NSAIDs
(Non-selective cox inhibitors: Aspirin & other commonly used NSAIDs)

DR SHAMS SULEMAN

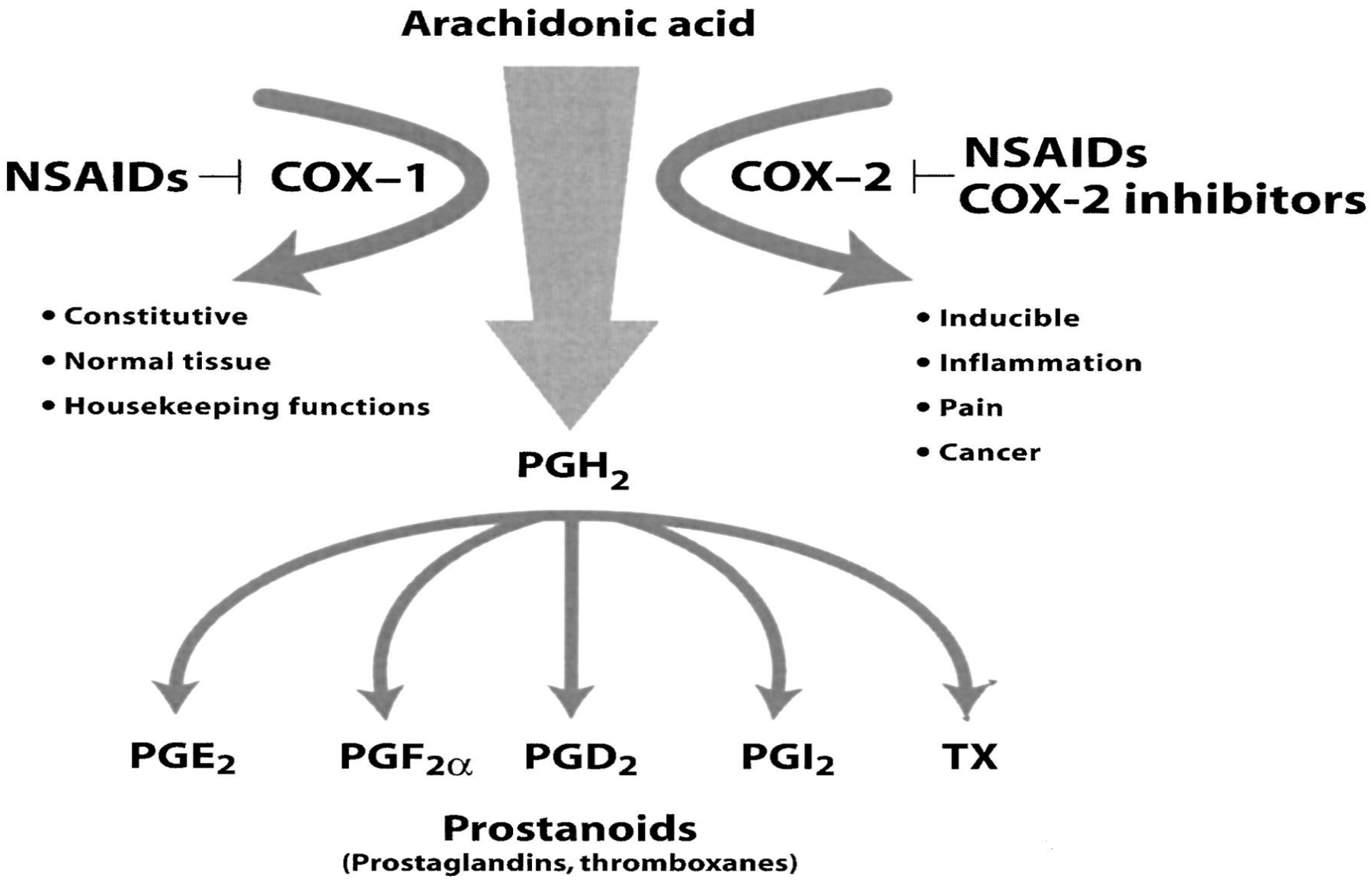
LEARNING OBJECTIVES

- Classify NSAIDs
- Differentiate between nonselective COX inhibitors and selective COX-2 inhibitors based on mechanism of action
- Name the prototype nonselective COX inhibitor
- Describe mechanism of action of Aspirin as antiplatelet, analgesic/antipyretic and as anti inflammatory drug
- Give the dose of Aspirin as antiplatelet, analgesic/antipyretic and as anti inflammatory drug
- Describe clinical uses of NSAIDs

LEARNING OBJECTIVES …..

- Describe the adverse effects of NSAIDs
- Describe the drug treatment of Aspirin poisoning
- Describe the pharmacokinetics with emphasis on dosage, duration of action and elimination of Diclofenac, Ibuprofen, Indomethacin, Mefenamic acid and Piroxicam in contrast to Aspirin
- Relate pharmacokinetics and pharmacodynamics of NSAIDs to their clinical applications

Cyclooxygenase enzymes



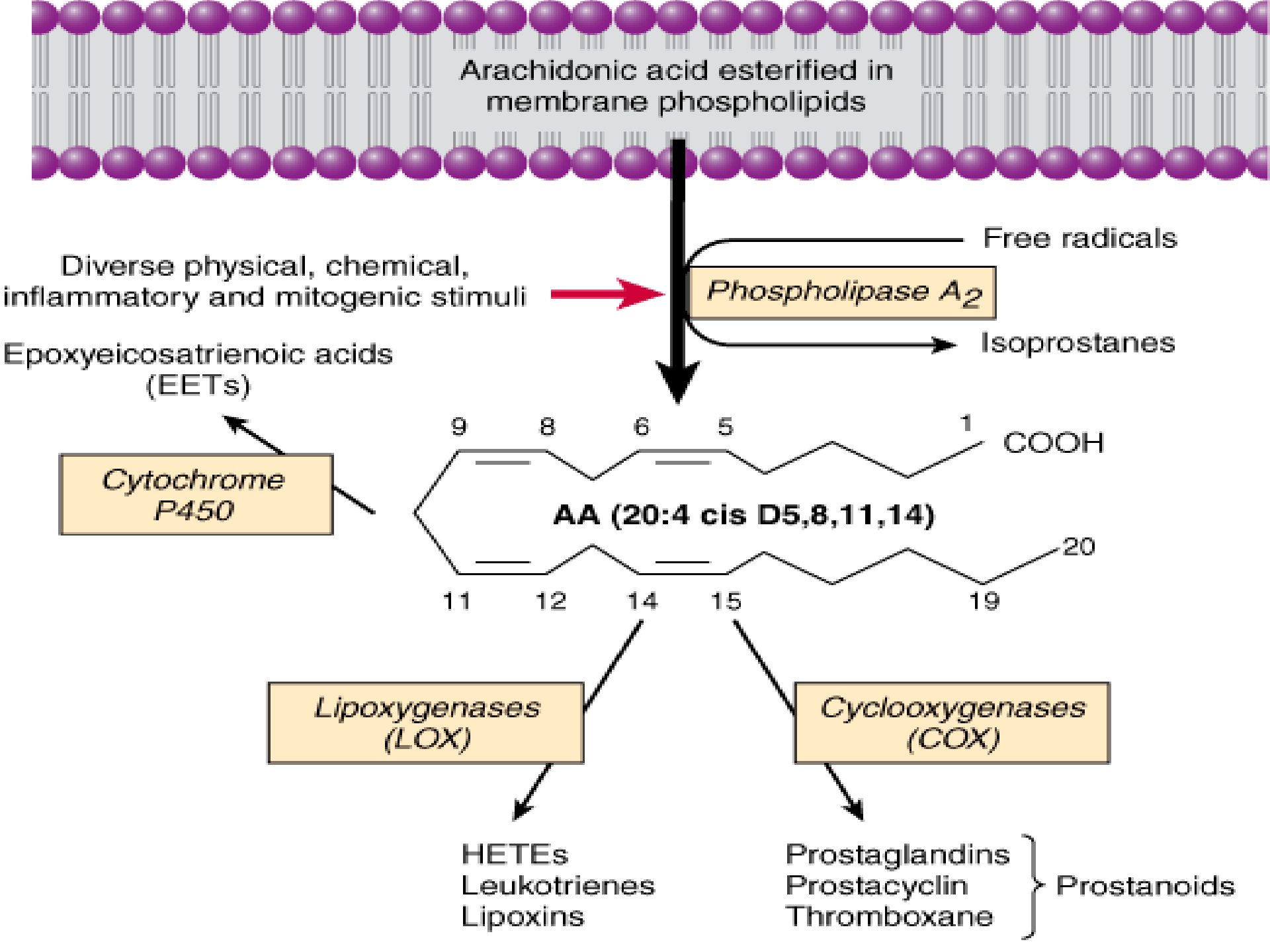
FUNCTIONS OF COX

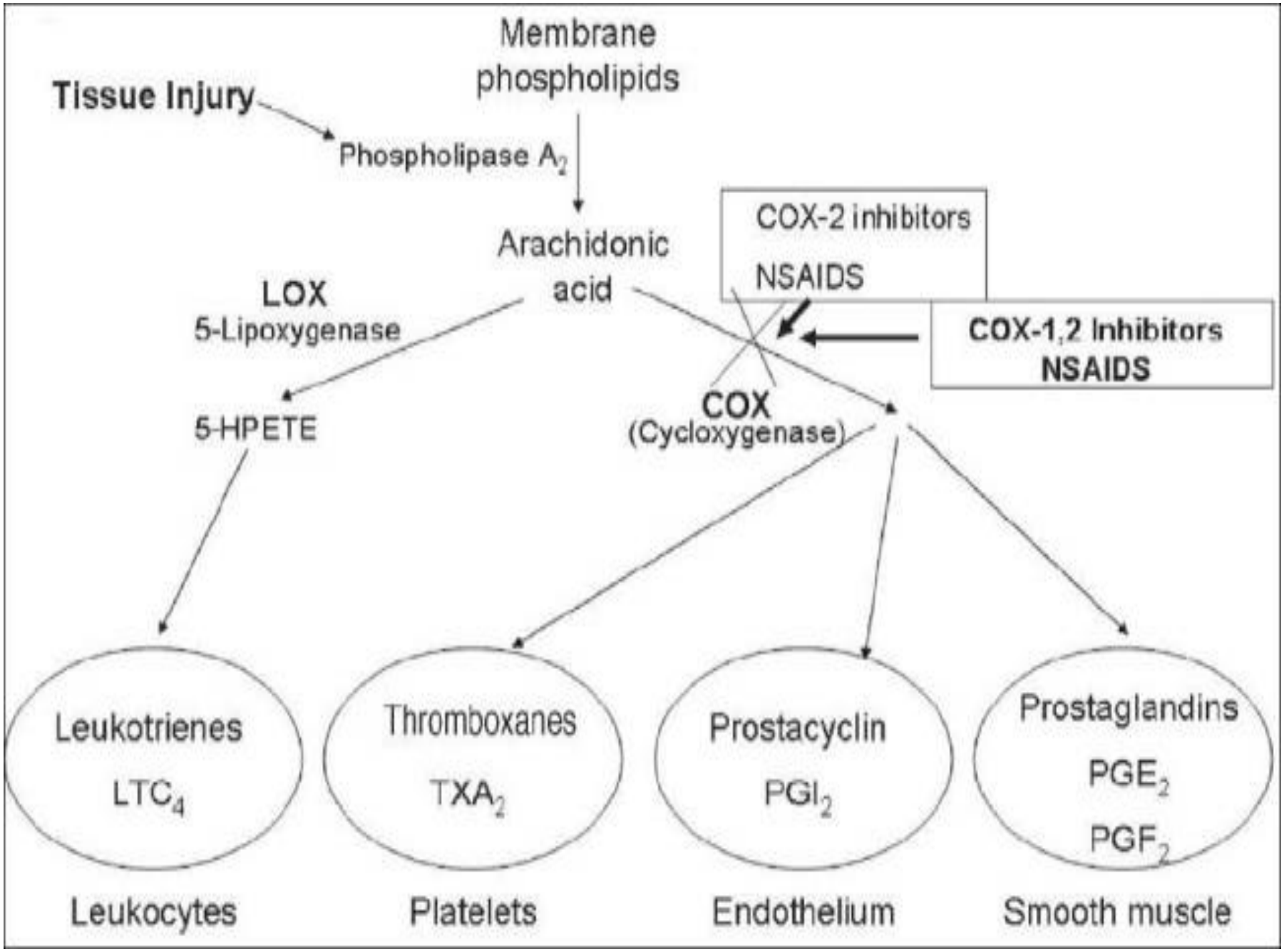
COX-1

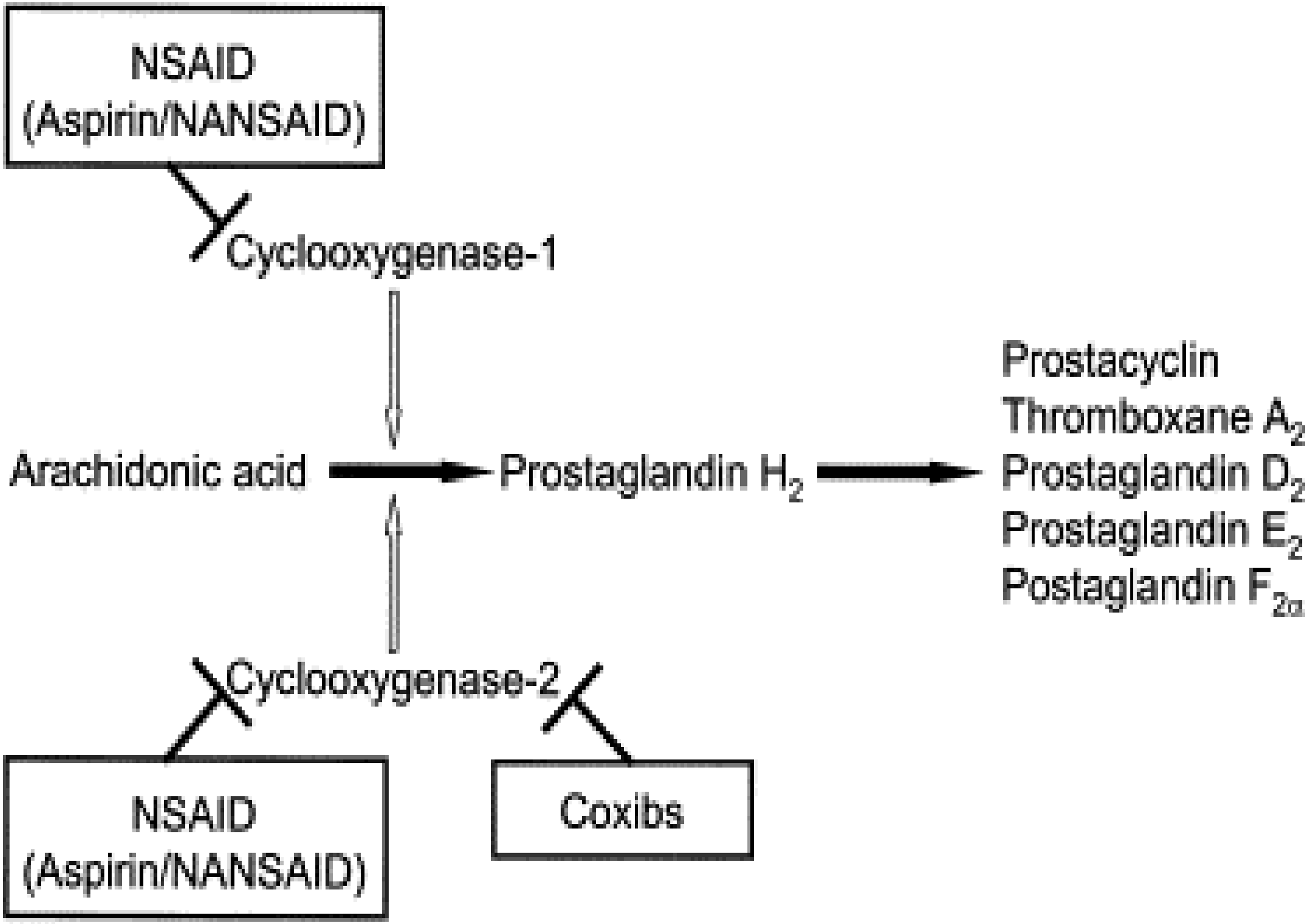
- Constitutively expressed
- Housekeeping functions
- Present in every organ stomach, intestine, kidney, **platelets,** vascular endothelium

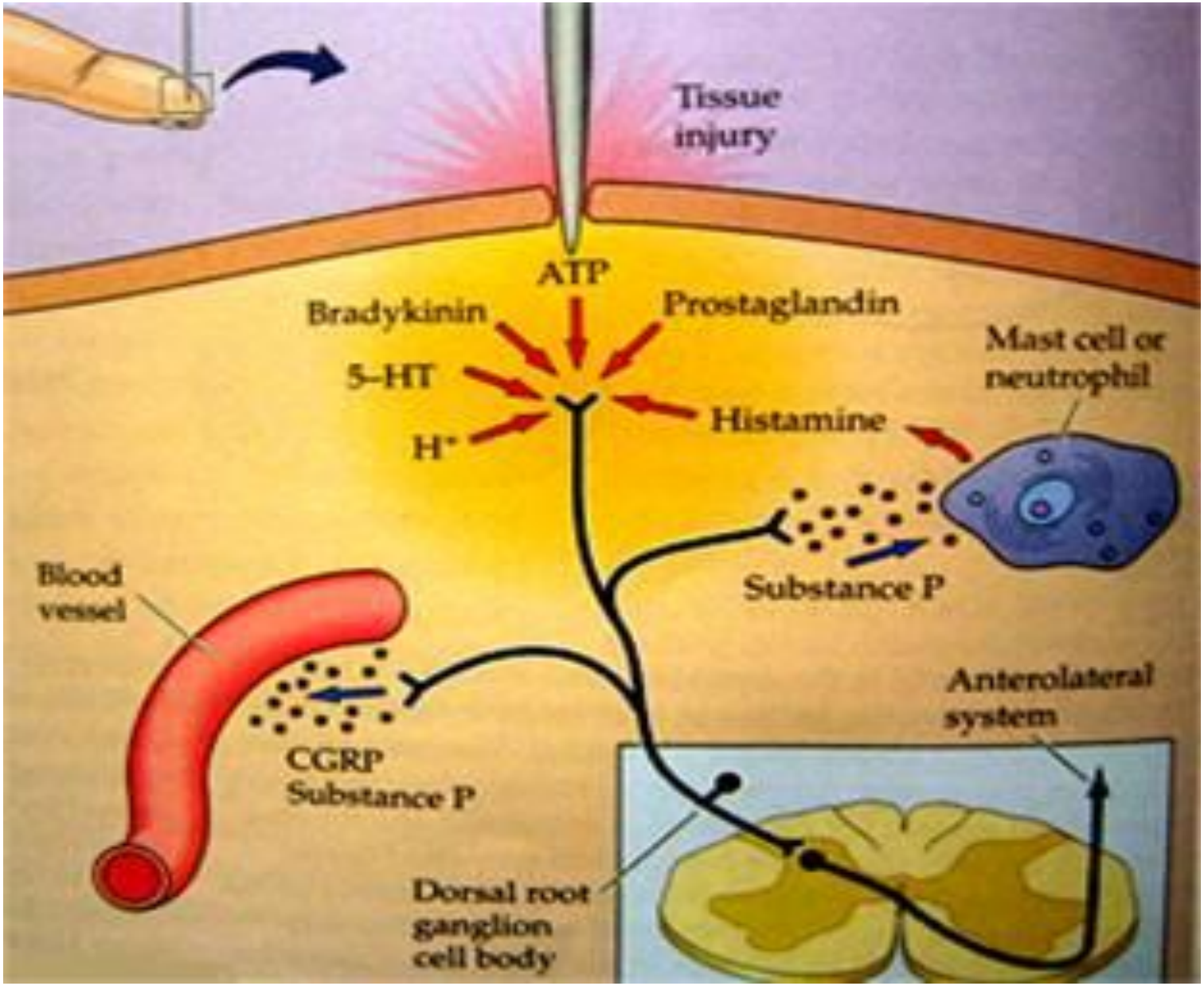
COX-2

- Inducible
- Inflammatory & neoplastic sites
- Also present in kidney, uterus, ovary, brain, small intestine

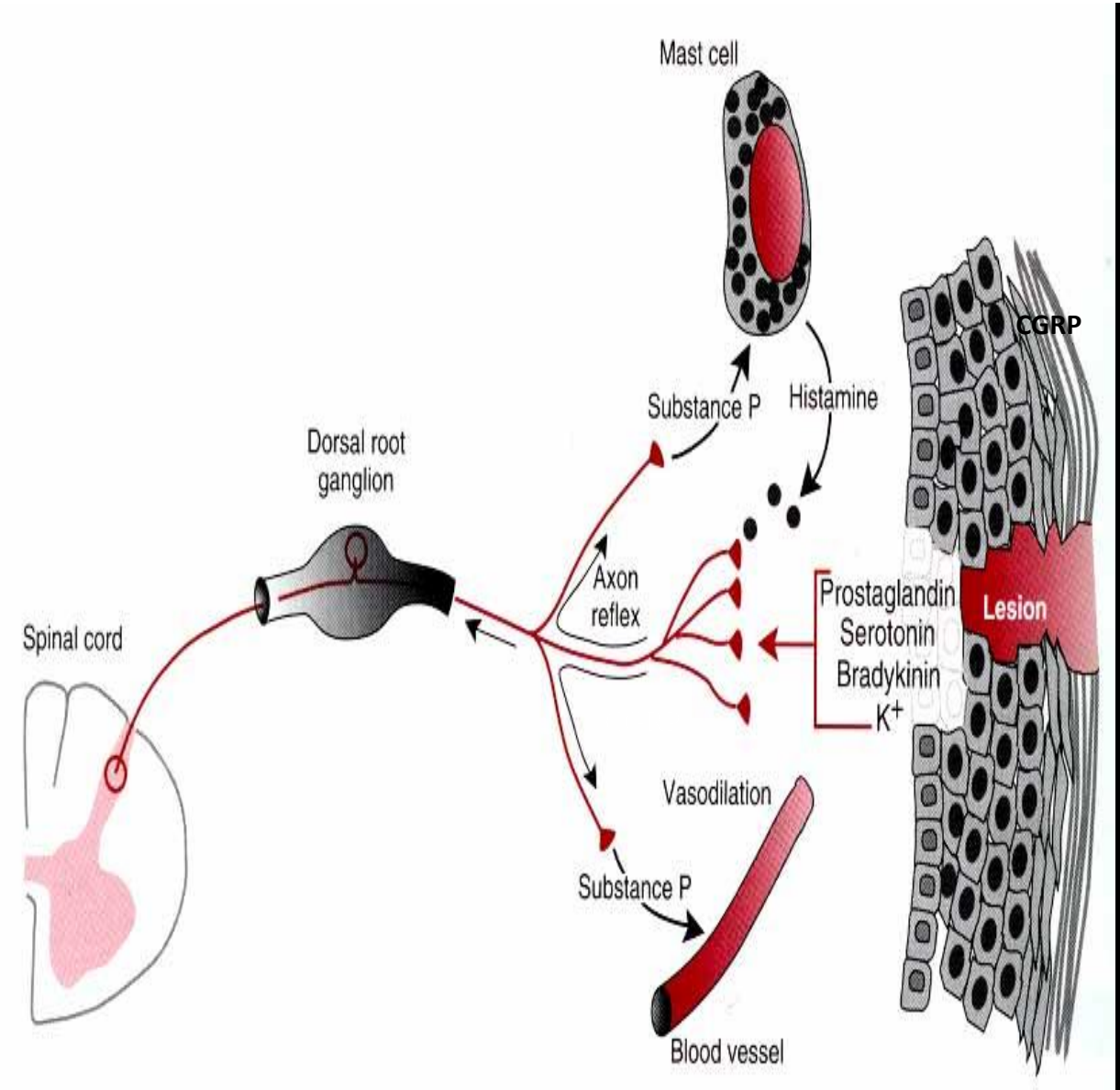

Arachidonic acid esterified in membrane phospholipids
Free radicals
Diverse physical, chemical, inflammatory and mitogenic stimuli
Phospholipase A2
Isoprostanes
Epoxyeicosatrienoic acids (EETs)
9
8
6
5
1
COOH
Cytochrome P450
AA (20:4 cis D5,8,11,14)
20
11
12
14
15
19
Lipoxygenases (LOX)
Cyclooxygenases (COX)
HETEs
Leukotrienes
Lipoxins
Prostaglandins
Prostacyclin
Thromboxane
Prostanoids

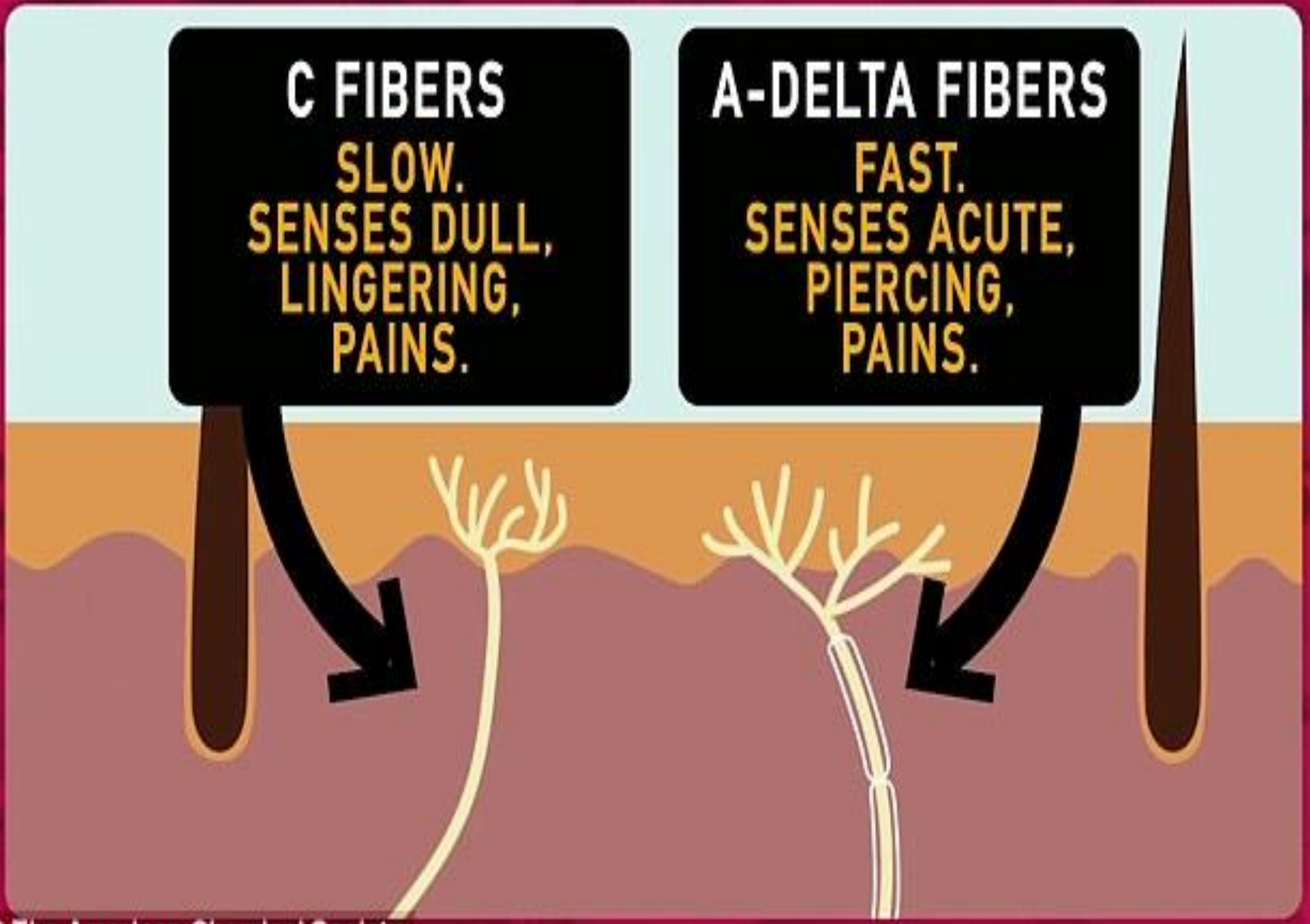

Membrane phospholipids
Tissue Injury
Phospholipase A_2
Arachidonic acid
COX-2 inhibitors
NSAIDS
LOX
5-Lipoxygenase
COX-1,2 Inhibitors
NSAIDS
5-HPETE
COX
(Cycloxygenase)
Leukotrienes
LTC_4
Thromboxanes
TXA_2
Prostacyclin
PGI_2
Prostaglandins
PGE_2
PGF_2
Leukocytes
Platelets
Endothelium
Smooth muscle


NSAID
(Aspirin/NANSAID)
Cyclooxygenase-1
Arachidonic acid
Prostaglandin H2
Prostacyclin
Thromboxane A2
Prostaglandin D2
Prostaglandin E2
Postaglandin F2α
Cyclooxygenase-2
NSAID
(Aspirin/NANSAID)
Coxibs


Tissue injury
ATP
Bradykinin
Prostaglandin
5-HT
H+
Histamine
Mast cell or neutrophil
Substance P
Blood vessel
CGRP
Substance P
Anterolateral system
Dorsal root ganglion cell body

PERIPHERAL SENSITIZATION TO PAIN





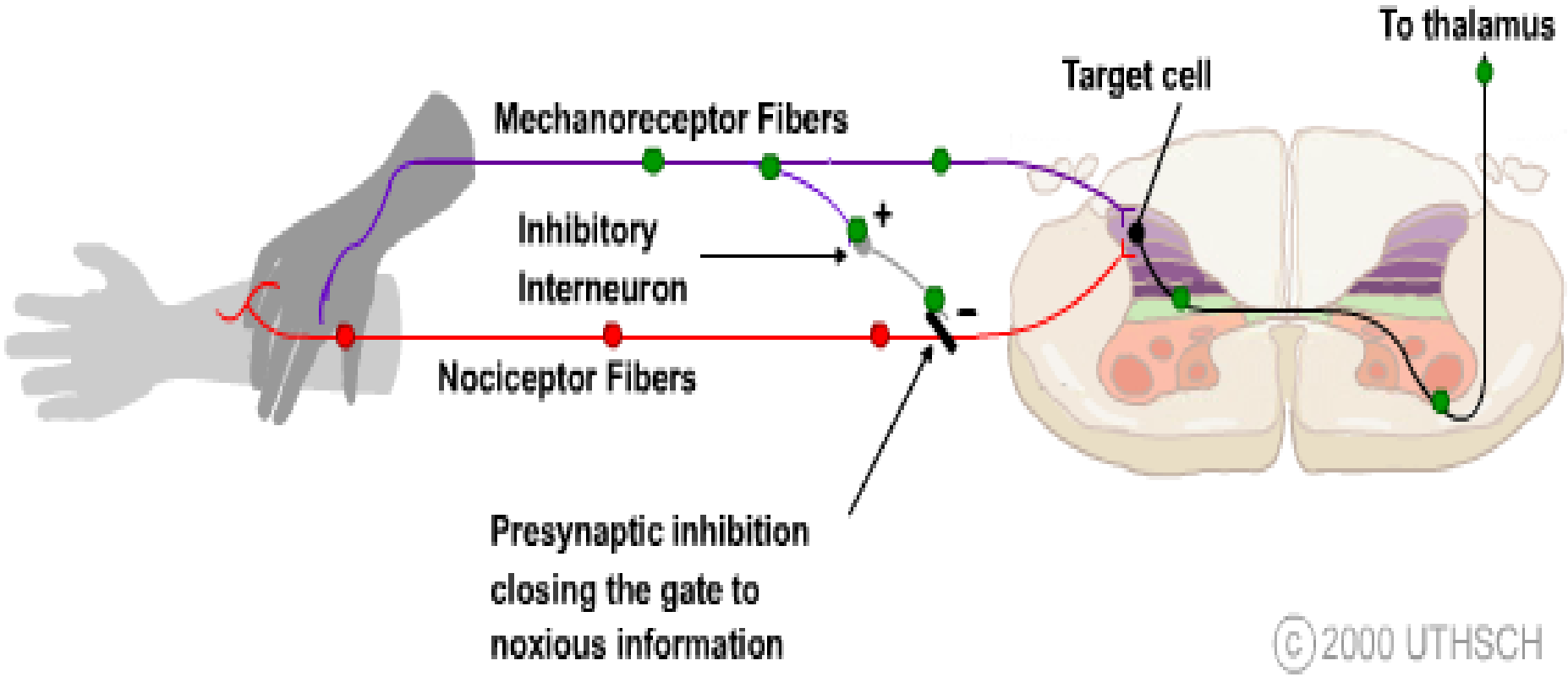
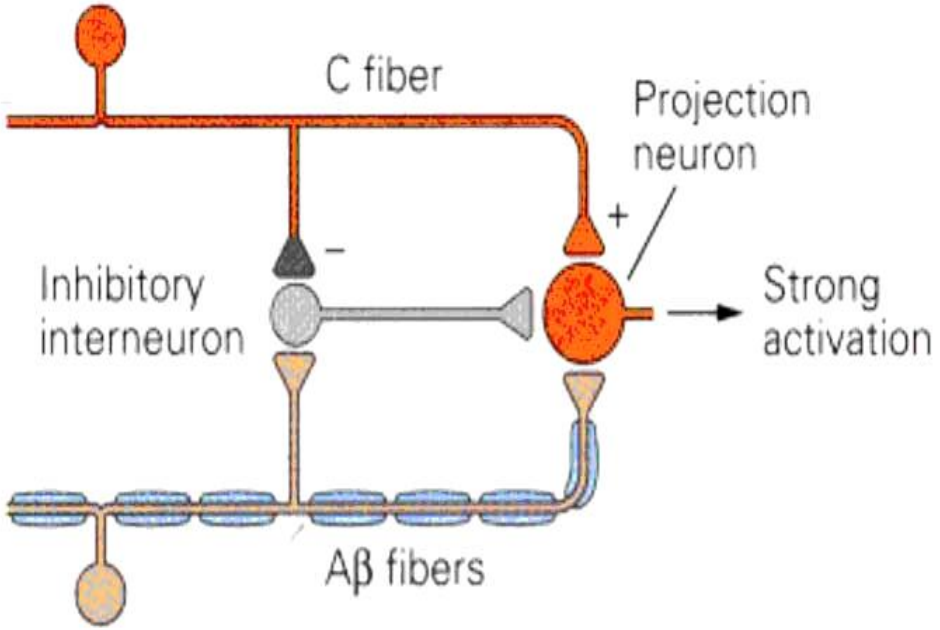


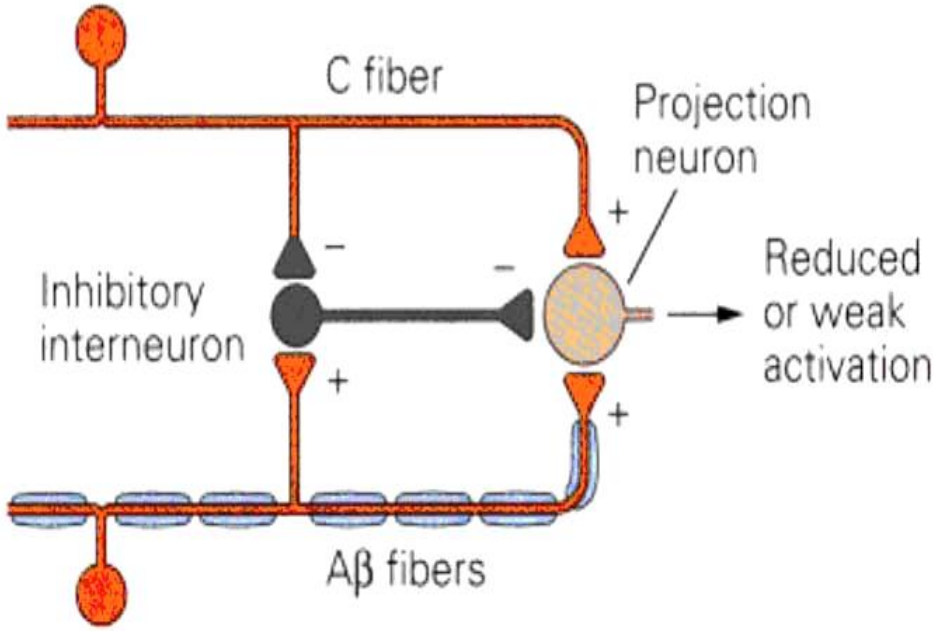
Figure 8.1

The gate control theory of pain modulation. The gate control theory is based on presynaptic inhibition of pain information produced by mechanical stimulation, and provides the basic rationale for the TENS.

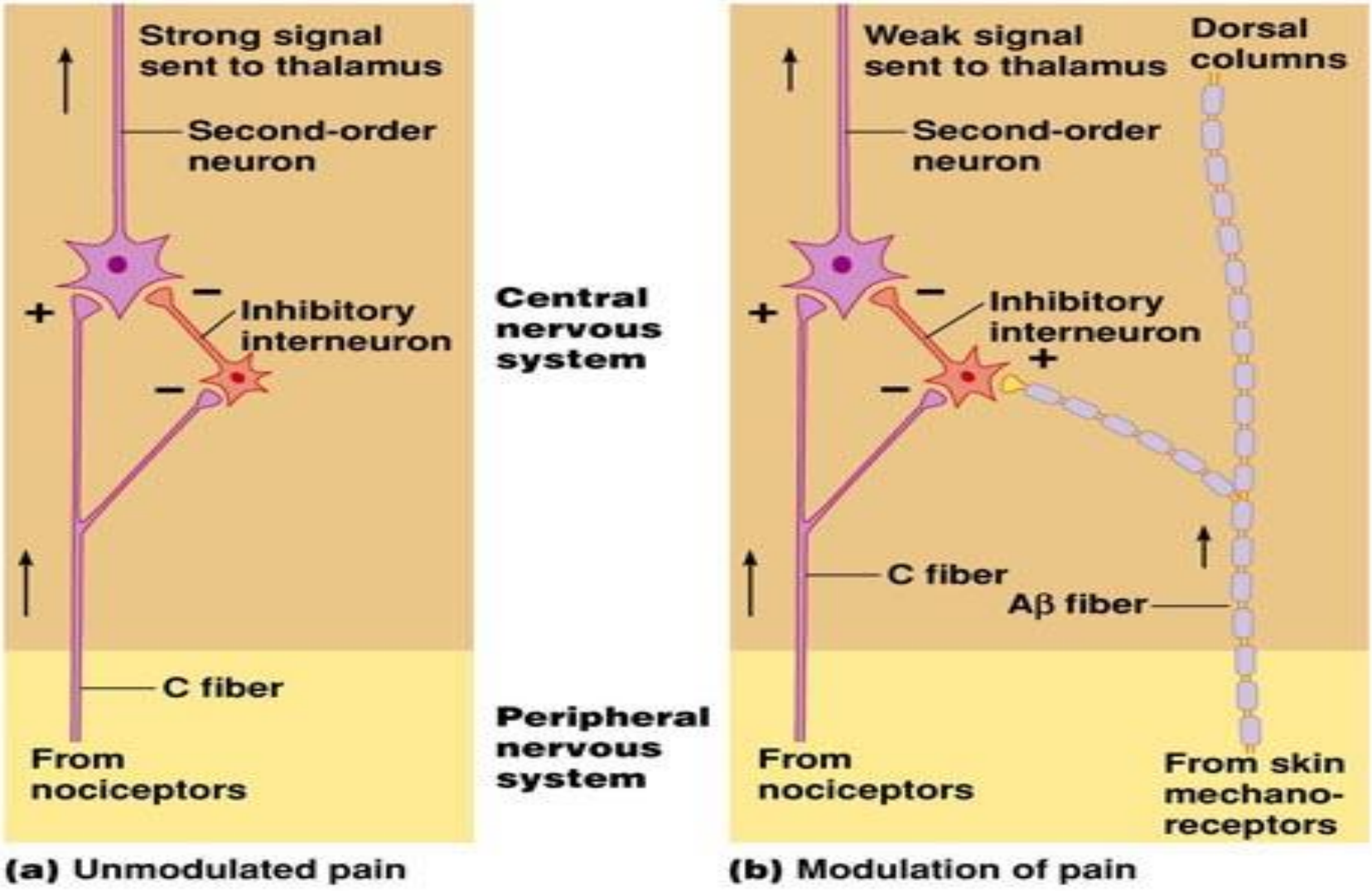
Gate Control Hypothesis:

- Interneurons activated by Aβ fibers act as a gate, controlling primarily the transmission of pain stimuli conveyed by C fibers to higher centers.
- Rubbing the skin near the site of injury to feel better.
- Transcutaneous electrical nerve stimulation (TENS).
- Dorsal column stimulation
- Acupuncture





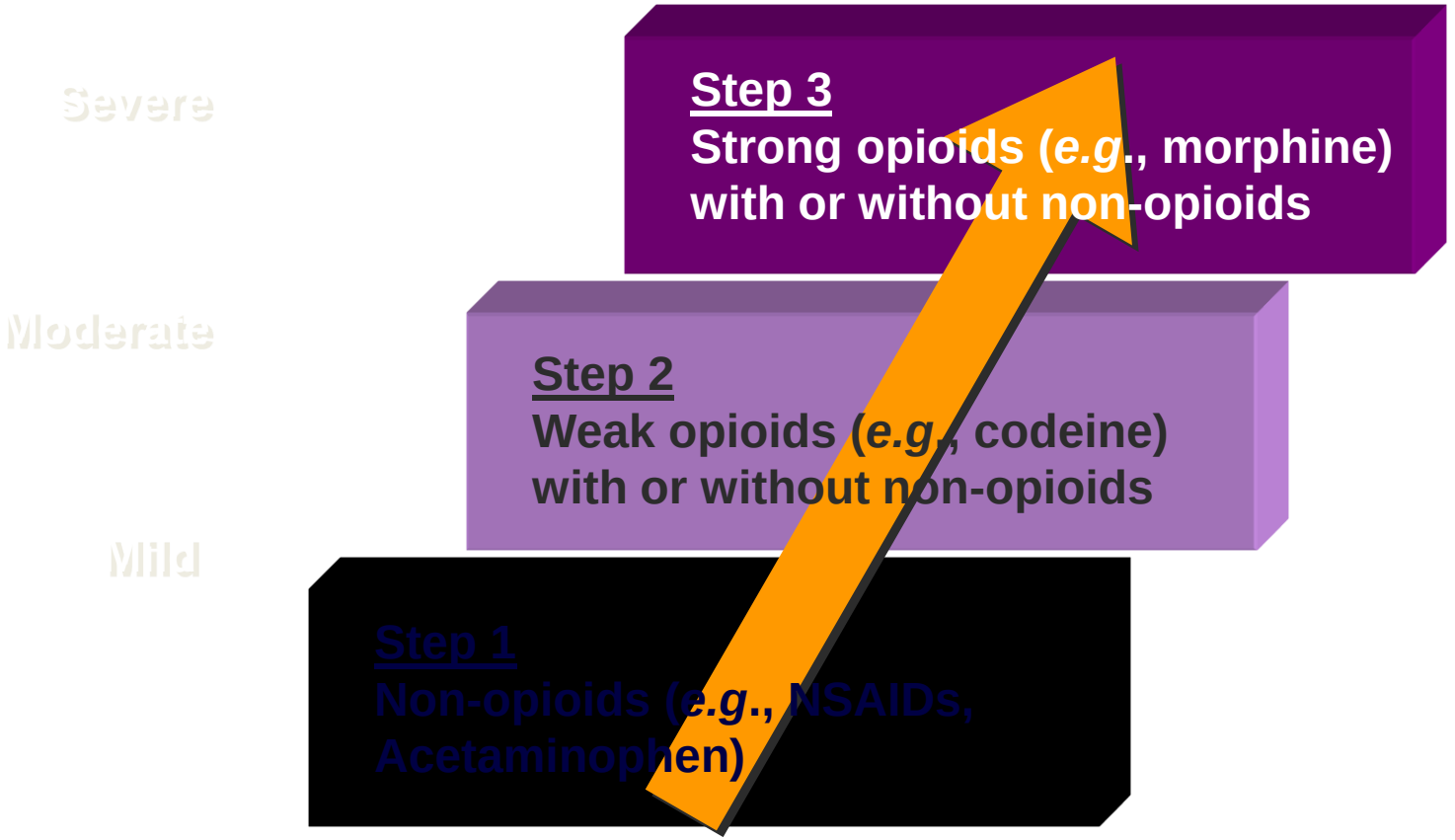
Gate-control theory of pain



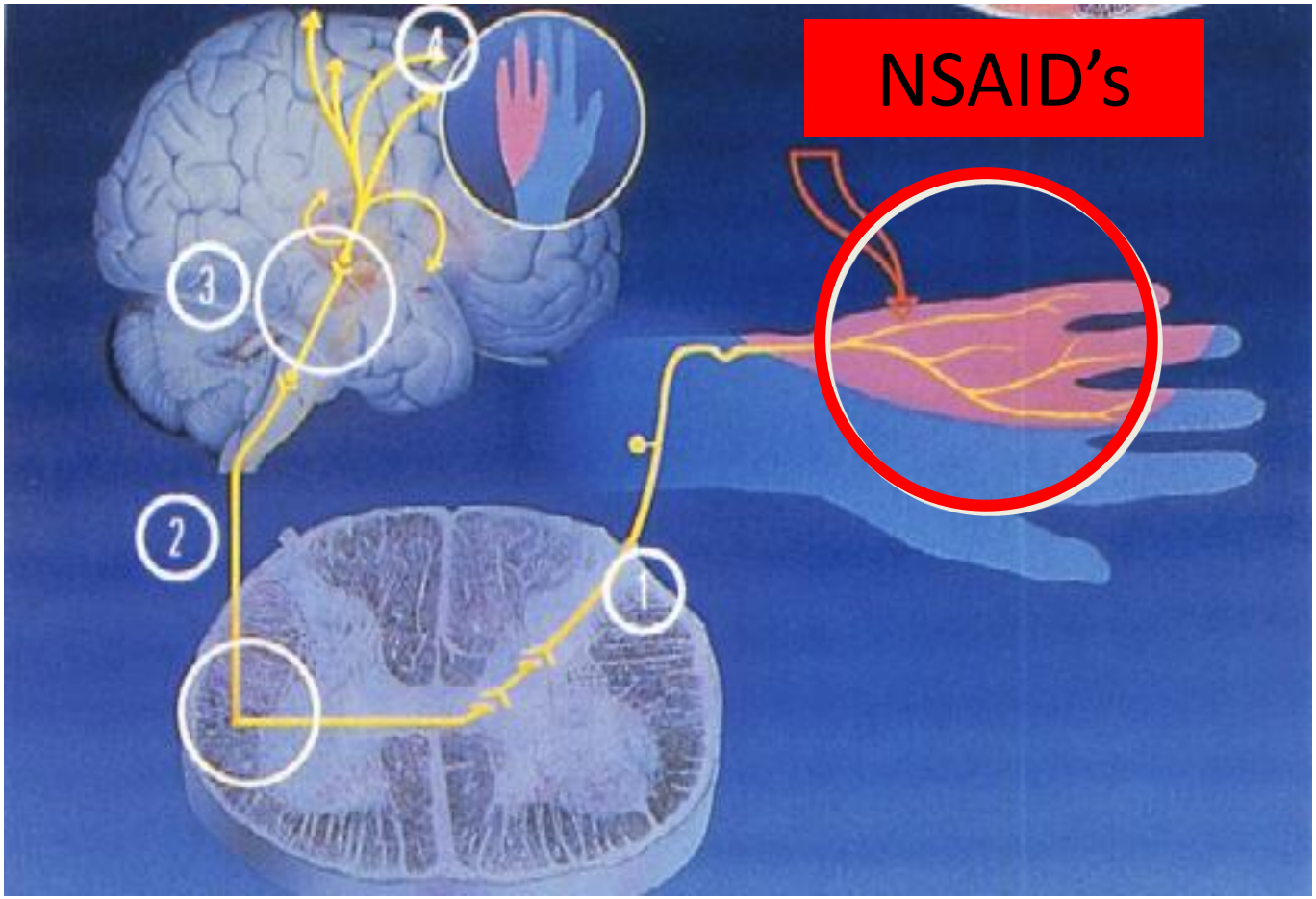
ANALGESICS

1) Act at the site of injury and decrease the pain associated with an inflammatory reaction (e.g. NSAIDs)
2) Alter nerve conduction (e.g. local anesthetics): block action potentials by blocking Na channels.
3) Modify transmission in the dorsal horn (e.g. opioids).
4) Affect the central component and the emotional aspects of pain (e.g. opioids, antidepressant).

WHO Analgesic ‘Ladder’



SITE OF ACTION



CLASSIFICATION (chemical)

SALICYLIC ACID DERIVATIVES

- Aspirin
- Sodium salicylate
- Methyl salicylate
- Choline salicylate
- Magnesium salicylate
- Diflunisal
- Benorylate

CLASSIFICATION (contd.)

FENAMIC ACID DERIVATIVES

- Mefenamic acid, meclofenamate sodium

PROPIONIC ACID DERIVATIVES

- Ibuprofen, naproxen, fenbufen, fenoprofen, flurbiprofen, ketoprofen

ENOLIC ACID DERIVATIVES

- Piroxicam, meloxicam (oxicams); nabumetone

CLASSIFICATION (contd.)

PYRAZOLON DERIVATIVES

- phenylbutazone, azapropazone, oxyphenbutazone

COX 2 SELECTIVE

- Celecoxib, etoricoxib, rolicoxib, lumaricoxib

CLASSIFICATION (contd.)

ACETIC ACID DERIVATIVES

- Indomethacin
- Diclofenac
- Etodolac
- Sulindac
- Ketorolac
- Tolmetin

CLASSIFICATION (contd.)

PARA-AMINO PHENOL DERIVATIVE

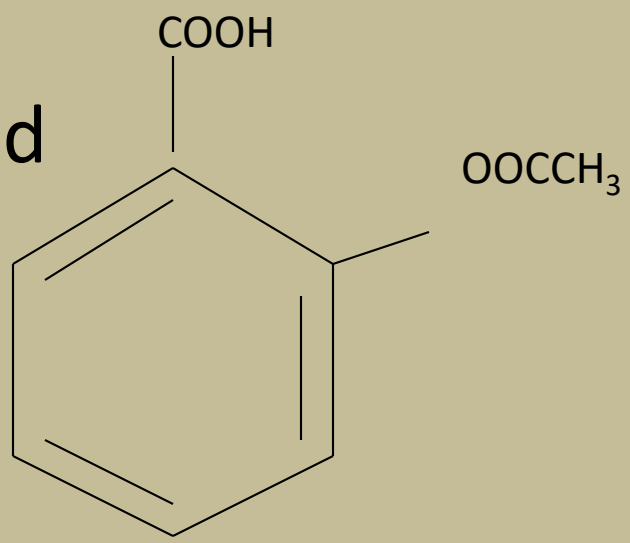
- Paracetamol

General properties in common:

- Organic acids EXCEPT nabumetone
- Well absorbed
- Strongly protein bound
- Highly metabolized
- Renal excretion mainly
- Varying enterohepatic circulation
- Distributed in synovial fluid

Aspirin (Acetylsalicylic acid; ASA)

- Willow bark- Salicin
- Synthesized in 1853
- Organic acid
- Ester of acetic acid



HISTORY

- Salicylic acid-natural product, present in the bark of willow and poplar trees
- Active ingredient, isolated by a French pharmacist in the 18th century, was Salicin, oxidized to Salicylic acid
- In 1828 a Swizz pharmacist, Lowig, distilled meadowsweet flowers and got salicylaldehyde
- 1897, a chemist at the Bayer Company produced acetylsalicylic acid
- The name ***Aspirin*** was coined by adding an ***a*** for acetyl to ***spirin*** from the name of the plant (*Spirea ulmaria)* from which salicylic acid was first isolated

ANTI INFLAMMATORY DRUGS

PHARMACOKINETICS

- All= weak acids except Nebutomone (ketone)
- Racemic, single (naproxen), non (diclofenac)
- Biotransformation= phase 1 & 2 reactions
- CYT P_{450} 2C, CYT P_{450} 3A
- Enterohepatic circulation
- Excretion = renal

Pharmacokinetics

- Rapidly absorbed from stomach and upper small intestine
- Hydrolyzed to acetic acid and salicylate by esterases in tissue and blood
- Bound to albumin
- **ZERO ORDER KINETICS**
- Conjugated in liver and cleared by kidney
- Excretion: 25 % excreted unchanged & 75 % as metabolites in urine ,enhanced by ALKALINIZATION
- $t_{1/2}$ 15mins but antiplatelet action 8-10 days

ANTI INFLAMMATORY DRUGS

PHARMACODYNAMICS

Inhibition of prostaglandins = cycloxygenase

Reversible acetylation (aspirin= irreversible)

Minor mechanisms

- Inhibition of chemotaxis
- IL 1 down regulation
- Decreased free radicals & superoxides
- Interference with intracellular calcium

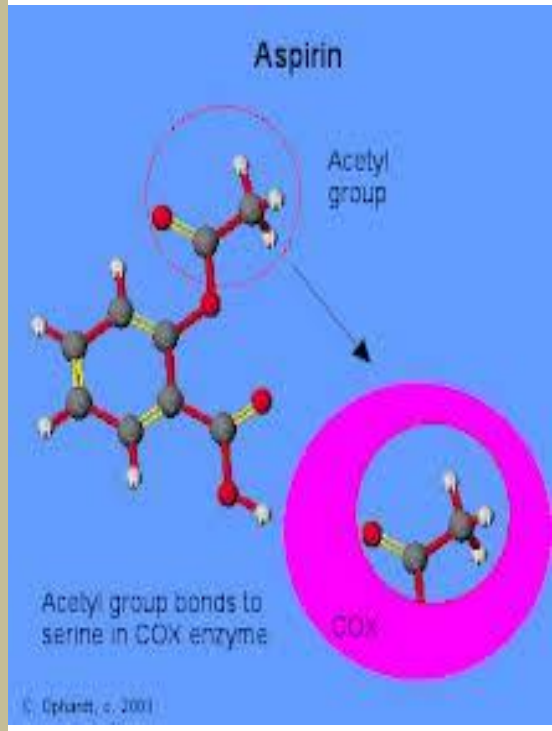
PHARMACODYNAMICS……

- ✓ NOT Disease Modifying
- ✓ Non selective inhibition = most
- ✓ Aspirin, indomethacin, piroxicam and sulindac = mostly COX 1
- ✓ Ibuprofen, meclofenamate = both equally
- ✓ Celecoxib, Refocoxib, Valdecoxib, melocoxib and etoricoxib = selective COX 2 inhibitors

  same efficacy, gastroprotection , more edema

Mechanism of Action

- Inhibits both COX-I and COX-II
  - Anti-inflammatory
  - Analgesic
  - Antipyretic
- Aspirin irreversibly inhibits platelet COX
  - Anti-platelet effect (lasts 8-10 days)



ANTI-INFLAMMATORY (in large doses)

- Rheumatoid arthritis
- Ac rheumatic fever along ē benzyl penicillin

ANTI-PYRETIC

- Lowers fever

AS ANTI-PLATELET (in low doses 75 – 100mg/day)

- For transient ischemic attacks & cerebrovascular stroke
- Prophylaxis of unstable angina, MI
- Thrombosis after coronary artery by pass grafting

Anti –inflammatory effect

Inhibits PG synthesis at the periphery

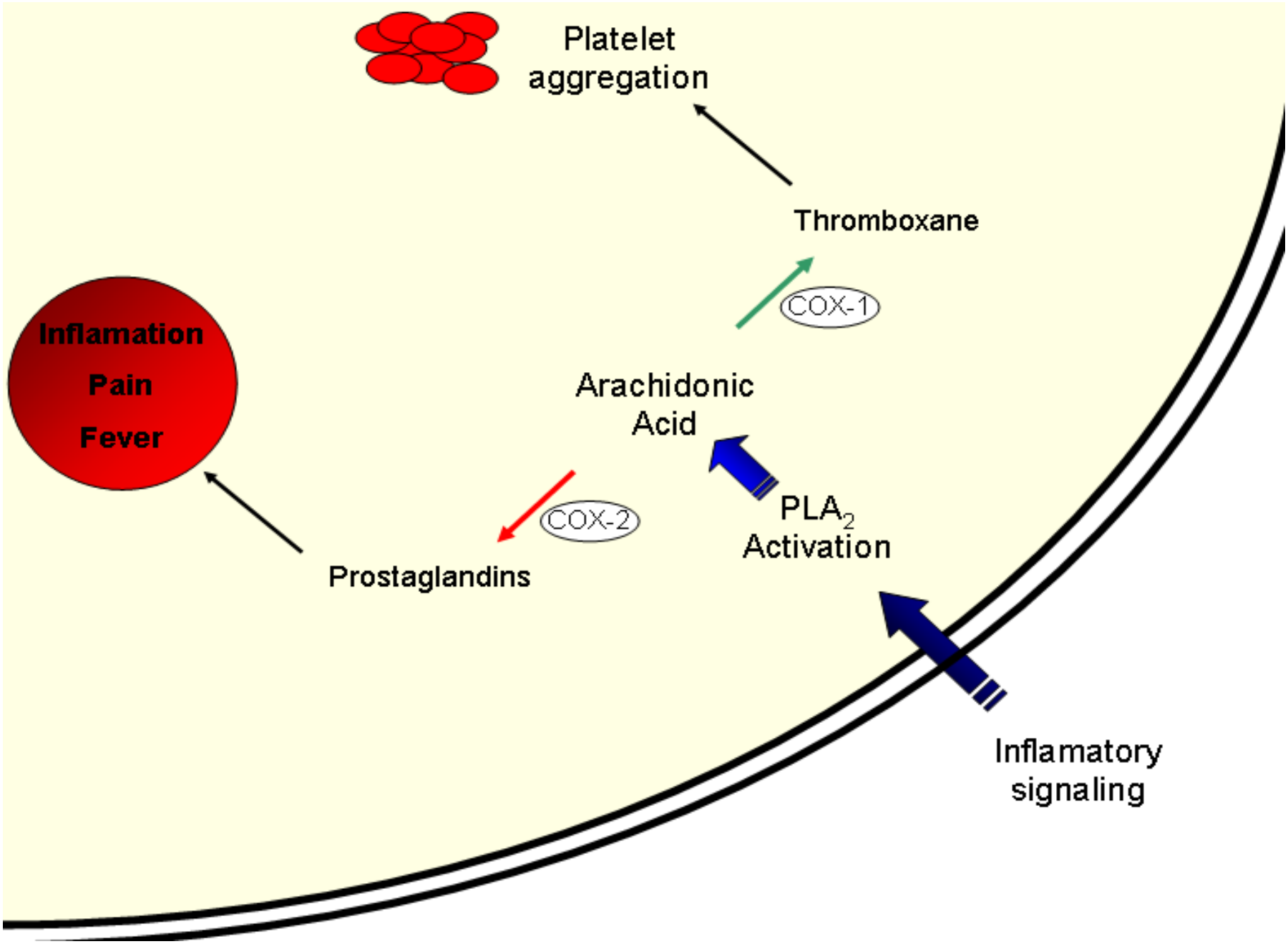
- Inhibit migration of polymorphs and macrophages at site of inflammation
- Inhibition of granulocytes adherence to damaged vasculature
- Stabilizes lysosomes
- Interferes with chemical mediators of kalikrein system

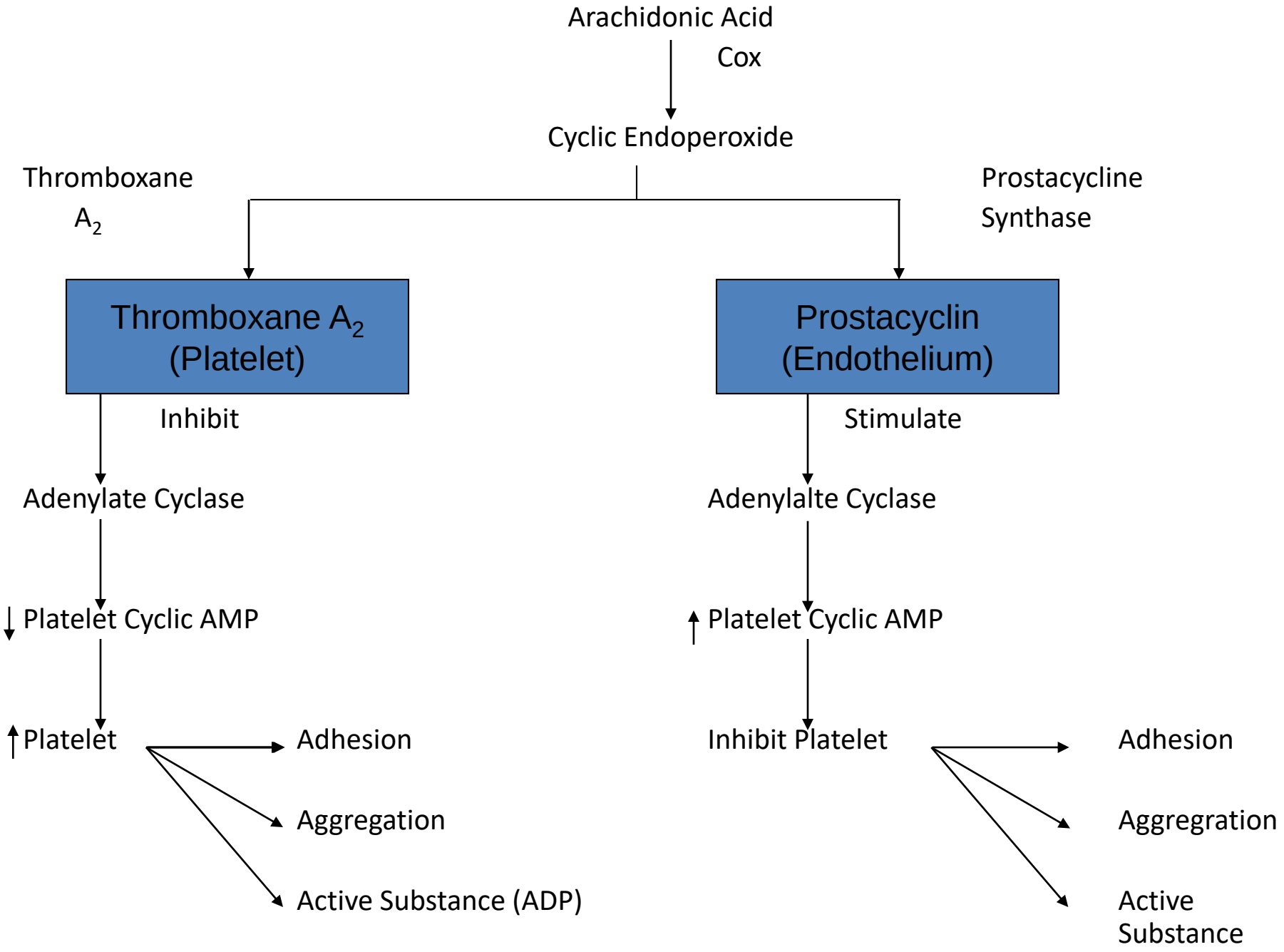
Antipyretic

- Aspirin reduces only elevated temperature & has no effect on normal temperature
- Aspirin resets the temperature regulating centre to normal by inhibition of PGE_2 synthesis
- Blocks the action of IL-1 released from macrophages by action of bacterial endotoxins / inflammation
- Vasodilatation of superficial blood vessels causing inc. dissipation of heat

Antiplatelet effect

- Aspirin in small doses decreases platelet aggregation by suppressing the synthesis of thromboxane A_2
- It irreversibly acetylates the COX
- Effect lasts for 8 – 10 days till new platelets are regenerated
- High doses suppress prostacyclins also & platelet inhibitory effect is lost


Platelet aggregation
Thromboxane
COX-1
Inflamation
Pain
Fever
Arachidonic Acid
COX-2
PLA2 Activation
Prostaglandins
Inflamatory signaling


Arachidonic Acid
Cox
Cyclic Endoperoxide
Thromboxane
A2
Prostacycline
Synthase
Thromboxane A2
(Platelet)
Prostacyclin
(Endothelium)
Inhibit
Stimulate
Adenylate Cyclase
Adenylalte Cyclase
Platelet Cyclic AMP
Platelet Cyclic AMP
Platelet
Adhesion
Aggregation
Active Substance (ADP)
Inhibit Platelet
Adhesion
Aggregration
Active
Substance

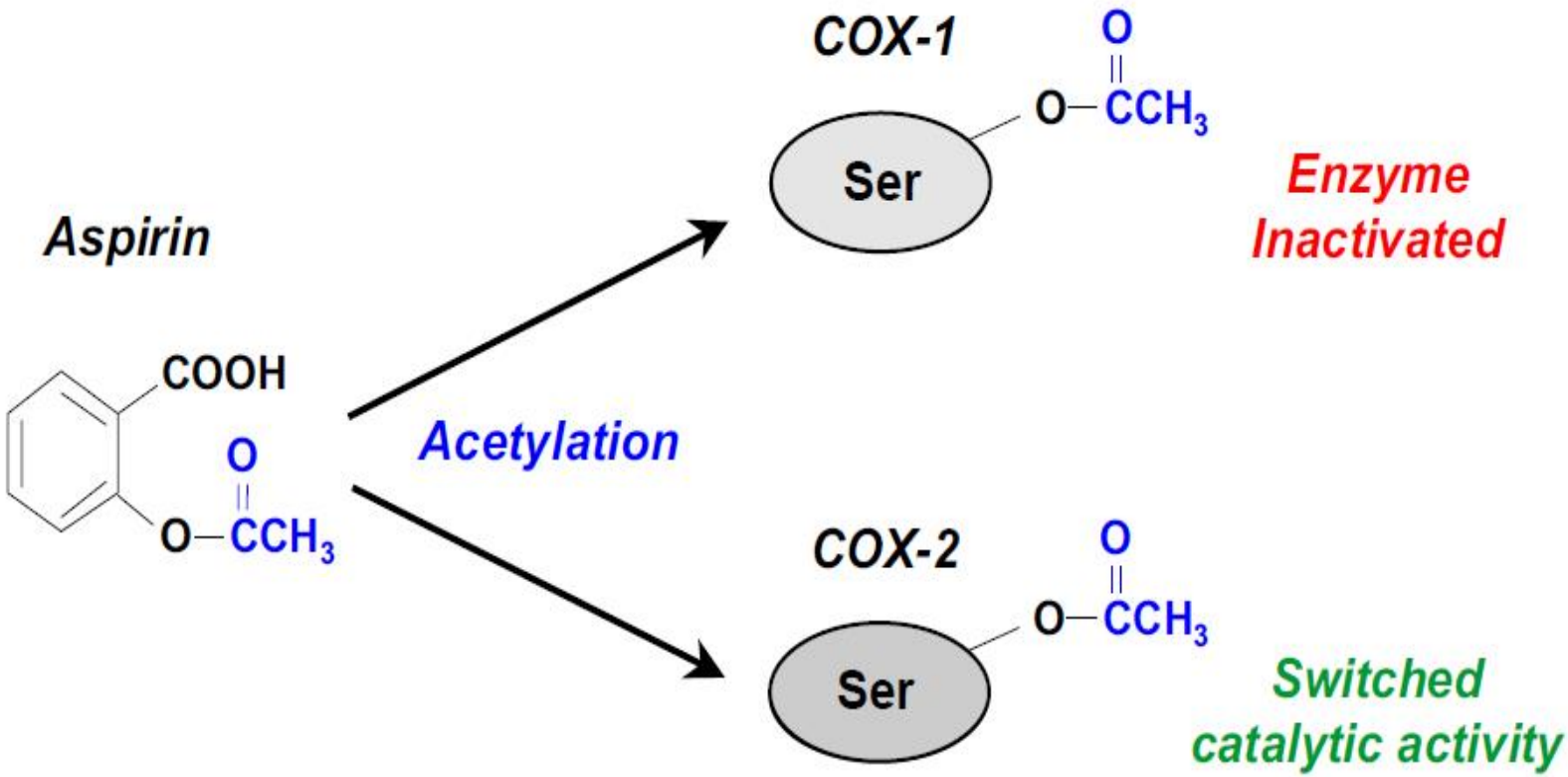
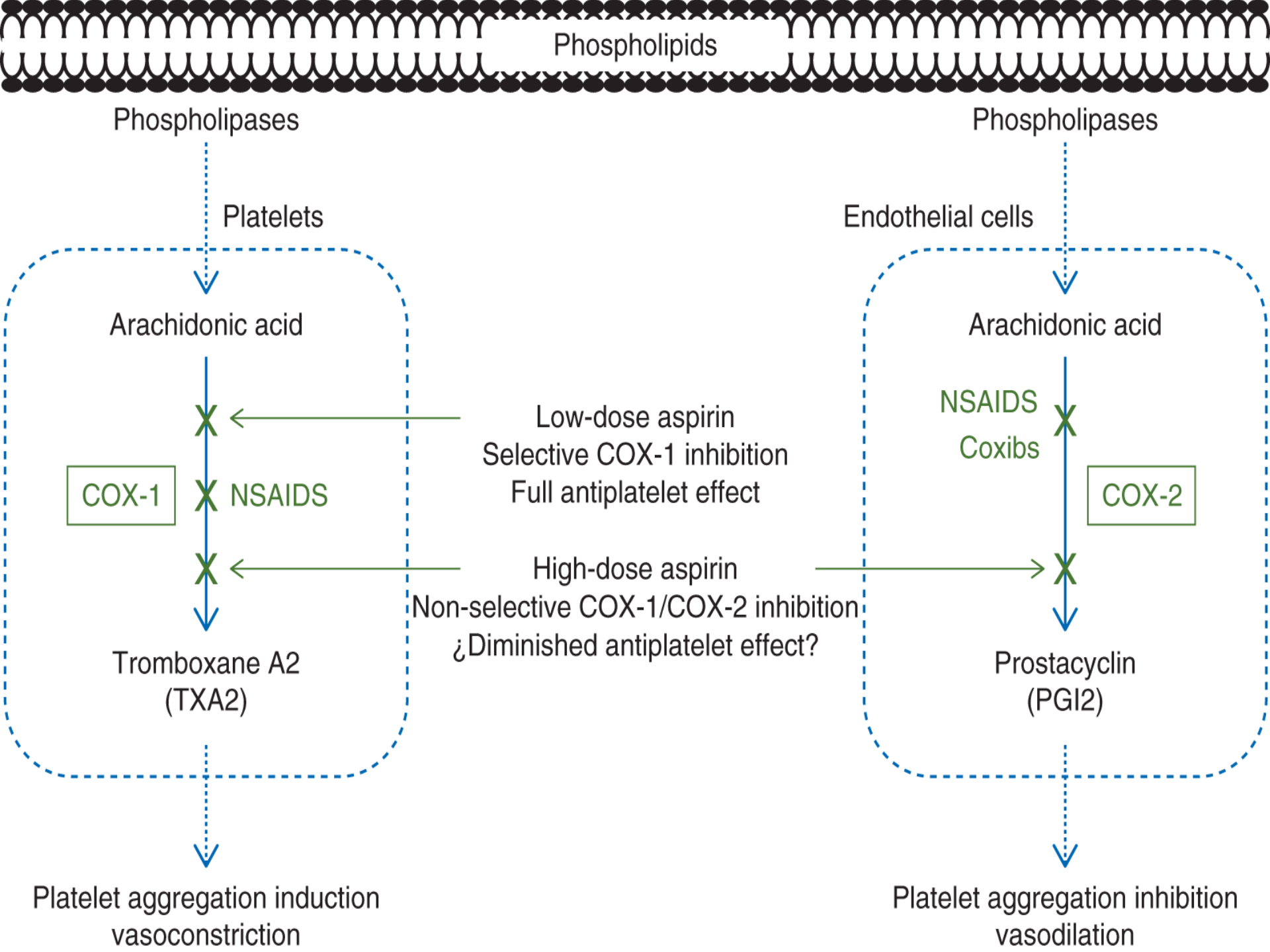
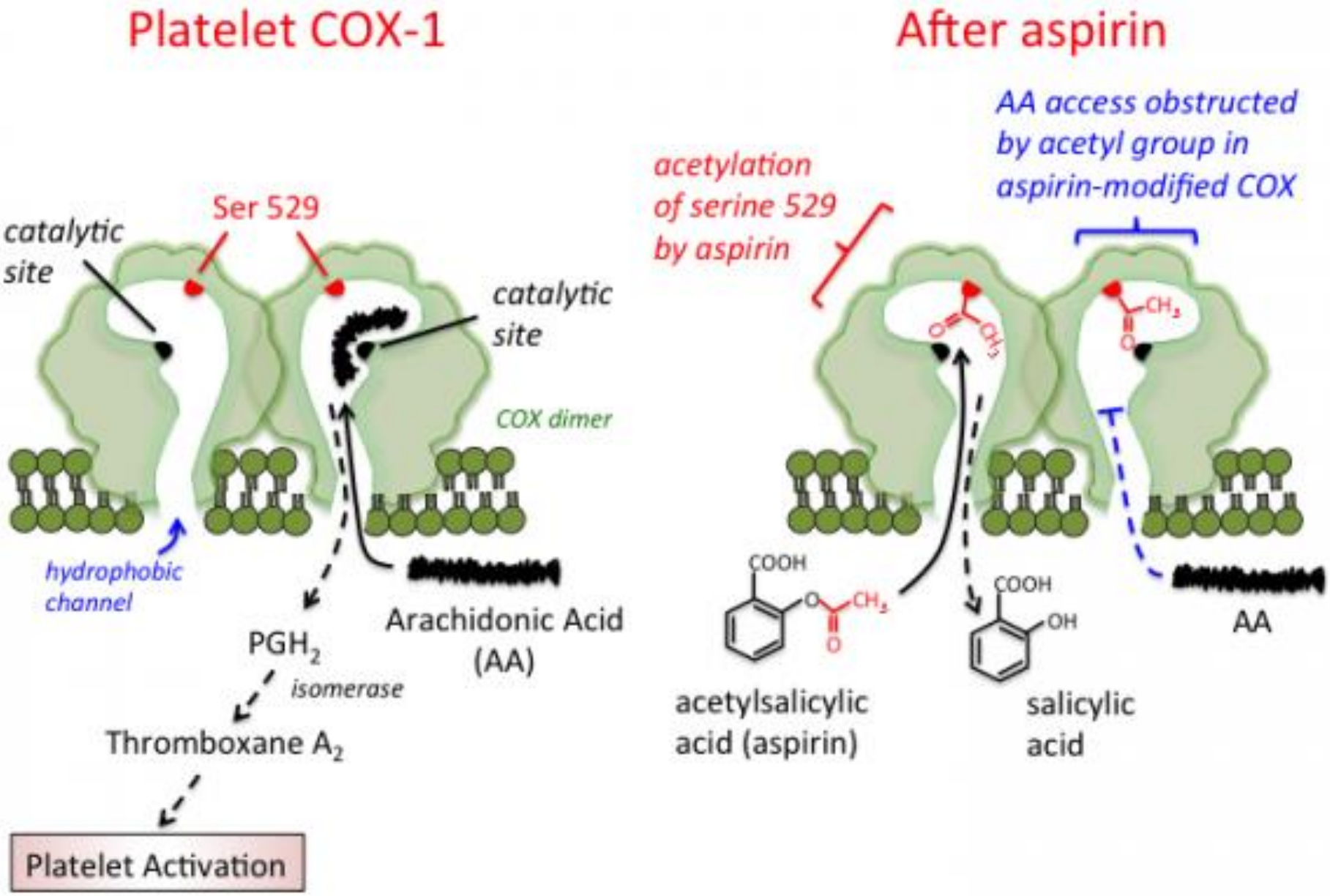


Figure 1. Aspirin mechanism of action -- acetylation of cyclooxygenase (COX). Aspirin acetylates a serine (Ser) residue of COX and irreversibly inactivates COX-1. In the case of COX-2, aspirin "turns off" its ability to generate prostaglandins, but "switches on" its capacity to produce novel protective lipid mediators.


Phospholipids
Phospholipases
Platelets
Arachidonic acid
COX-1
NSAIDS
Tromboxane A2
(TXA2)
Platelet aggregation induction
vasoconstriction
Low-dose aspirin
Selective COX-1 inhibition
Full antiplatelet effect
High-dose aspirin
Non-selective COX-1/COX-2 inhibition
¿Diminished antiplatelet effect?
Phospholipases
Endothelial cells
Arachidonic acid
NSAIDS
Coxibs
COX-2
Prostacyclin
(PGI2)
Platelet aggregation inhibition
vasodilation


Platelet COX-1
After aspirin
AA access obstructed by acetyl group in aspirin-modified COX
acetylation of serine 529 by aspirin
Ser 529
catalytic site
catalytic site
COX dimer
hydrophobic channel
Arachidonic Acid (AA)
PGH2
isomerase
Thromboxane A2
Platelet Activation
COOH
CH3
COOH
OH
AA
acetylsalicylic acid (aspirin)
salicylic acid

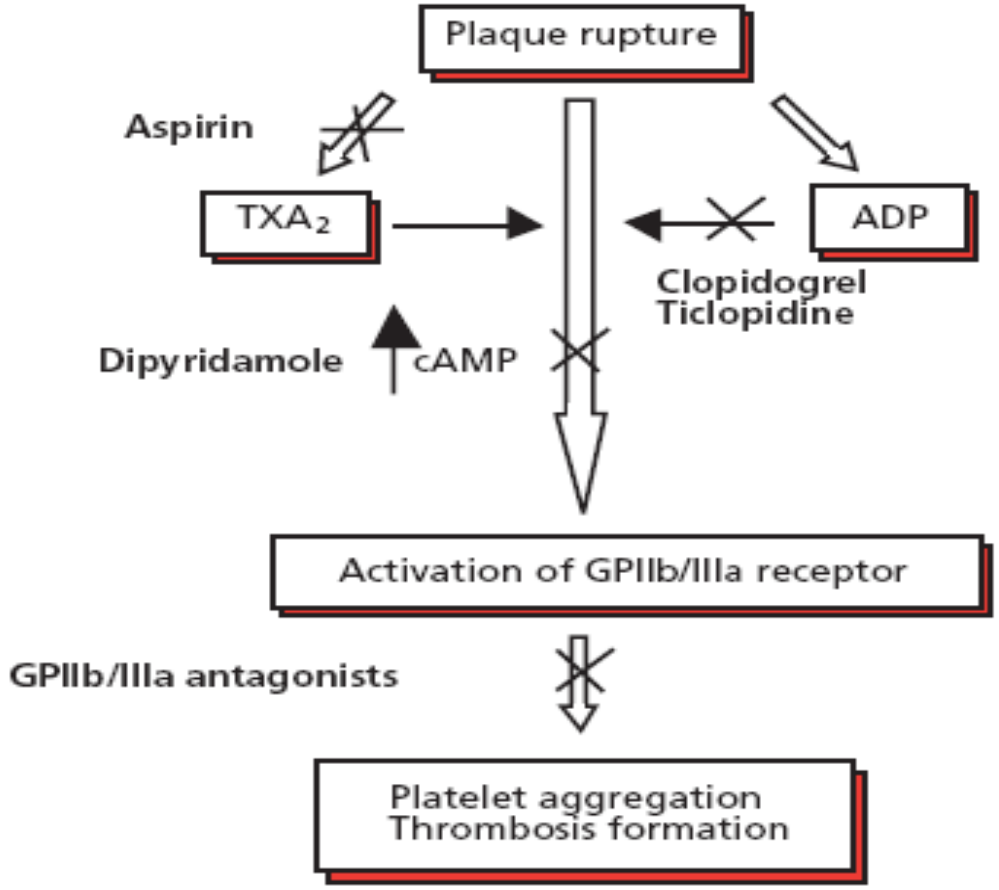
- The aspirin induced suppression of thromboxane A2 synthetase and the resulting suppression of platelet aggregation last for the life of the anucleate platelet approximatery 7 to 10 days. Thus asprin induced prolongation of B.T last for 5-7 day

ANTIPLATELET DRUGS

These are the drugs which interfare with platelet function and useful in the prophylaxis of thromboembolic disorders.

Clinically important antiplatelet drugs are:

- Aspirin
- Dipyridamole
- Ticlopidine
- Eptifibatide
- Clopidogrel
- Abciximab
- Tirofiban



Key: TXA_2 = thromboxane; GP = glycoprotein; ADP = adenosine diphosphate; CAMP = cyclic adenosine monophosphate

Analgesic Effect

- Reduces mild to moderate pain of varying cause (pain of musculoskeletal structures) relieved better than of visceral origin
- Mainly acts at periphery at nociceptive level so effective in pain associated with inflammation (pain of muscular, vascular & dental origin, postpartum states, arthritis & bursitis is relieved)

Effect on GIT

a. Vomiting-- Stimulation of CTZ
b. Dose related gastric ulceration & hemorrhage, due to inhibition of protective PGI_2
   - Ischemia of gastric mucosa
   - Increased gastric acid secretion & pepsin
   - Inhibition of gastric mucous secretion

Other effects

- **Uricosuric action**: dependent on dose
- In high doses above 4 gms
- **CVS:**

a) In low doses--- cardioprotective effect
b) In large doses--- increased circulating volume and peripheral vasodilatation
c) In toxic doses--- depress circulation directly & by central Vasomotor paralysis

- **Respiration:**

a) In therapeutic doses, Increased depth of resp.
b) In large doses-Compensated resp. alkalosis
c) In toxic doses - Uncompensated resp. acidosis

ANTI INFLAMMATORY DRUGS

USES; most NSAIDS are effective

- Rheumatoid arthritis/Rheumatic heart disease
- Ischemic heart disease
- Inflammatory bowel disease/reactive arthritis
- Ankylosing spondylitis,Psoriatic arthritis, Gout
- Trauma, post operative, dental diseases
- Menstrual disorders/ dysmenorrhoea
- Patent ductus arteriosus, carcinoma colon

INDOMETHACIN & OTHERS….

Additional uses (Indomethacin)

- PDA
- Juvenile RA/ post laminectomy syndrome
- Pleurisy
- Nephrotic syndrome/Diabetes insipidus
- Post arthroplasty (heterotropic calcification)
- Corneal abrasions (opthalmic drops)
- Gingivitis (oral gel)

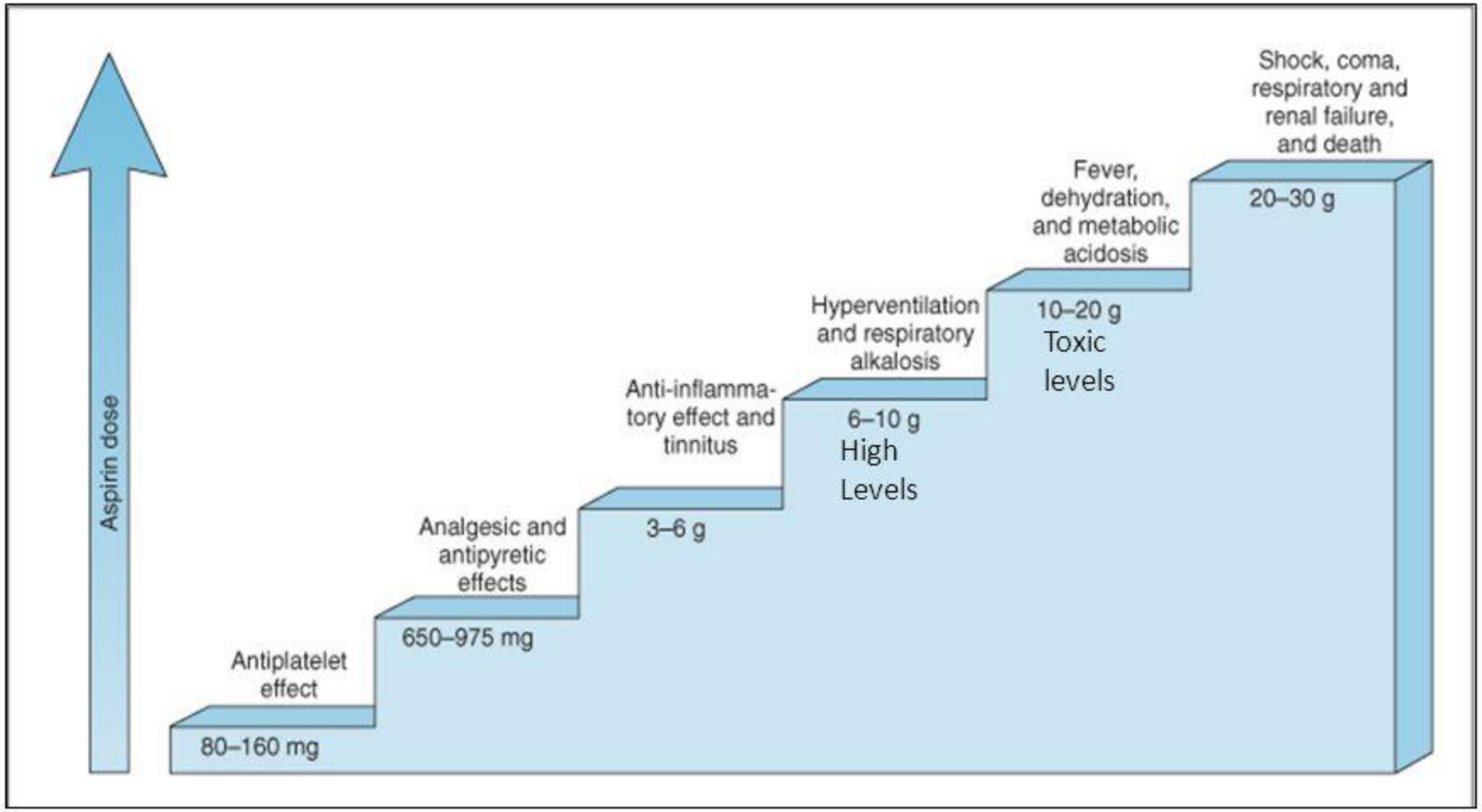
ASPIRIN (ASA)

- ASA = Pka, 3.5 vs 3.0 (salicylic acid)
- Esterases = 15 minutes ---acetic acid and salicylates--- stomach, upper GIT
- Avoid = concomitant ibuprofen, probenecid
- Can use acetaminophen
- Albumin bound, Elimination $t_{1/2}$ = 3-5 hours
- Salicylism, respiratory alkalosis, metabolic acidosis--- urinary alkalization, dialysis

DOSAGE

- Prevention of stroke and MI 75-150 mg inhibits platelet aggregation
- Analgesic effect 300 mg 6 hourly to max of 4 gm daily
- Osteoarthritis and rheumatoid arthritis, 900 mg every 6 hourly
- Acute rheumatic fever, 0.9-1.2 g every 4 hourly max of 8 gm

Dose dependent effects of Aspirin



ANTI INFLAMMATORY DRUGS

ADVERSE EFFECTS

- CNS= headache, tinnitis, dizziness
- CVS= edema, hypertension, CCF
- GIT= Dyspepsia, bleeding, nausea, vomiting
- Hematological= thrombocytopenia, aplastic anemia(rare), neutropenia
- Renal= Hyperkalemia, proteinuria, azotemia
- Hepatitis, asthma, rashes, SJ syndrome

ADVERSE EFFECTS OF ASPIRIN

1. **Gastric upsets:**

- Erosive gastritis & Gastric ulceration
  - Hematemesis
  - Melena
  - Occult Blood In stool

- Dyspepsia and heart burn
- Nausea & vomiting

2) Effects on CNS

Salicylism:

- (In large doses): Tinnitis, deafness, dimness of vision, dizziness, ataxia, mental confusion, vertigo, nausea & vomiting, sweating, thirst
- (In Toxic Doses): Hyperpyrexia, CV collapse, convulsions, ketosis, coma

3) Related to Kidney:

Analgesic Nephropathy

4) **Reye syndrome**

4. **Respiratory system**
- Hyperventilation
- Compensated respiratory alkalosis (high doses)
- Uncompensated acidosis (toxic doses)

5. **Blood**
- Hypoprothrombinaemia
- Increase bleeding tendency

6. **Allergic / Hypersensitivity Reactions**
- Bronchospasm
- Urticaria
- Rhinitis
- Hay Fever

IBUPROFEN

- Phenylpropionic acid derivative
- Anti inflammatory effect start at 2400 mg/dl (equivalent to 4gm aspirin anti-inflammatory effect)
- Lower dose has analgesic effect
- Closure of patent ductus arteriosus in preterm infants
- Less decrease in urine output, less fluid retention
- Decreases antiplatelet effect of aspirin
- Oral I/V, topical

INDOMETHACIN

- Indole derivative
- Potent non-selective COX inhibitor and may also inhibit phospholipase A and C
- Reduce neutrophil migration and decrease T-cell and B-cell proliferation
- Effective in joint pain, swelling & tenderness
- Gout, arthritis
- Accelerate closure of patent ductus arteriosus
- Pancreatitis, frontal headache
- $t_{1/2}$ prolonged by probenicid

DICLOFENAC SODIUM

- Phenylacetic acid derivative
- Combinations are available (+ misoprostol)
- 150 mg/d impair renal blood flow & GFR
- GI ulceration less frequent
- Elevation of serum aminotransferases

Preparations: eye drops, topical gel, suppository

Dose: 50-75mg qid

OTHERS….

KETOPROFEN

- Both lipoxygenase and cycloxygenase enzymes are inhibited
- Intravenous and oral

KETOROLAC

- Analgesic without much anti inflammatiory properties
- May obviate the need for opiods

OTHERS….

- MEFANAMIC ACID
- Inhibits both cycloxygenase and phospholipase A
- DICLOFENAC SODIUM
- Avoid with Aspirin
- Hepatotoxic : like Sulindac

DRUG INTERACTIONS

- Concomitant NSAID's & low dose aspirin
- ACE inhibitors
- Warfarin
- Sulfonylurea hypoglycemics
- Methotrexate

Management of aspirin/salicylate overdose toxicity/poisoning (salicylism)

1. Gastric lavage
2. Activated charcoal
3. Correct fluid, electrolyte & acid base balance
4. Maintain high urine out put
5. Keep airway patent
6. ↓ Body temp. by cold sponging
7. Vit. K I/V to correct hypopthrombinemia
8. Diazepam I/V for convulsions
9. Promote excretion of salicylates by $NaHCO_3$ I/V to alkalinize urine ,maintain pH at 8.0
10. Hemodialysis in pts. with severe acidosis & coma

1. Choose the drug which alter surface receptors on platelet membrane to inhibit aggregration
   a. Dipyridamole
   b. Ticlopidine
   c. Aspirin
   d. Heparin

2. Following drug increase cyclic AMP in platelets and inhibit their aggregation without altering levels of thromboxane A_2 or prostacycline.
   a. Aspirin
   b. Dipyridamole
   c. Abciximab
   d. Sulfnipyrazone

3. Aspirin prolongs bleeding time by inhibiting the synthesis of
   a. Clotting factor in liver
   b. Cyclic AMP in platelet
   c. Prostacycline in vascular endothelium
   d. Thromboxane A_2 in platelet

New drug classes in development for pain and inflammation

- NO-linked NSAIDs
- Dual LOX/COX inhibitors
- iNOS inhibitors
- PAR2 receptor antagonists
- Selective opioids
- Cannabinoid receptor antagonists
- Calcium channel blockers
- Vanilloid receptor antagonists
- *N*-acetylcholine receptor antagonists
- Glycine antagonists
- Neurokinin antagonists
- Calcitonin gene-related antagonists
- COX-3 inhibitors

REFERENCES

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Email address for queries on the topic

drshams11@hotmail.com