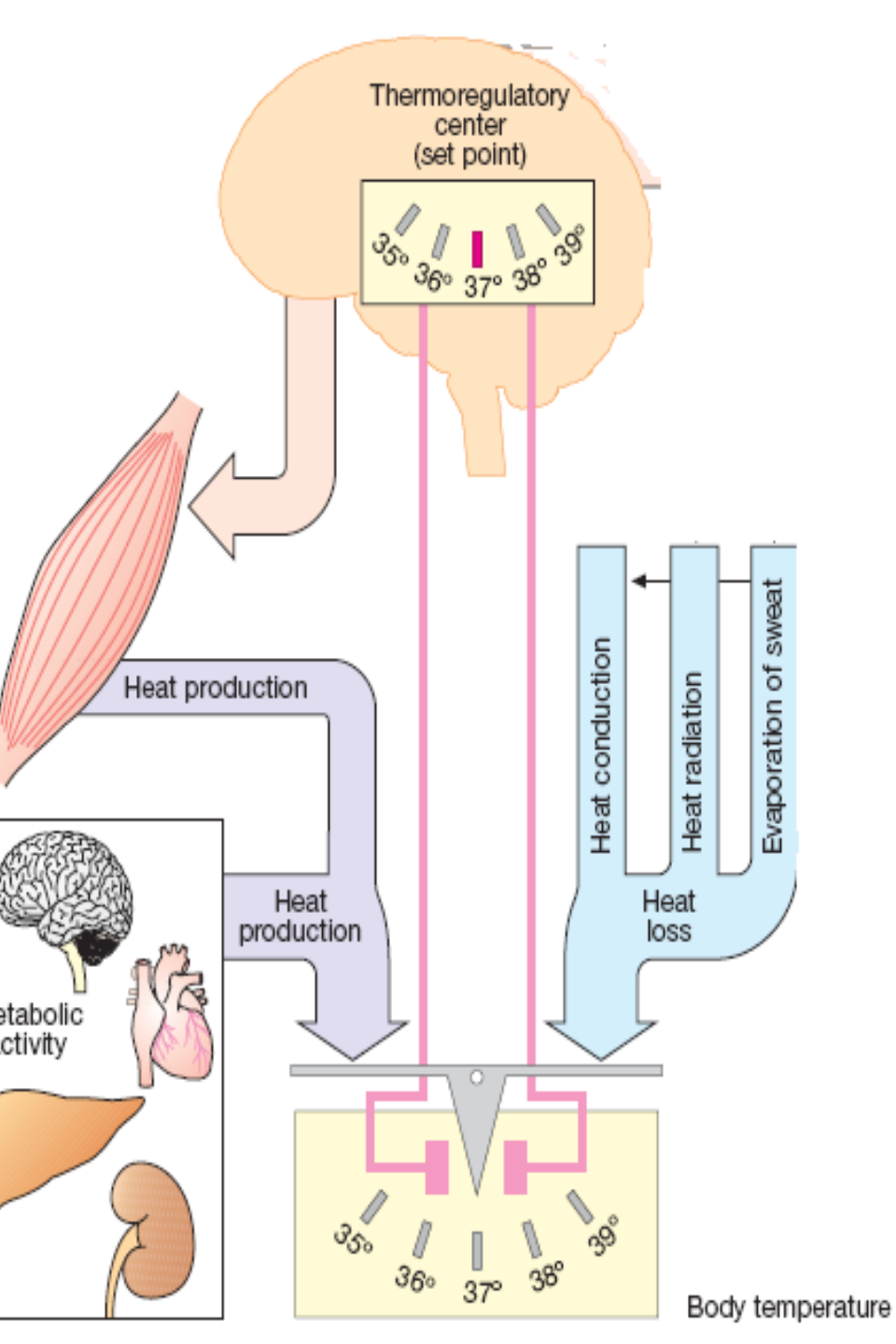


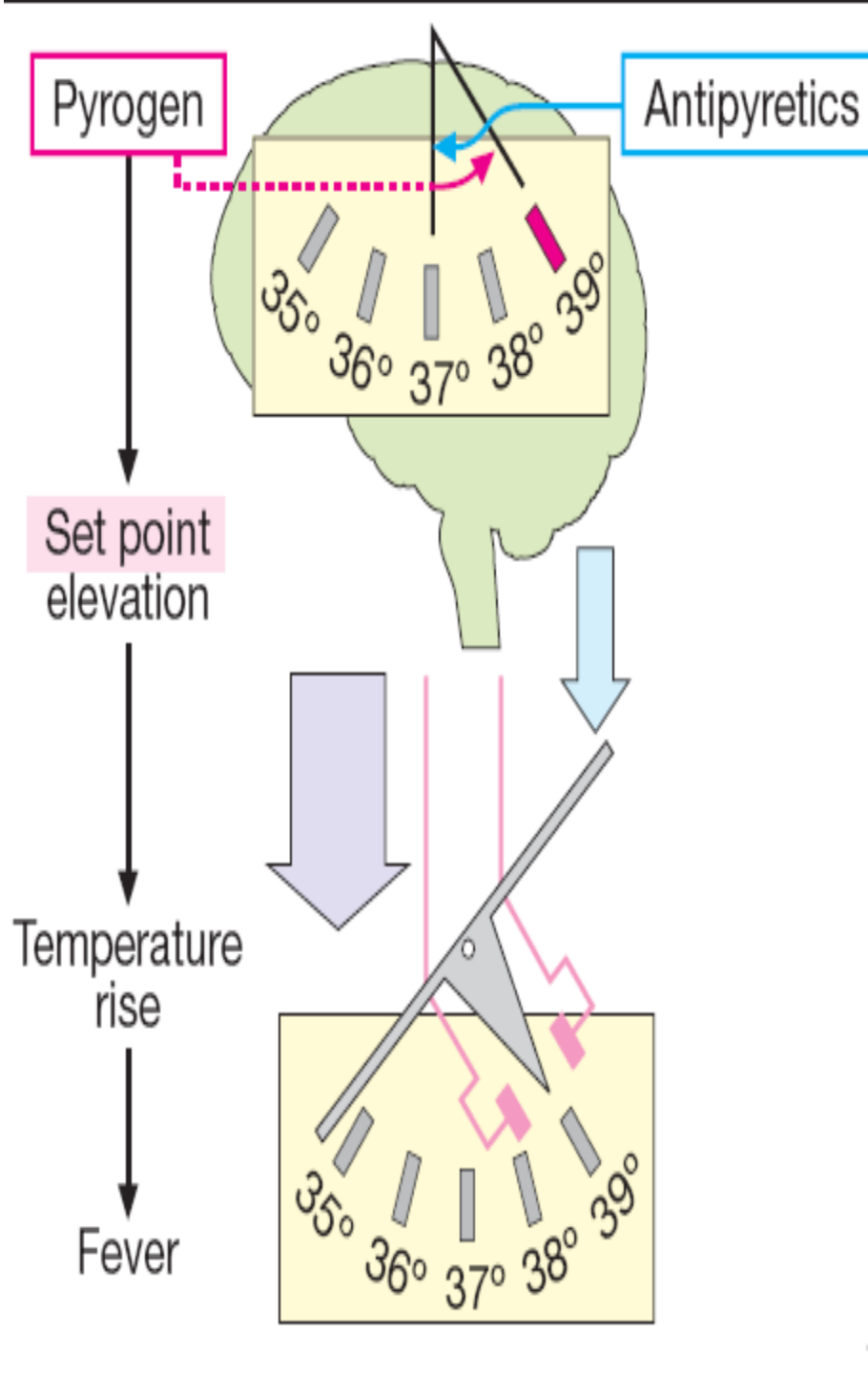
COX-1 and COX-2 Inhibition Effect





Nonnarcotic painkillers work by blocking the prostaglandins that are released by damaged cells.


Thermoregulatory center (set point)
35° 36° 37° 38° 39°
Heat production
Heat production
Heat conduction
Heat radiation
Evaporation of sweat
Heat loss
etabolic
ctivity
35° 36° 37° 38° 39°
Body temperature


Pyrogen
Antipyretics
35° 36° 37° 38° 39°
Set point elevation
Temperature rise
Fever
35° 36° 37° 38° 39°

Aspirin (salicylate)

- It Is the prototype, was first isolated in 1829.
- It is the most commonly used anti-inflammatory agents (other agents compare to it).
- However, about 15% of patient show intolerance to Aspirin, And some of the newer NSAIDs are superior to Aspirin and cause less gastric irritation, and/or they can be taken less frequently.
- Aspirin is unique in the ability to acetylates the cyclooxygenase irreversibly. Other NSAIDs are reversible inhibitors of cyclooxygenase.

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Aspirin

- Aspirin is rapidly break down in the body to produce salicylate, which has anti-inflammatory, antipyretic, an analgesic effects.

Aspirin anti-inflammatory effect

- This effect is a result of its ability to diminish the formation of prostaglandins that mediate the inflammation process.

  The primary clinical application of this action is in the treatment of the musculoskeletal disorders, such as rheumatoid arthritis.

  Importantly, aspirin still the first line therapy for rheumatoid arthritis.

  Although it inhibits inflammation in arthritis, it does not arrest the progression of the disease nor induce remission.

Aspirin analgesic effect

- Relief of pain occurs through both peripheral and central mechanism:

  Peripherally, the salicylates inhibit synthesis of prostaglandins in inflamed tissue, thus preventing the sensitization of pain receptors.

  Centrally, effect the analgesic site exists in the hypothalamus.

- Used usually for the management of pain of low to moderate intensity (headache, arthritis).

Aspirin antipyretic

- Fever occurs when the set-point of the anterior hypothalamus thermoregulatory centre is elevated.

- The effect of aspirin and other salicylates is centrally mediated and thought to be due to inhibition the synthesis and the release of the PGE2 in the hypothalamus, (PGE2 stimulate the temperature elevation).

- Aspirin is rapidly effective in febrile patients, in which Aspirin also increase heat dissipation as a result of peripheral vasodilation and sweating.

Aspirin other uses

- External application: used topically to treat corns, epidermatitis.

- Cardiovascular application: used to inhibit platelet aggregation. At low doses Aspirin is used prophylactically to decrease the incidence of transient ischemia attacks and unstable angina in men.

- In colon cancer, there is evidence that chronic use of aspirin reduces the incidence of clororectal cancer.

Aspirin interaction and adverse effects

- Drug interaction, administration of salicylates with many classes of drugs may produce undesirable side effects:

  Drugs includes Phenytoin, Thiopental do increase the blood concentration of aspirin.

  Aspirin administration with Heparin and oral anticoagulant may increase the risk of hemorrhage.

- Aspirin adverse effect:

  The most common is the gastrointestinal effects including epigastric distress, and vomiting. So Aspirin should be taken with food and extra fluids to diminish the GI disturbances.

Aspirin adverse effects

- Should not be taken for at least one week prior to surgery, as it result in inhibition of platelet aggregation and prolong bleeding time.

- Reye syndrome, aspirin given during viral infection (especially in children) has been associated with an increased incidence of Reye syndrome.

Acetaminophen (A)

- Produce antipyretic and analgesic effect through inhibition of prostaglandins synthesis.
- Has a week anti inflammatory effect, because it has less effect on the cyclooxygenase enzyme in the peripheral tissue.
- Does not effect the platelet function, nor increase the blood clotting time.
- It is suitable substitute for analgesic and antipyretic effect of aspirin for those patient with gastric complaints, or those whom prolonging the bleeding time is disadvantage.

Acetaminophen

- Is the drug of choice for children with viral infection or chickenpox, because aspirin increase the risk of Reye syndrome.

- At therapeutic doses it is free of any significant side effects.

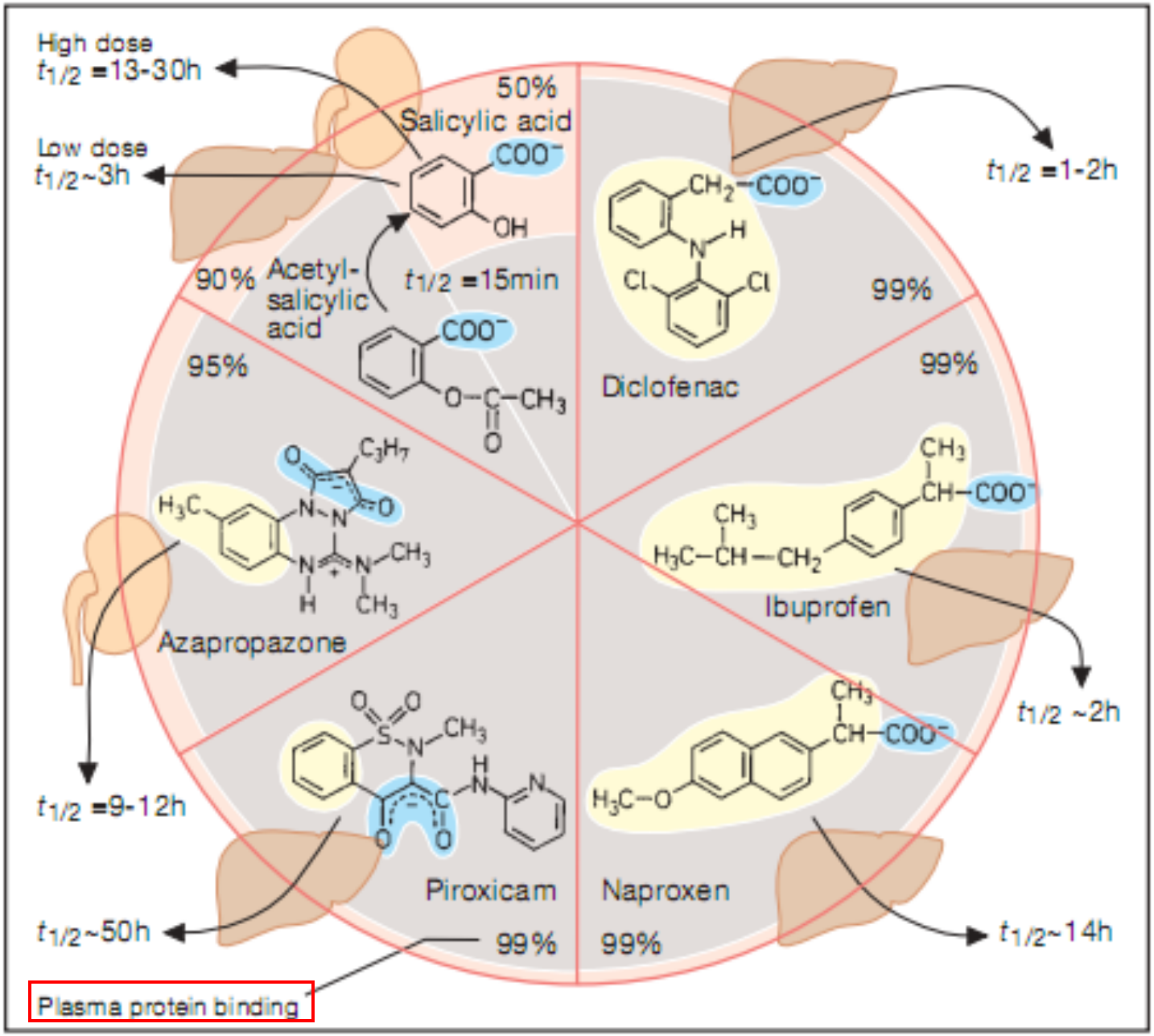
Pregnancy

acetaminophen is the analgesic of choice for all stages of gestation

used to treat mild to moderate pain and fevers

short term usage is believed to be safe

avoid chronic and large doses of acetaminophen



Lüllmann, Color Atlas of Pharmacology – 2nd Ed. (2000)

Indometacin

is a potent ***nonselective COX inhibitor may also inhibit phospholipase A and C, reduce neutrophil migration, and decrease T cell and B cell proliferation***.

use in juvenile rheumatoid arthritis, gout and ankylosing spondylitis.

It has been used to **treat patent ductusarteriosus**.
An ophthalmic preparation seems to be efficacious for conjunctival inflammation. **Gingival inflammation** is reduced after administration of indometacin **oral rinse**.

A high incidence (up to 50%) of GI and CNS side effects is produced: GI bleeding,diarrhoea, frontal headache, **mental confusion**.

Meloxicam

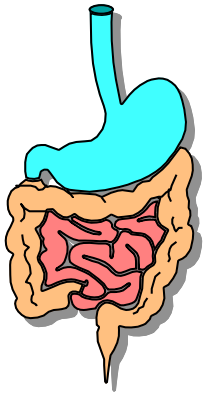
preferentially" selective rather than "highly" selective.
particularly at its lowest therapeutic dose of 7.5 mg/d.

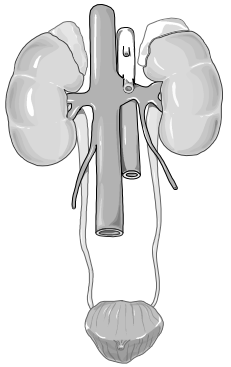
The drug has been approved for the treatment of osteoarthritis and rheumatoid arthritis.

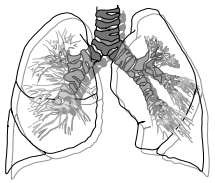
It is associated with fewer clinical GI symptoms and complications than piroxicam, diclofenac, and naproxen.

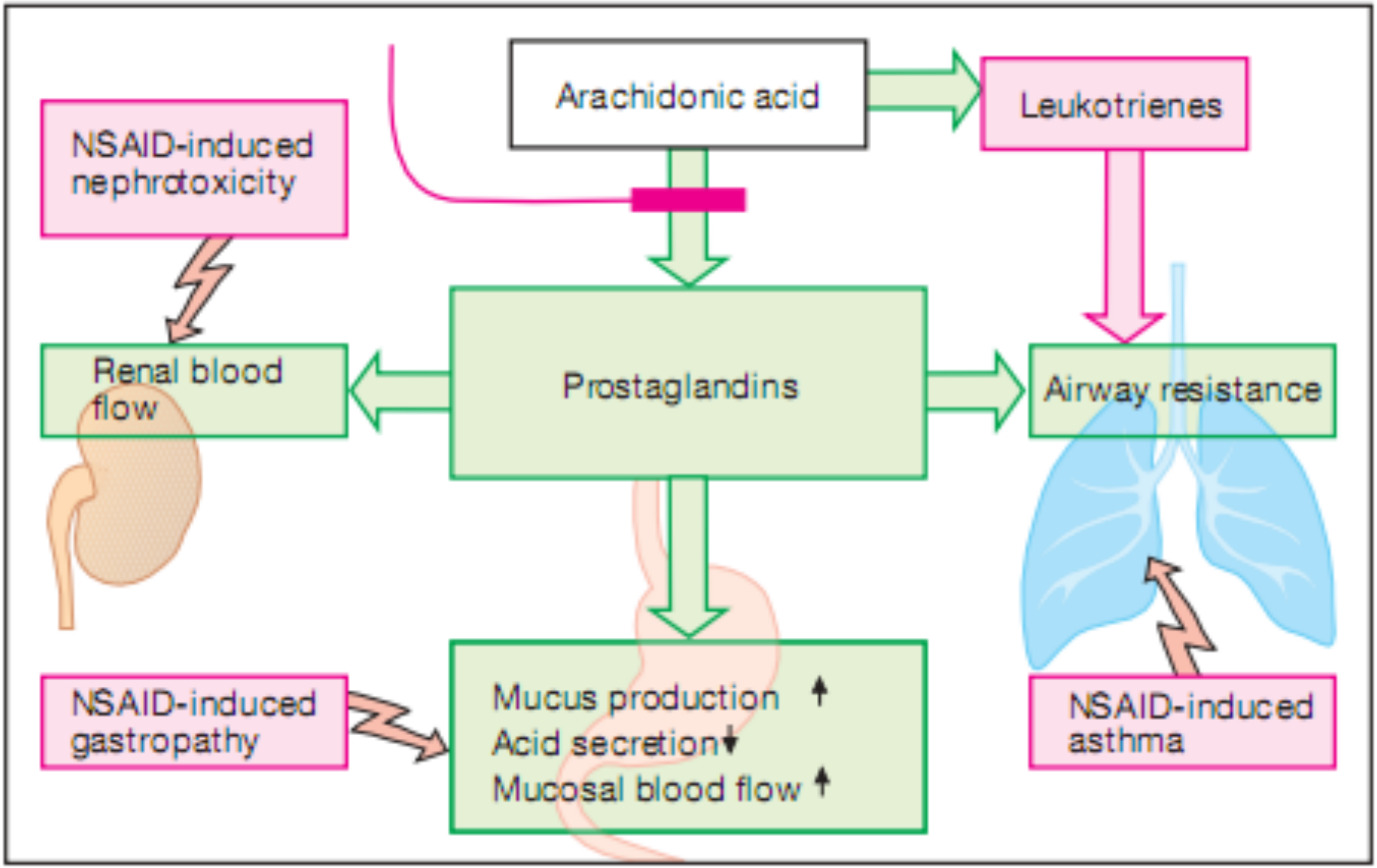
Shared toxicities of NSAIDs due to prostanoid synthesis inhibition

1. **Gastric mucosal damage** connected with PGE inhibition
2. **Bleeding:** inhibition of platelet function (TxA_2 synthesis)
3. **Limitation of renal blood flow** Na^+ and water retention
4. **Delay / prolongation of labour** connected with $PGF_{2\alpha}$ inhibition
5. **Asthma and anaphylactoid reactions** connected with $PGF_{2\alpha}$ inhibition









NSAIDs: group-specific adverse effects

Lüllmann, Color Atlas of Pharmacology – 2nd Ed. (2000)

Bextra® (Valde[illegible]): Pfizer (penalty!)

Many severe side effects

- Infertility (> $PGF_{2\alpha}$)
- Thrombosis (< PGI_2; > TxA_2)

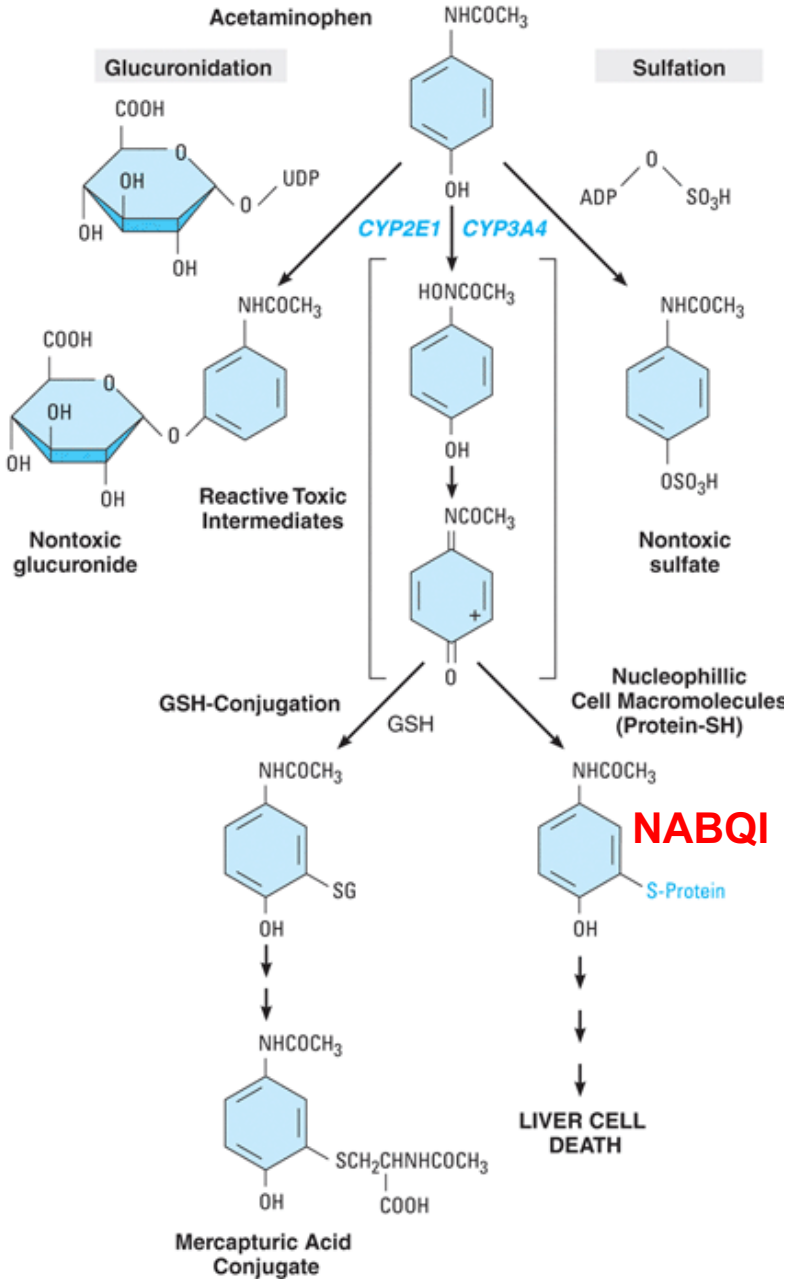
Metabolism of paracetamol to hepatotoxic metabolites (NABQI etc.)

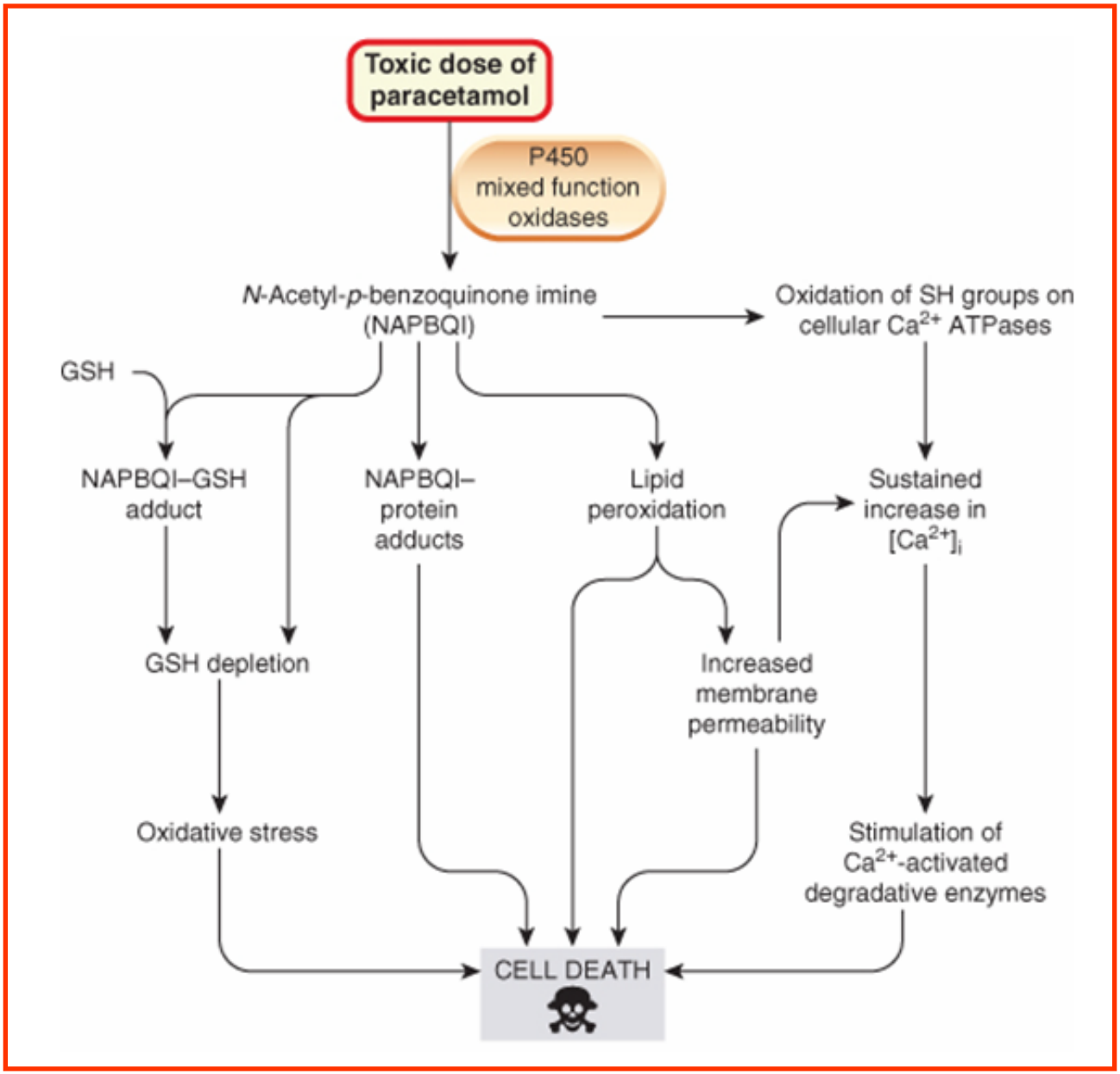
(GSH – glutathione; SG – glutathione moiety)

Daily dose > 7.5 g:
hepatotoxicity and nephrotoxicity

NB: Acetylcysteine and GSH contain **–SH** groups.

Basic & Clinical Pharmacology – 10th Ed. (2007)





Rang et al. *Pharmacology* – 6th Ed. (2007)

4. Metabolic effects of Aspirin and other NSAIDs are significant only at antiinflammatory doses. Cellular metabolism is increased, especially in skeletal muscles, due to uncoupling of oxidative phosphorylation as a

result of increased heat production. There is increased utilization of glucose and blood sugar may decrease (specially in diabetics) and liver glycogen is depleted. However, *hyperglycemia is often seen at toxic doses*: this is due to central sympathetic stimulation and release of adrenaline and GCS. Chronic use of large doses cause negative nitrogen balance by increased conversion of protein to carbohydrate. Plasma free fatty and cholesterol are reduced.

5. Respirations. At antiinflammatory doses respiration is stimulated by peripheral (increased CO_2 production) and central (increased sensitivity of respiratory centre to CO_2) action. Hyperventilation is prominent in salicylate poisoning. Further raise in the salicylate level causes respiratory depression and failure, and death.

6. Acid-base and electrolyte balance. Antiinflammatory doses produce significant changes. Initially respiratory stimulation predominates and tends to wash out CO_2 despite increased production and the result is respiratory **alkalosis**, which is compensated by increased renal excretion of HCO_3^- (with accompanying Na^+, K^+, and water). Most adults treated with 4–6 g/daily of Aspirin stay in a state of compensated respiratory alkalosis. Still higher doses cause respiratory depression with CO_2 retention, while excess CO_2 production continues to develop respiratory **acidosis**. To this are added dissociated salicylic acid as well as metabolic acid (because there is rebound depression). It develops **uncompensated metabolic acidosis**. **Dehydration** occurs in poisoning due to increased water loss in urine.

Comparative action between COX inhibitors	COX-1/COX-2 inhibitors	COX-2 inhibitors
1. Analgesic action	(+)	(+) (+)
2. Antipyretic action	(+)	(+)
3. Antiinflammatory action	(+)	(+) (+)
4. Antiplatelet aggregatory	(+)	(-)
5. Gastric mucosal damage	(+) (+) (+)	(+)
6. Renal salt / water retention	(+)	(+)
7. Delay/prolongation of labor	(+) (+)	(+)
8. Infertility	(-)	(+) (+)
9. Ductus arteriosus closure	(+)	?
10. Aspirin-like asthma	(+)	?
11. Cardiotoxicity	(-)	(+) (+)