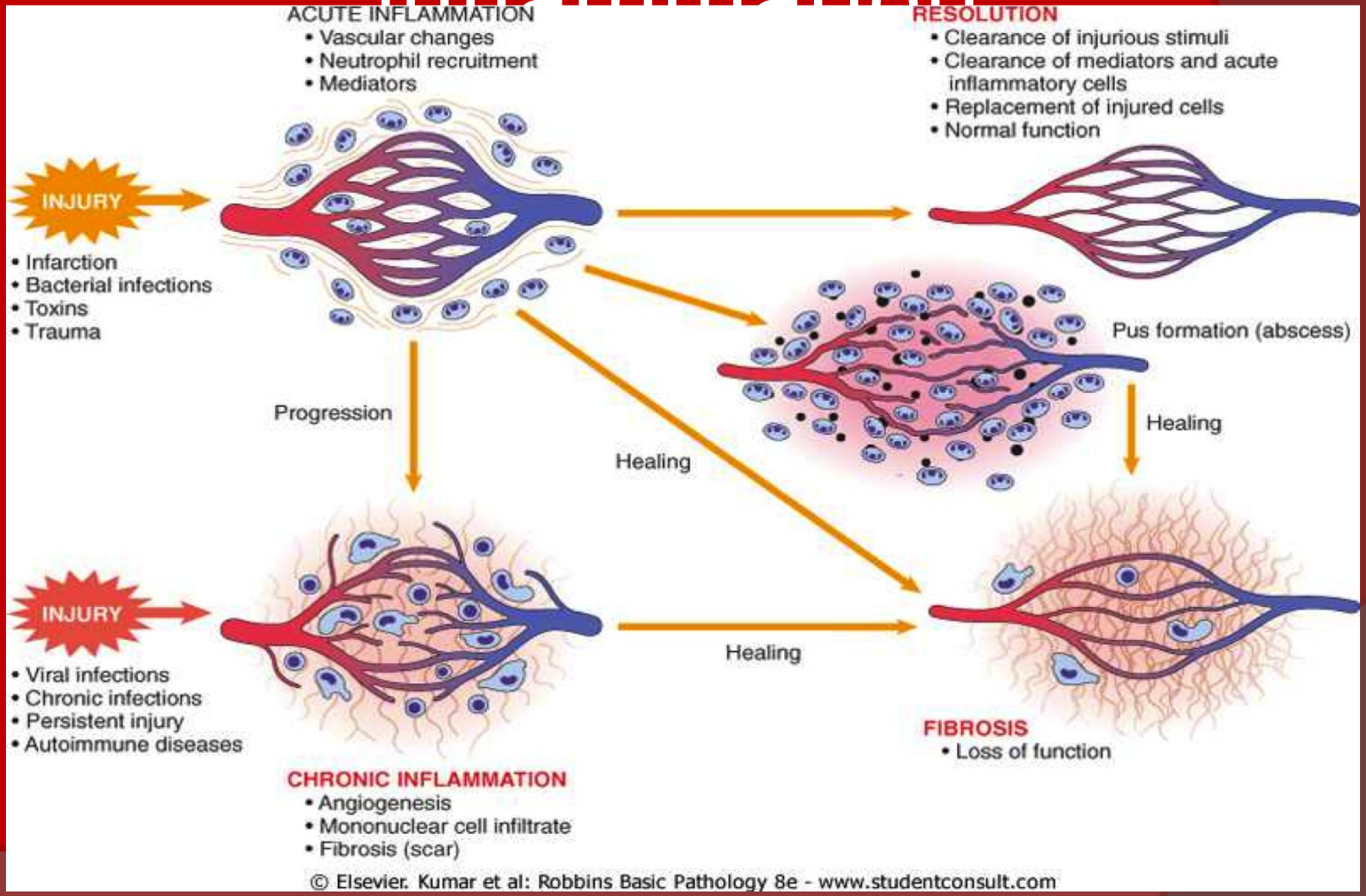
NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAID's) PARACETAMOL

THE INFLAMMATORY RESPONSE

- A protective response involving host cells, blood vessels and inflammatory mediators
- Calor (Heat)
- Dolor (Pain)
- Rubor (Redness)
- Tumor (Swelling)
- Loss of function

Outcomes of inflammation



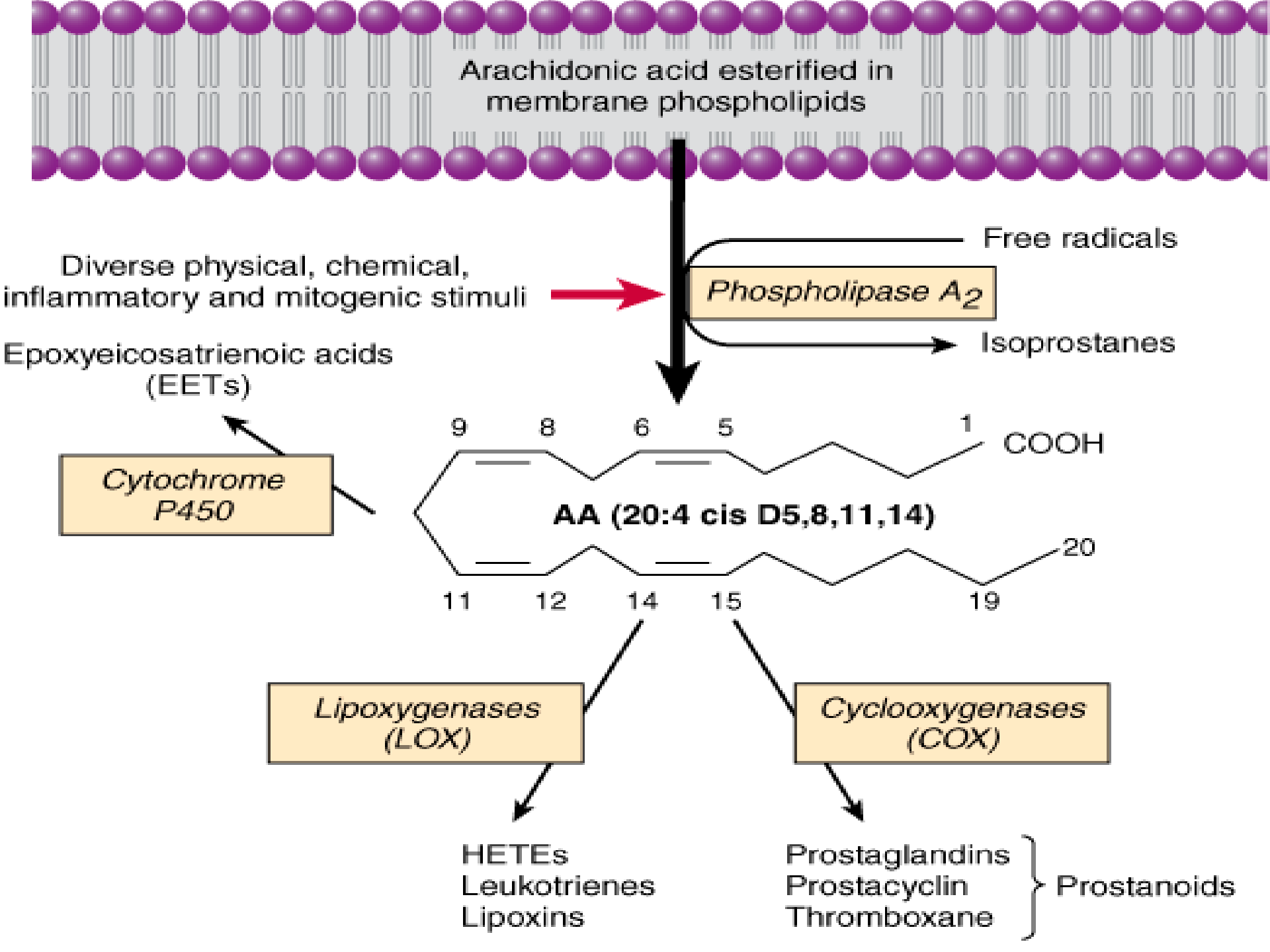
FUNCTIONS OF COX

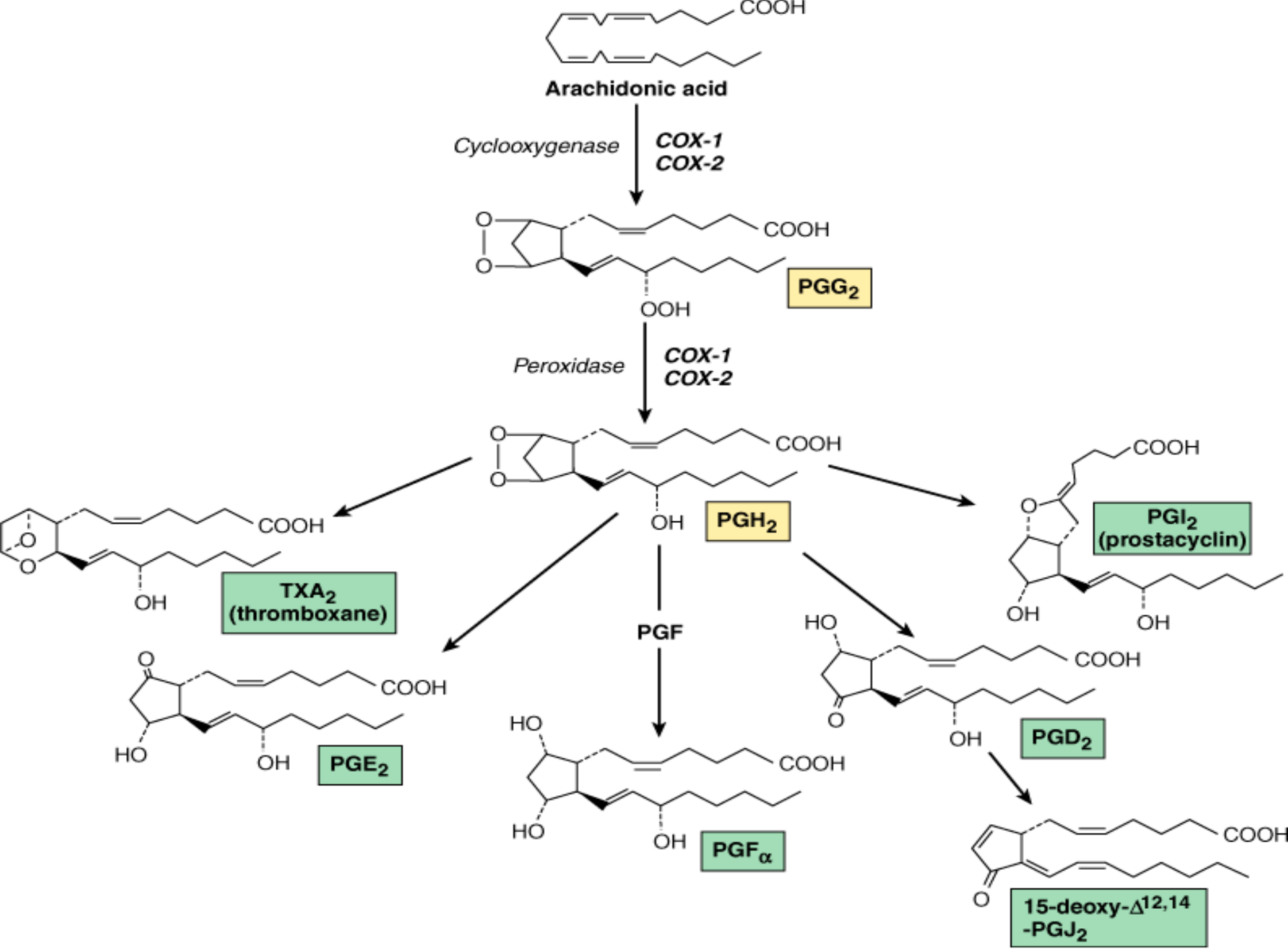
COX-1

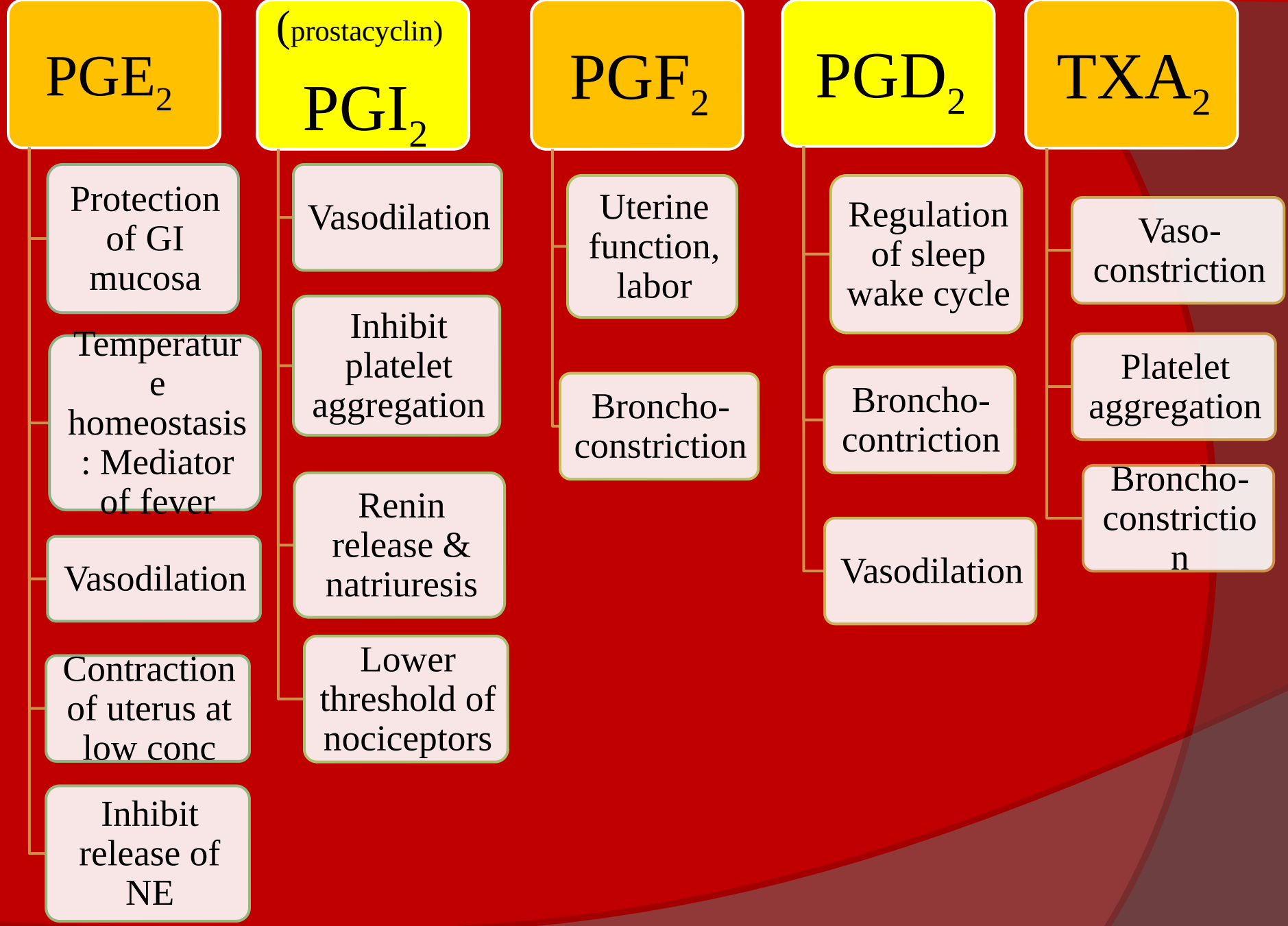
- Constitutively expressed
- Housekeeping functions
- Present in every organ stomach, intestine, kidney, **platelets,** vascular endothelium

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


COOH
Arachidonic acid
Cyclooxygenase
COX-1
COX-2
COOH
OOH
PGG2
Peroxidase
COX-1
COX-2
COOH
OH
PGH2
COOH
OH
TXA2
(thromboxane)
COOH
PGI2
(prostacyclin)
OH
OH
PGF
HO
COOH
O
OH
PGD2
COOH
HO
OH
PGE2
HO
COOH
HO
OH
PGFα
COOH
O
15-deoxy-Δ12,14
-PGJ2

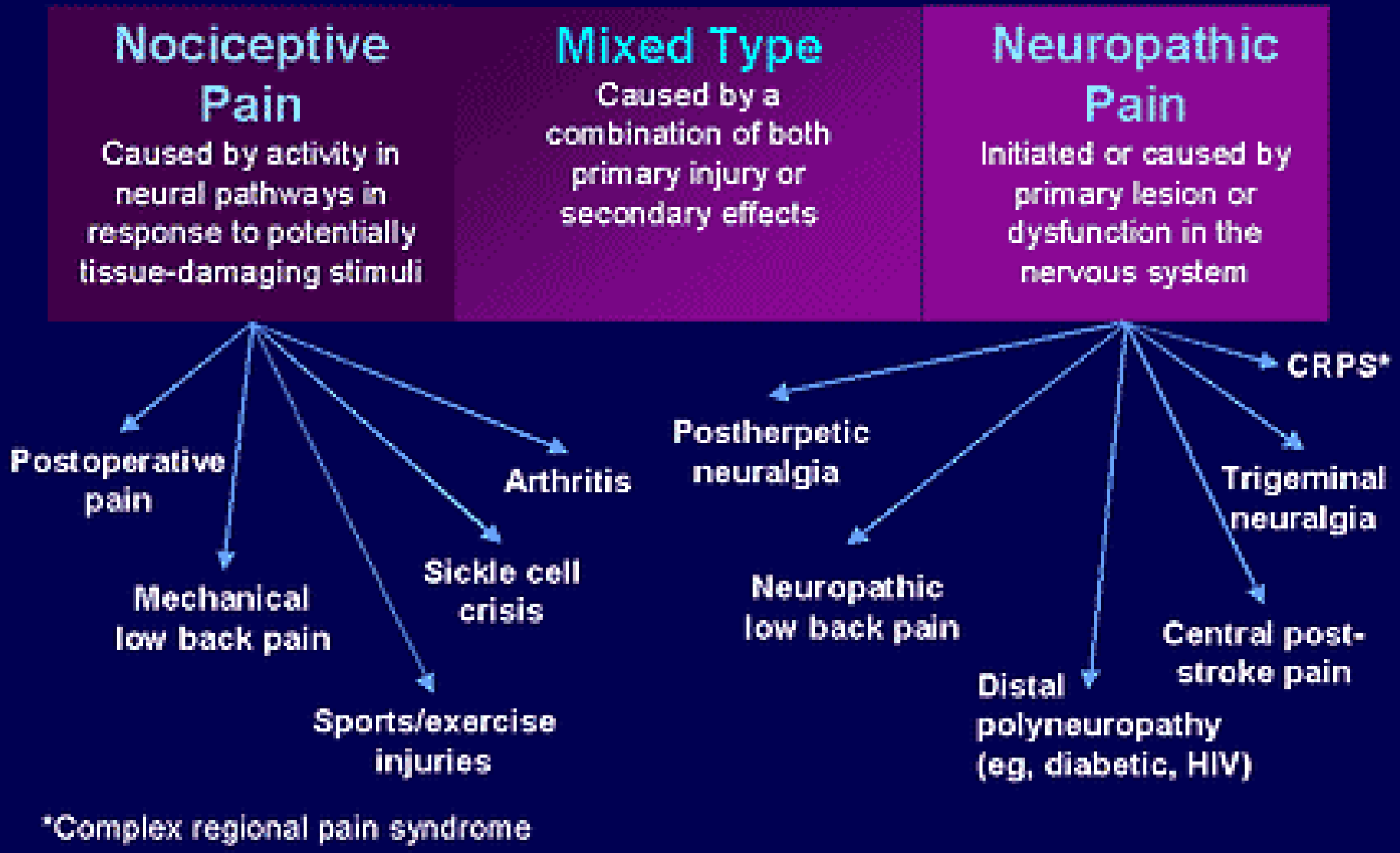

PGE_2
Protection of GI mucosa
Temperature homeostasis : Mediator of fever
Vasodilation
Contraction of uterus at low conc
Inhibit release of NE
(prostacyclin)
PGI_2
Vasodilation
Inhibit platelet aggregation
Renin release & natriuresis
Lower threshold of nociceptors
PGF_2
Uterine function, labor
Broncho-constriction
PGD_2
Regulation of sleep wake cycle
Broncho-contriction
Vasodilation
TXA_2
Vaso-constriction
Platelet aggregation
Broncho-constriction

PAIN: an unpleasant sensory or emotional experience

2 clinical states of pain:

- **Physiological (nociceptive) pain** direct stimulation of nociceptors
- **Neuropathic (intractable) pain** result from injury to the peripheral or central nervous system that causes permanent changes in circuit sensitivity and CNS connections

Nociceptive vs Neuropathic Pain



a

Primary afferent axons

Thermal threshold

Aα and Aβ fibres

Myelinated
Large diameter
Proprioception, light touch

None

Aδ Fibre

Lightly myelinated
Medium diameter
Nociception
(mechanical, thermal, chemical)

~ 53 °C Type I

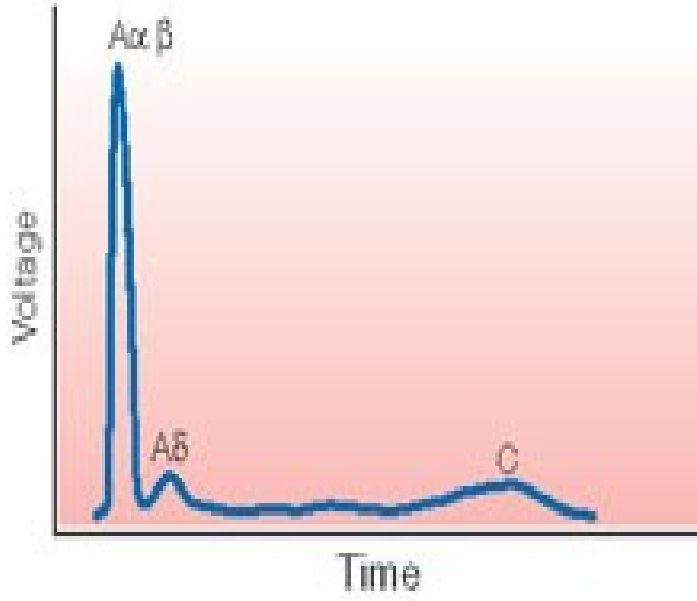
~ 43 °C Type II

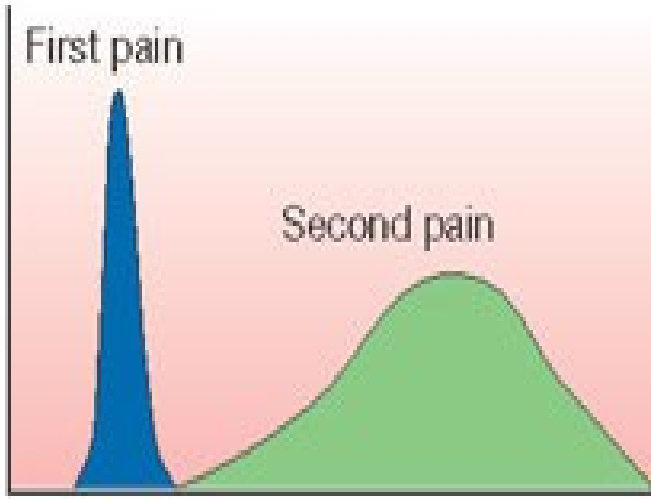
C fibre

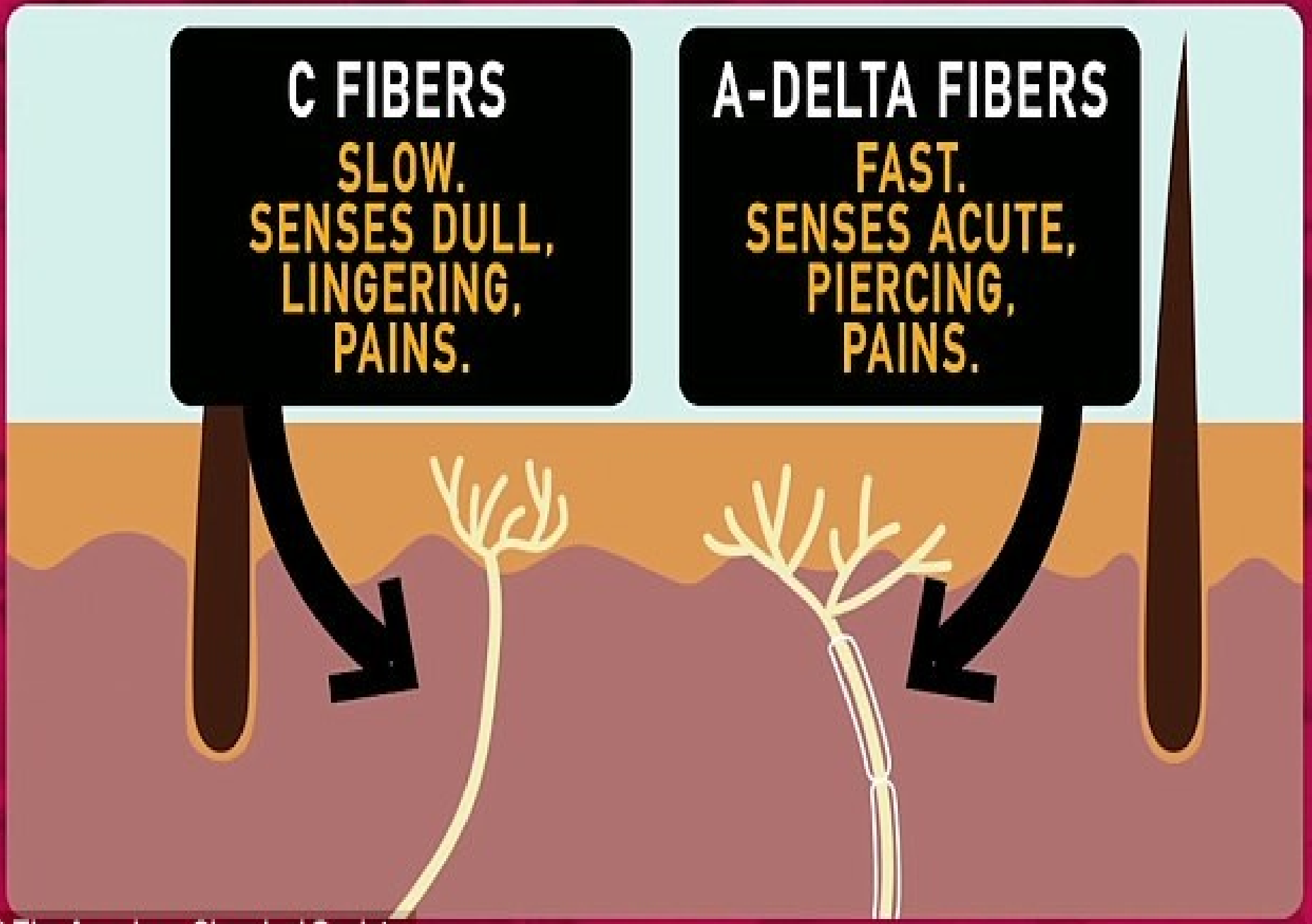
Unmyelinated
Small diameter
Innocuous temperature, itch
Nociception
(mechanical, thermal, chemical)

~ 43 °C

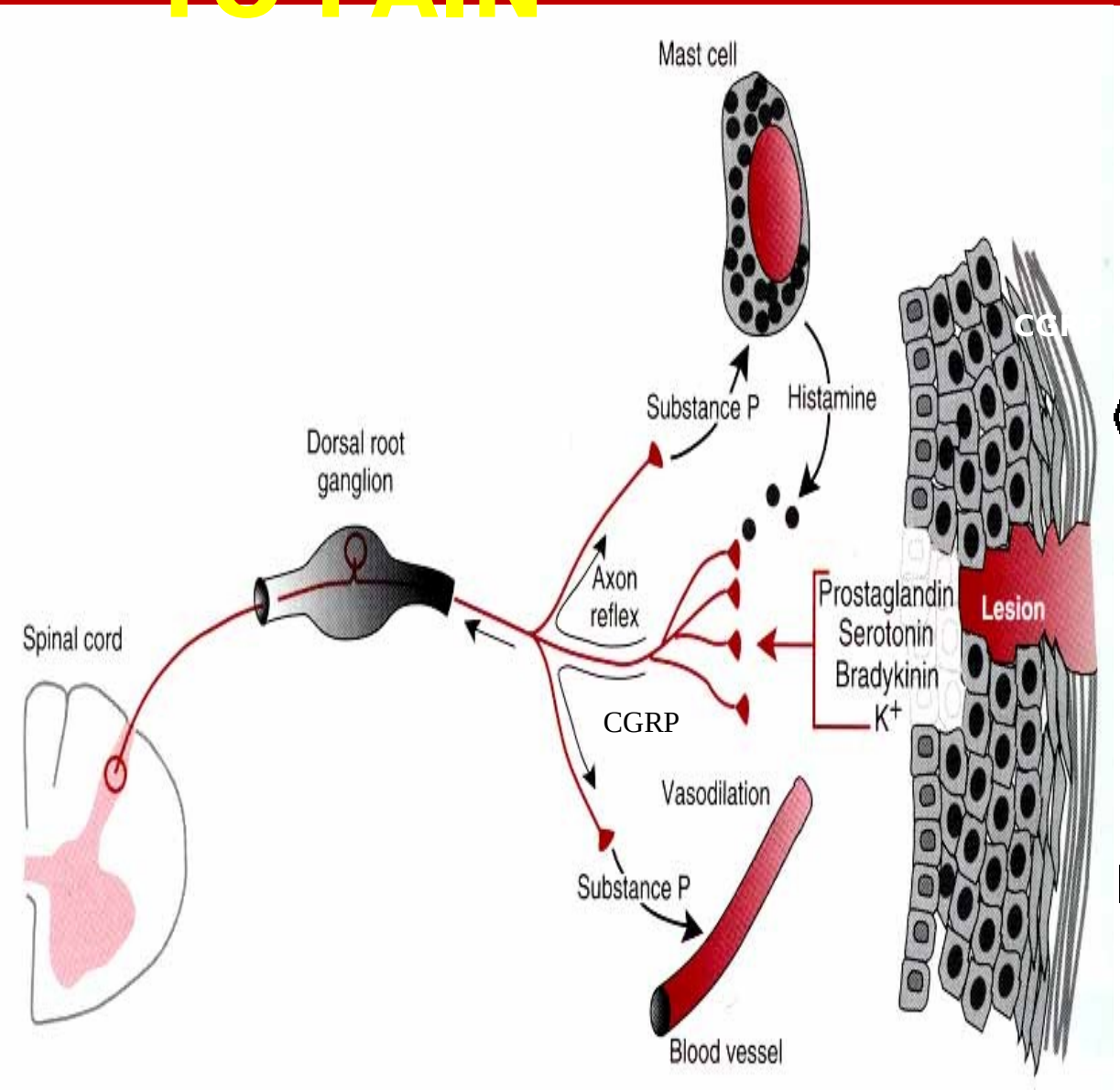
b

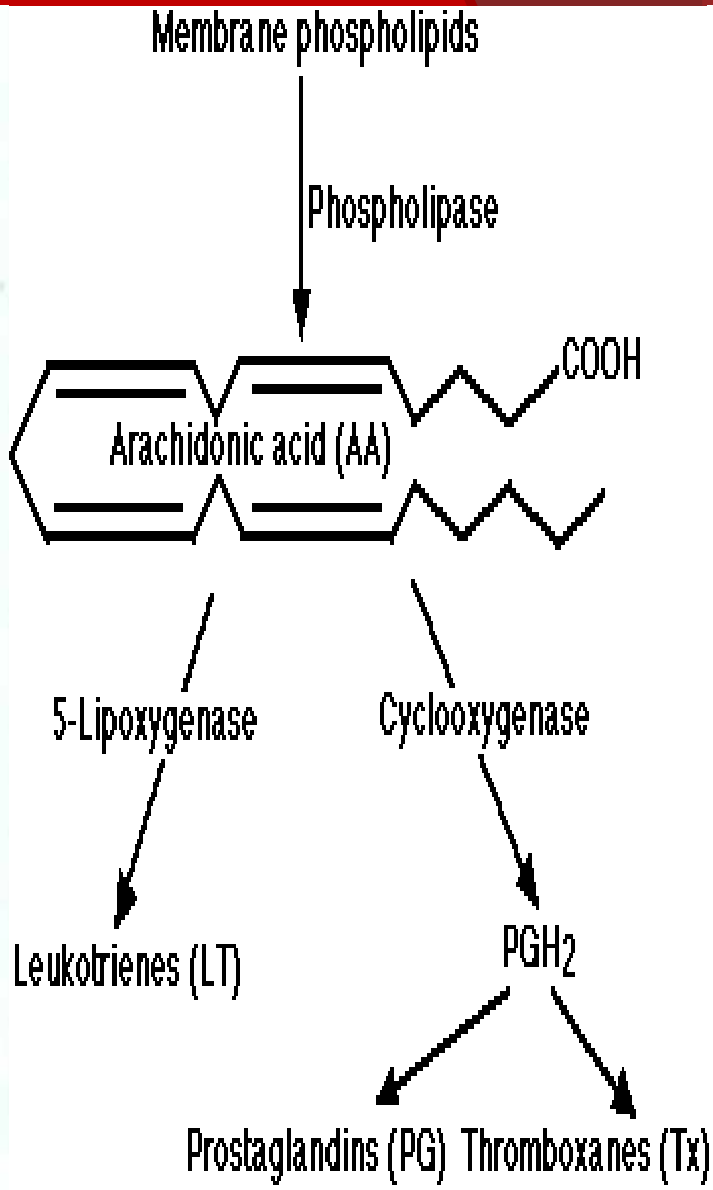


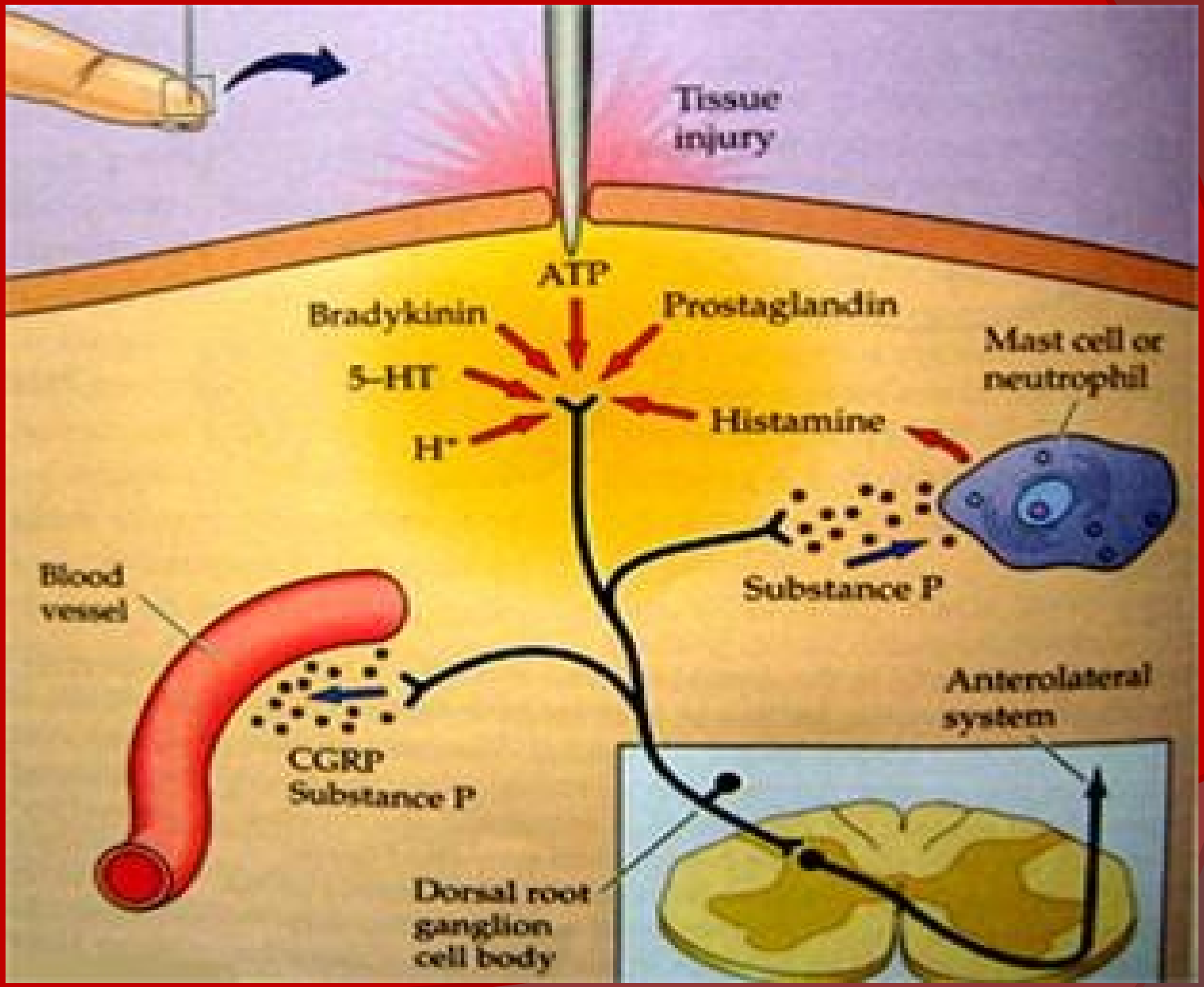




PERIPHERAL SENSITIZATION TO PAIN






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

Agents that Activate or Sensitize Nociceptors:

Cell injury → arachidonic acid → prostaglandins → ↑ vasc. permeability
(cyclo-oxygenase) → sensitizes nociceptor

Cell injury → arachidonic acid → leukotrienes → ↑ vasc. permeability
(lipoxygenase) → sensitizes nociceptor

Cell injury → ↑ tissue acidity → ↑ kallikrein → ↑ bradykinin → ↑ vasc. permeability
→ activates nociceptors
→ ↑ synthesis & release of prostaglandins

Substance P (released by free nerve endings) → sensitize nociceptors
→ ↑ vasc. perm., plasma extravasation
(neurogenic inflammation)
→ releases histamine (from mast cells)

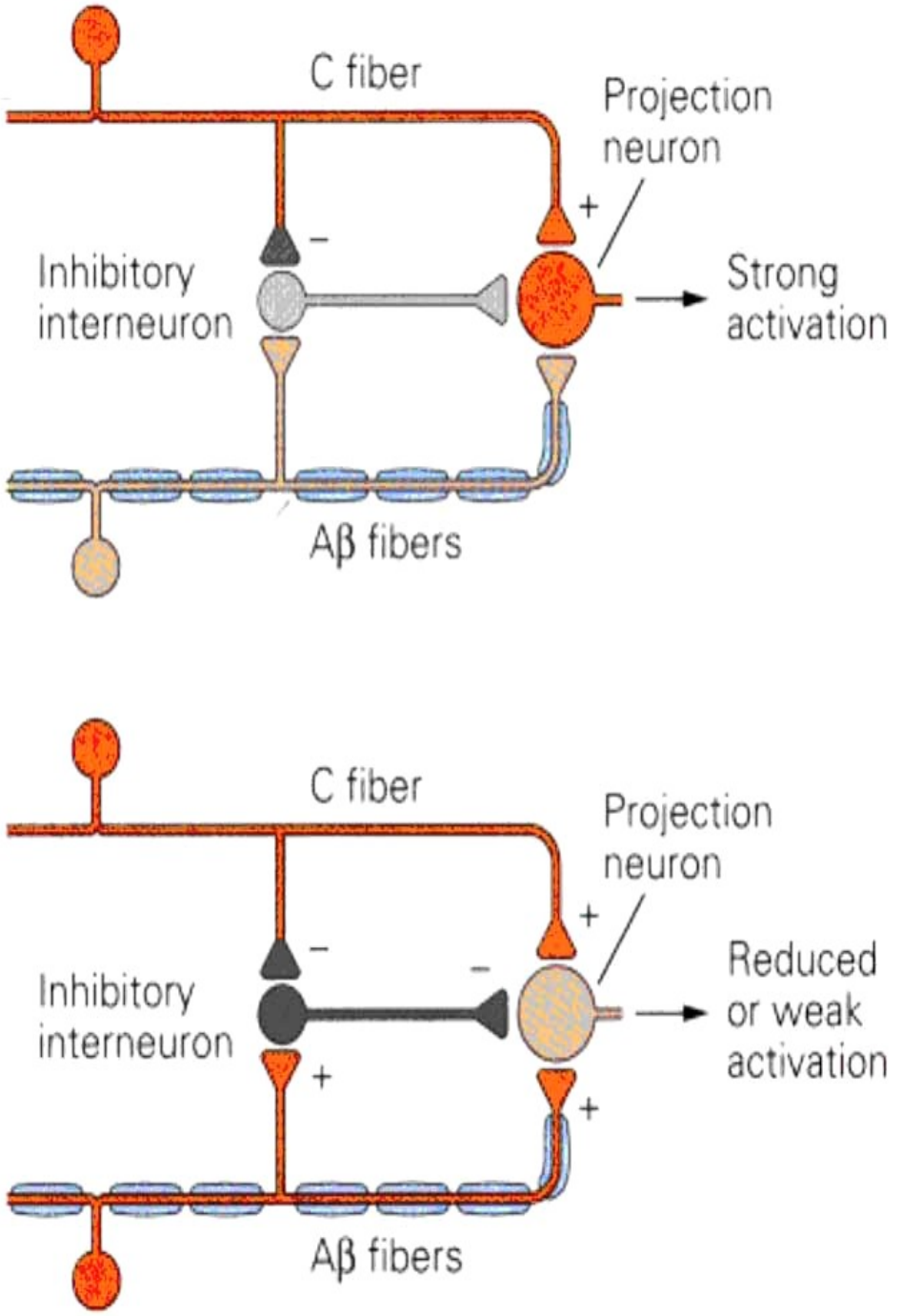
Calcitonin gene related peptide (free nerve endings) → dilation of peripheral capillaries

Serotonin (released from platelets & damaged endothelial cells) → activates nociceptors

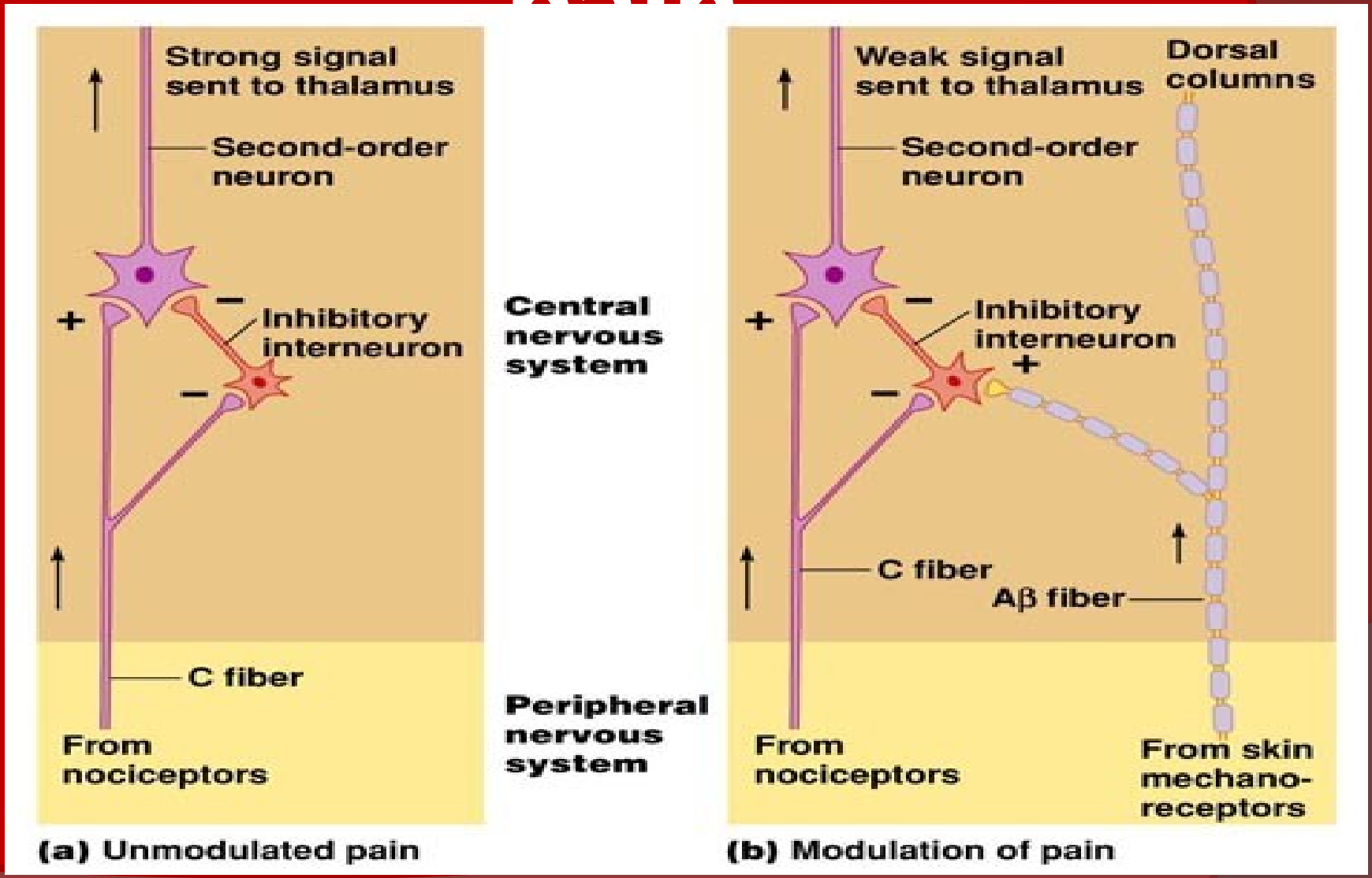
Cell injury → potassium → activates nociceptors

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).



Gate-control theory of pain



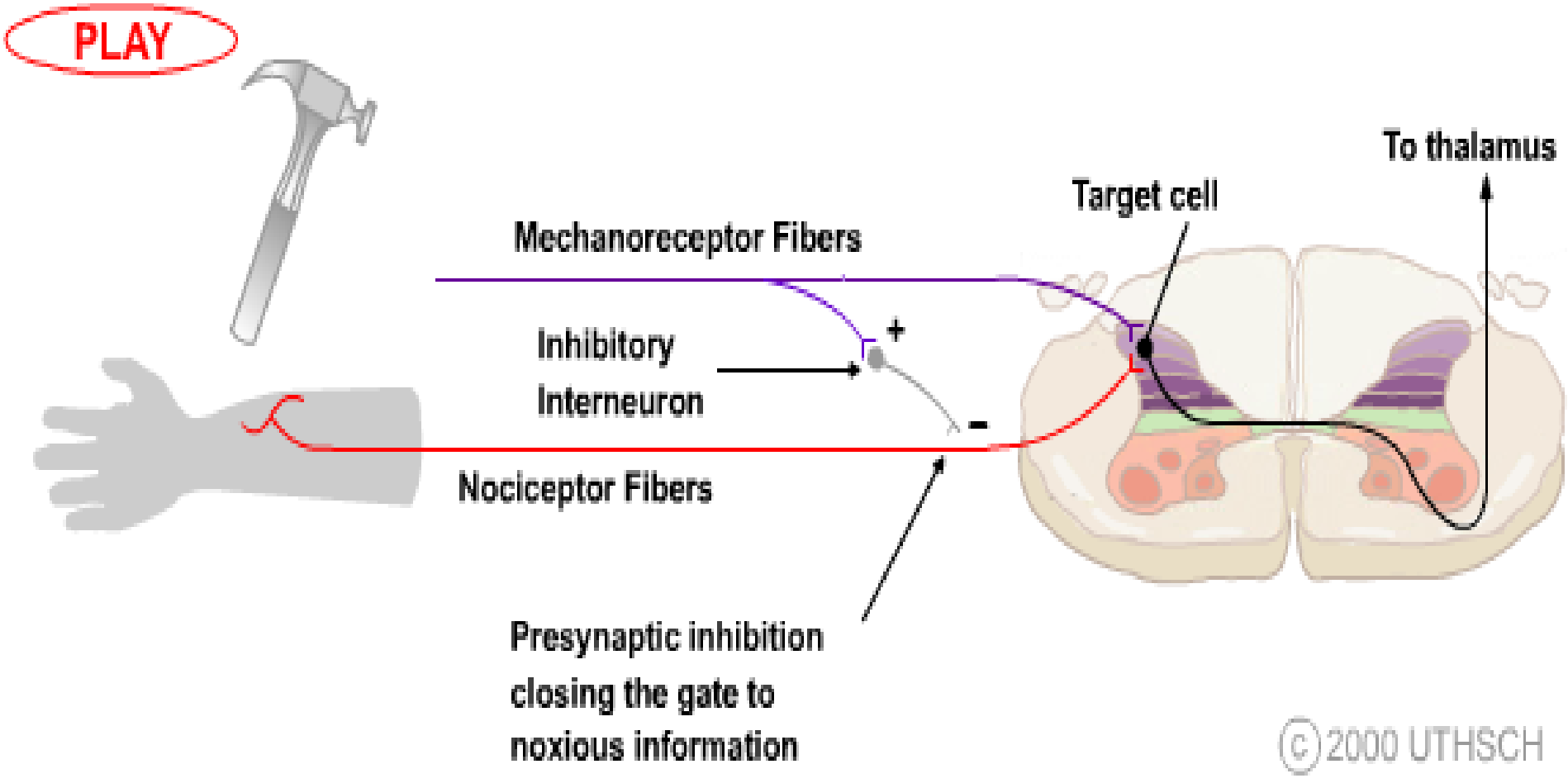


Figure 8.1

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.

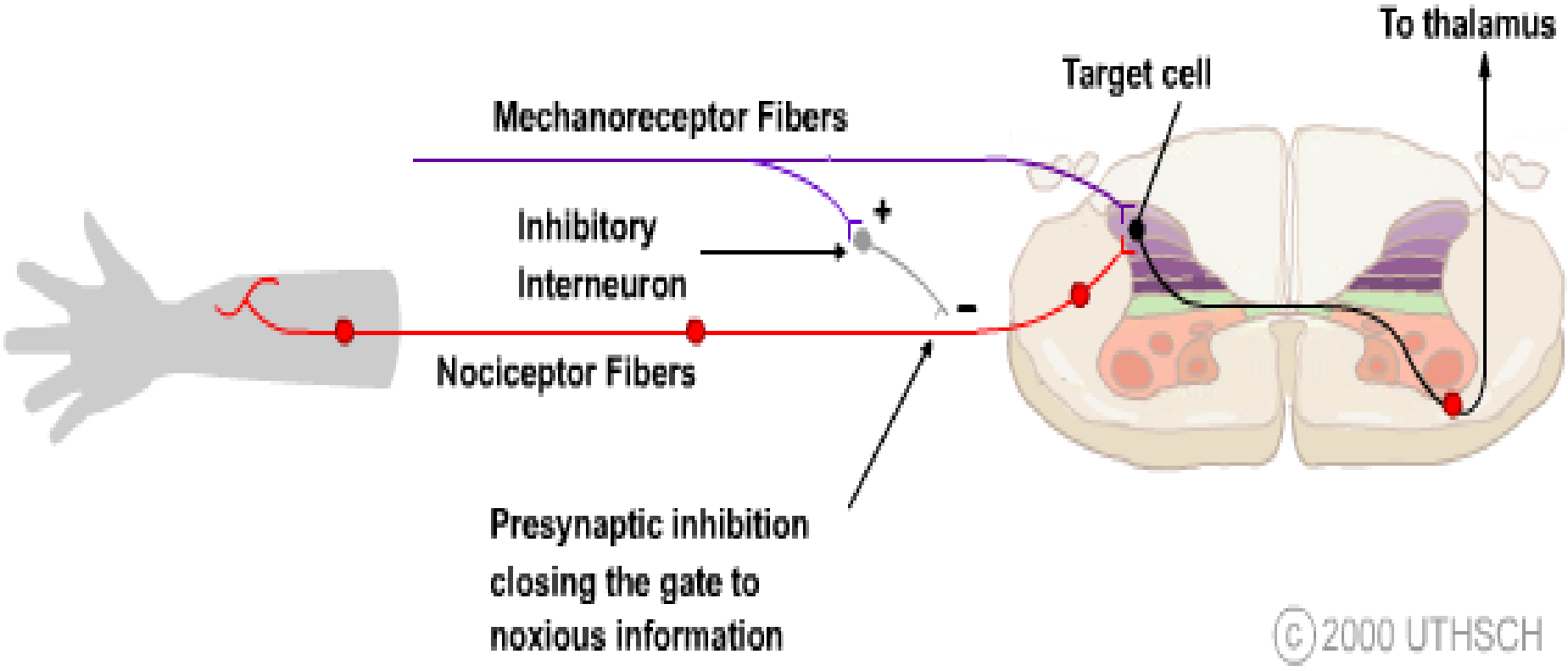


Figure 8.1

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.

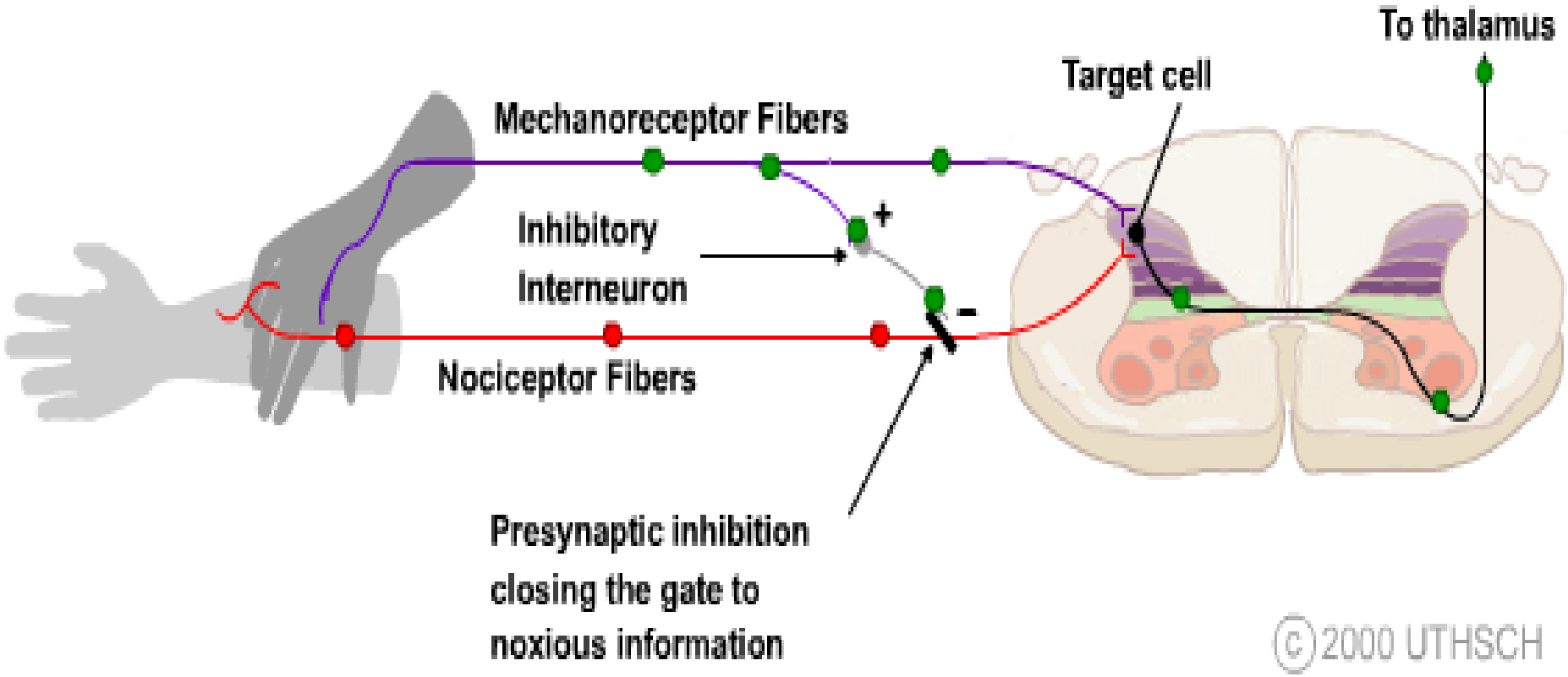


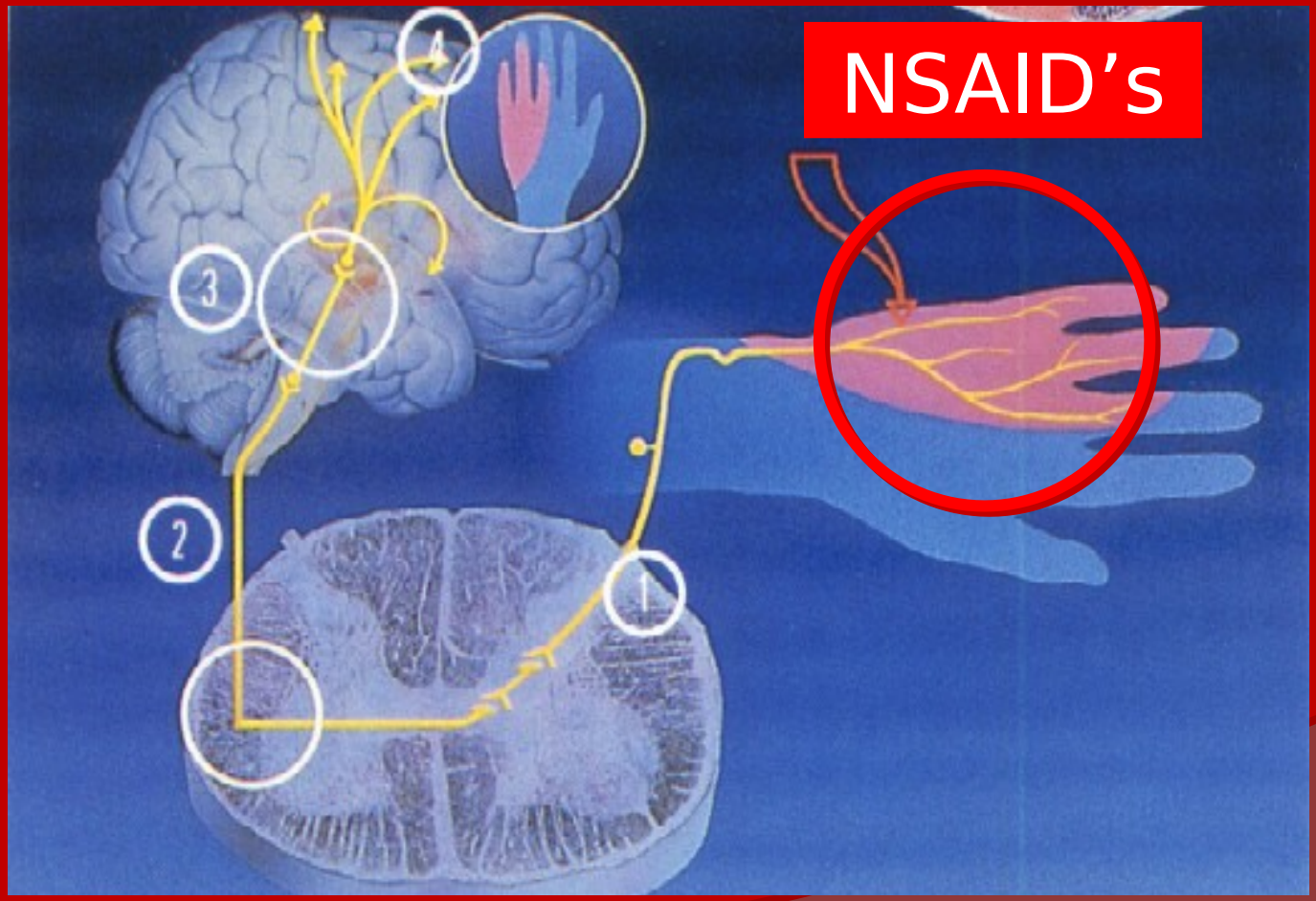
Figure 8.1

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.

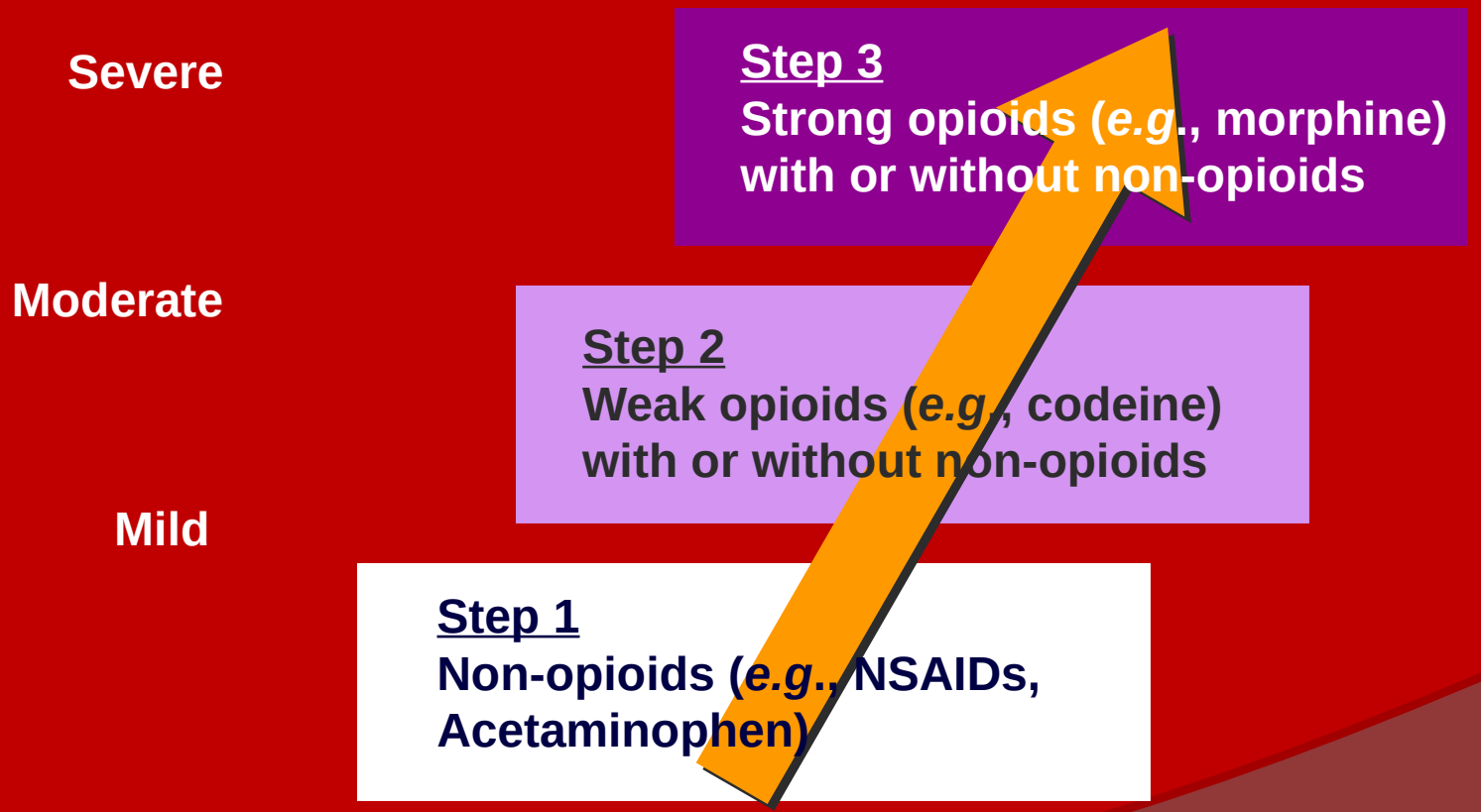
ANALGESICS

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).

SITE OF ACTION



WHO Analgesic 'Ladder'



CLASSIFICATION (chemical)

SALICYLIC ACID DERIVATIVES

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

CLASSIFICATION (contd.)

PARA-AMINO PHENOL DERIVATIVE

- Paracetamol

ACETIC ACID DERIVATIVES

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

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

PROPERTIES OF NSAID’s

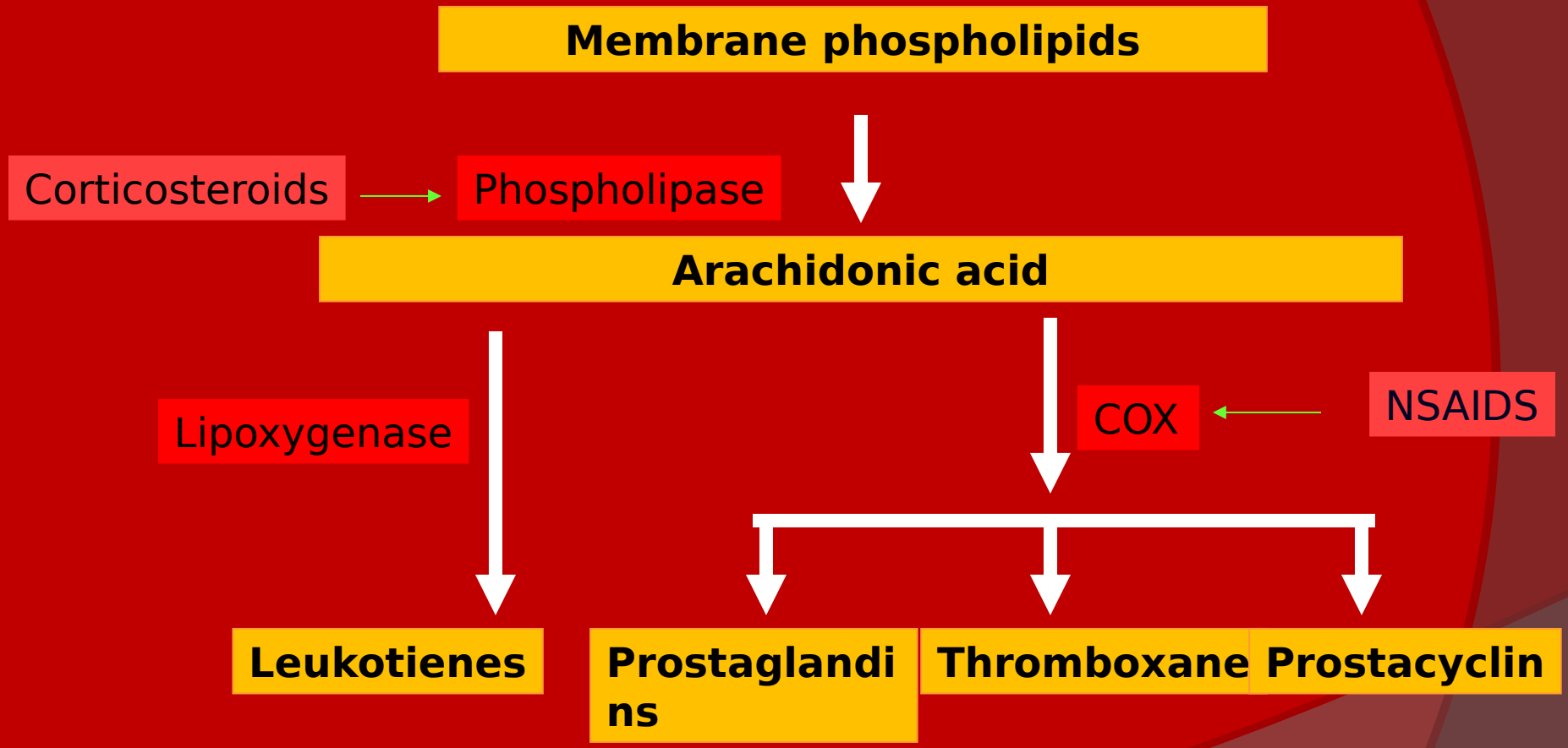
- ✓ Common general properties
- ✓ Common mechanism of action (cyclooxygenase inhibition)
- ✓ Common therapeutic indications
- ✓ Common adverse effects
- ✓ Different pharmacokinetics and potency
- ✓ Different chemical families
- ✓ Different selectivity's to COX I and II

- ❖ Similarities more striking than differences

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

MECHANISM OF ACTION

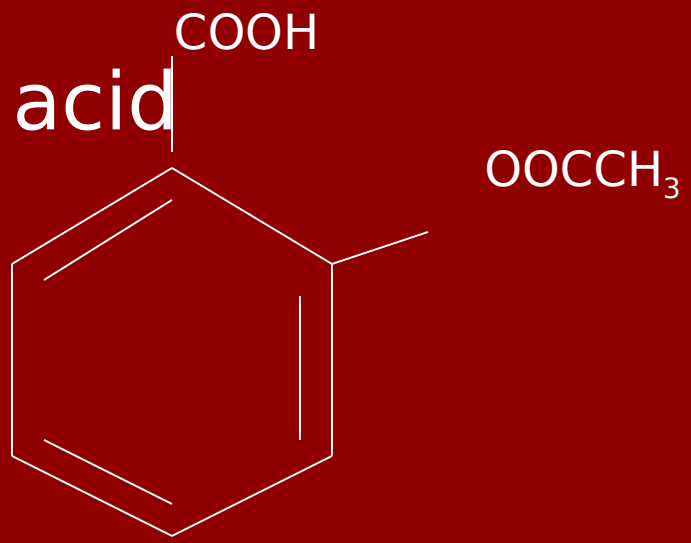


ADVERSE EFFECTS OF NSAID'S

1. CNS
2. CVS
3. GIT
4. HEMATOLOGIC
5. HEPATIC
6. PULMONARY
7. RASHES
8. RENAL

Aspirin (Acetylsalicylic acid; ASA)

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

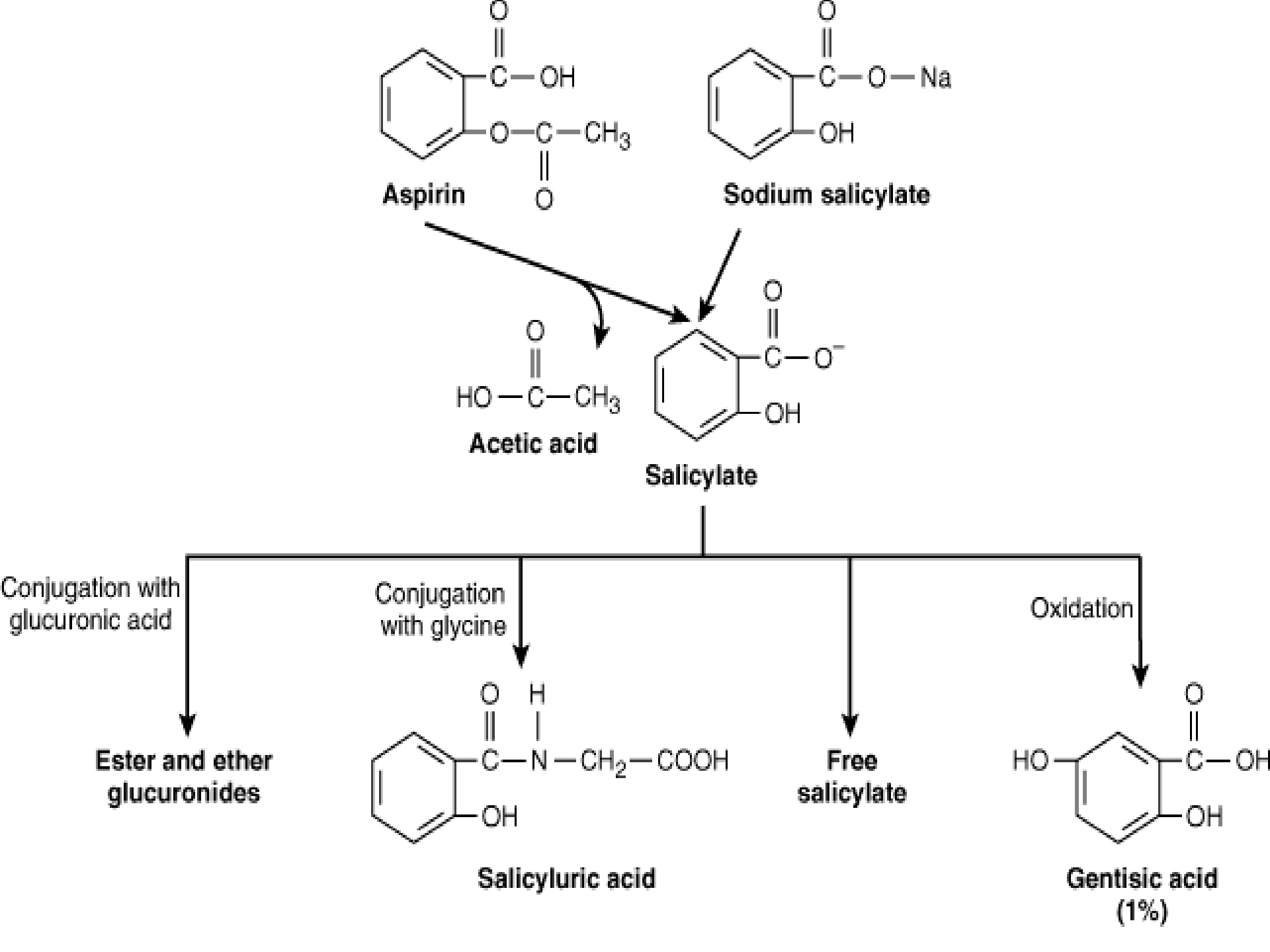


HISTORY

- 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

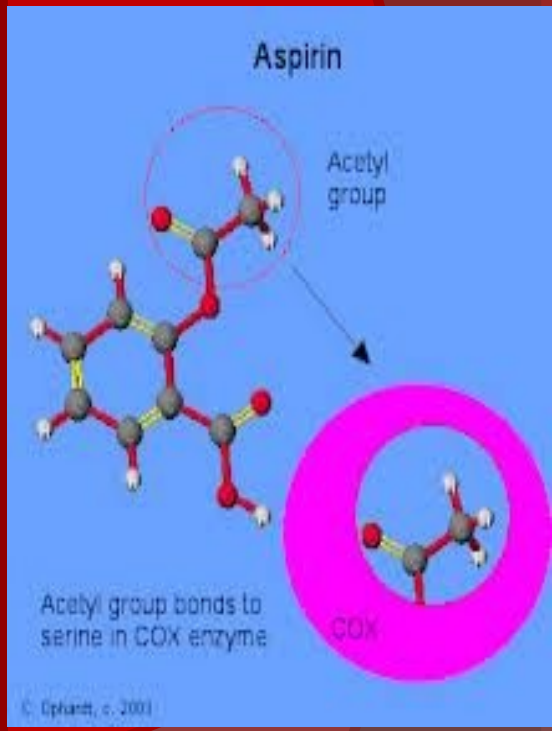
Pharmacokinetics

- 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

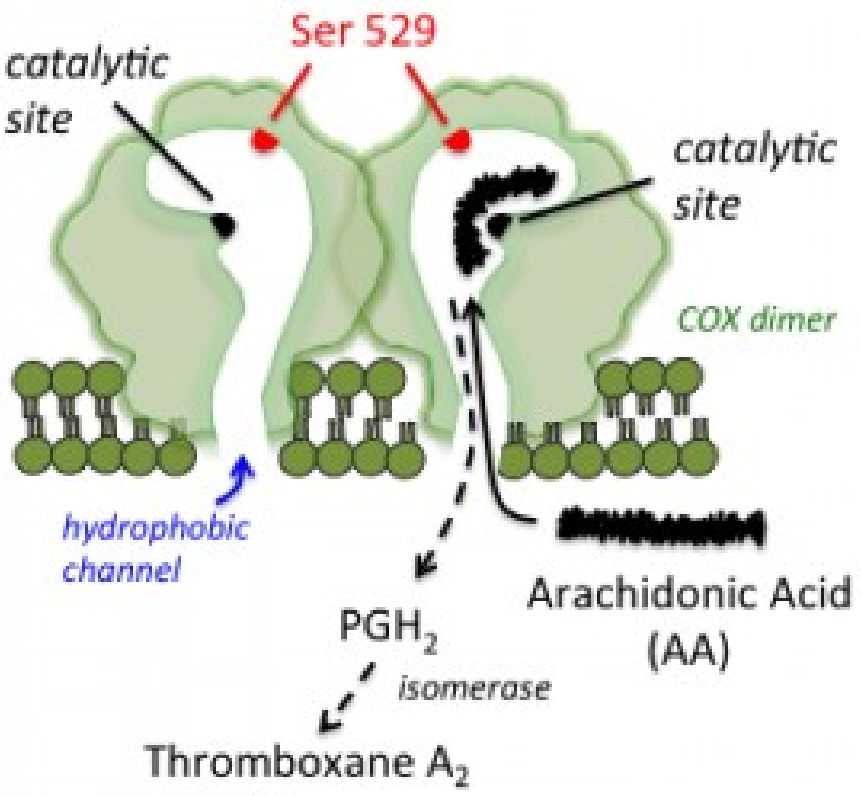

Aspirin
Sodium salicylate
Acetic acid
Salicylate
Conjugation with glucuronic acid
Conjugation with glycine
Oxidation
Ester and ether glucuronides
Salicyluric acid
Free salicylate
Gentisic acid (1%)

Mechanism of Action

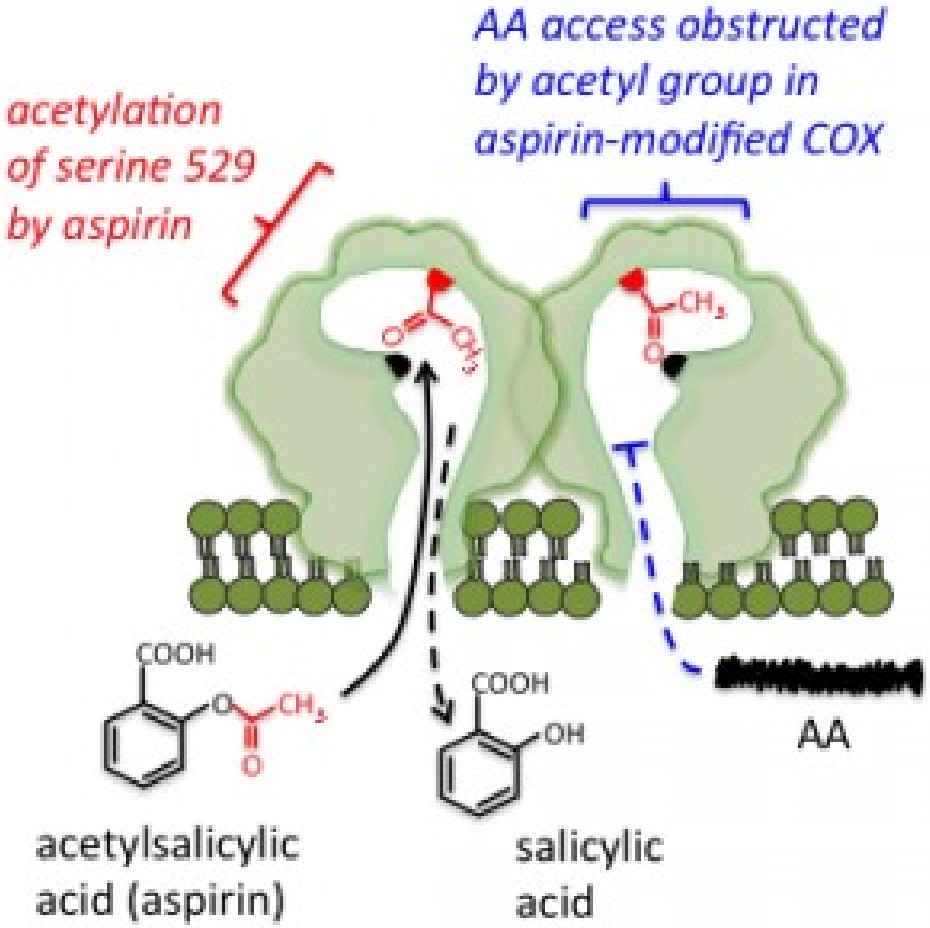
- Inhibits both COX-I and COX-II
  - Anti-inflammatory
  - Analgesic
  - Antipyretic
- Aspirin irreversibly inhibits platelet COX
  - Anti-platelet effect (lasts 8-10 days)



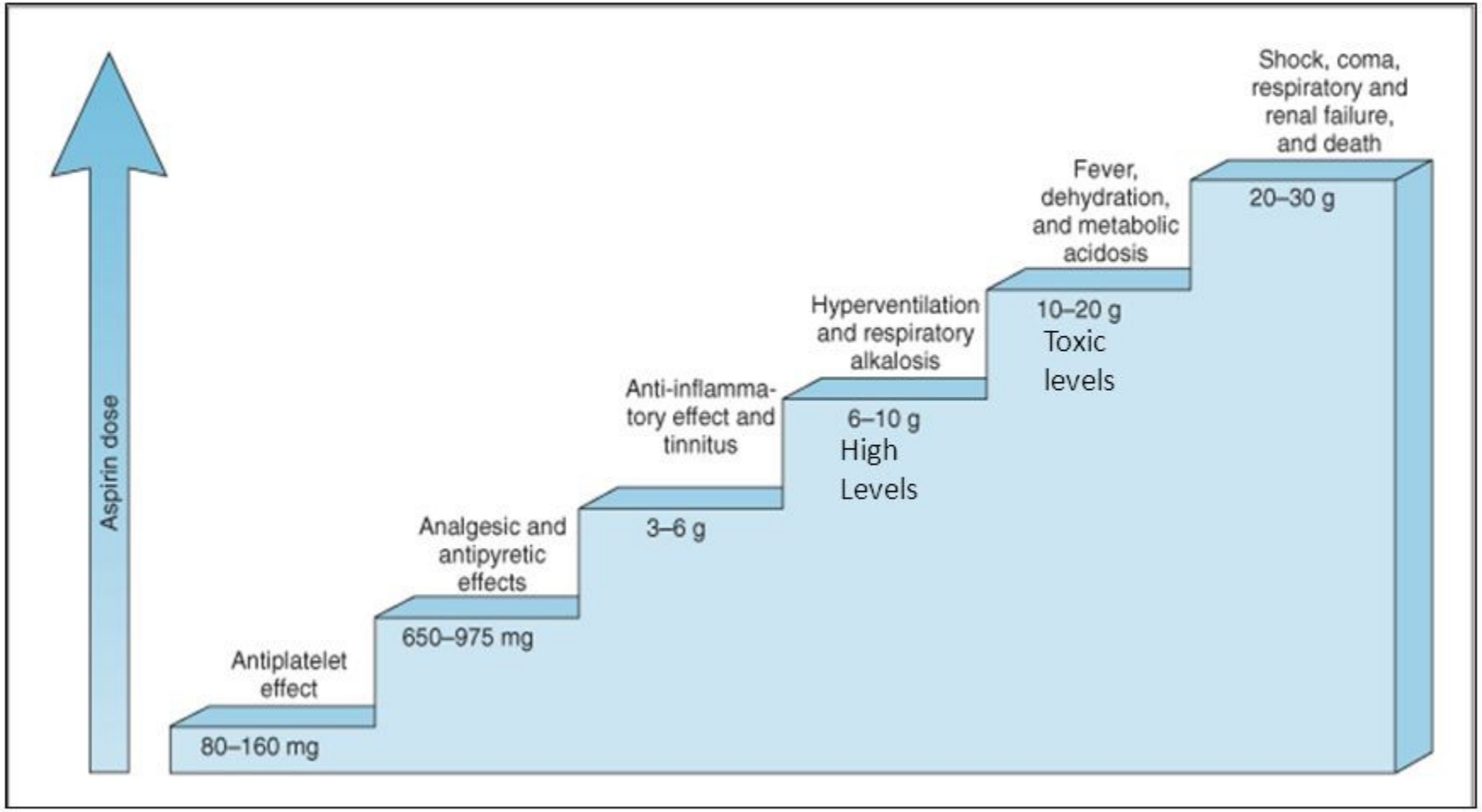
Platelet COX-1



After aspirin



Dose dependent effects of Aspirin



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

Analgesic Effect

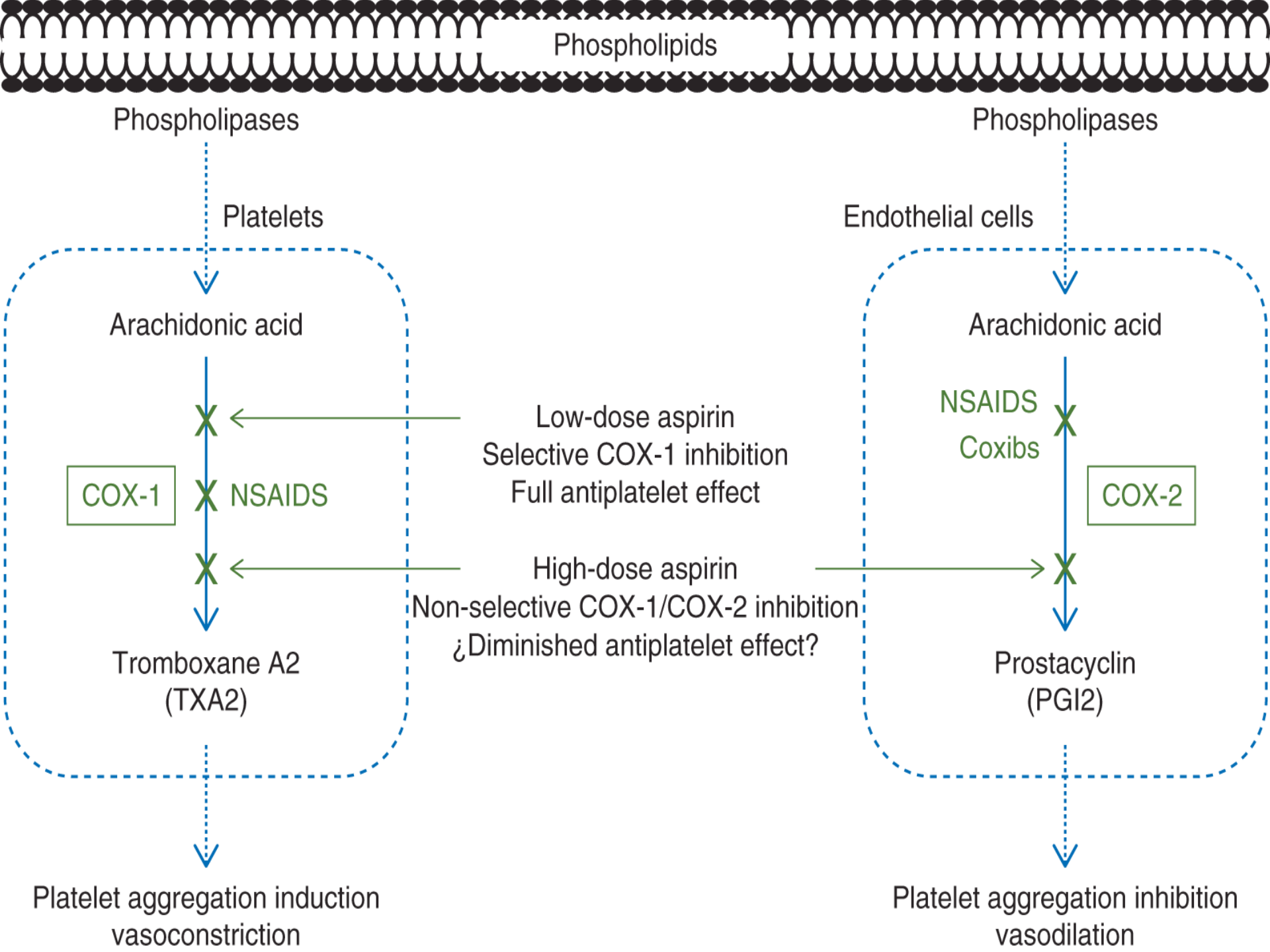
- Reduces mild to moderate pain of varying cause (pain of musculoskeletal structures) relieved better than of visceral origin
- Mainly acts at periphery at nociceptive level so effective in pain associated with inflammation (pain of muscular, vascular & dental origin, postpartum states, arthritis & bursitis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

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


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

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**: dependant 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

- Nephropathy
- Prolongation of gestation & inhibition of labor
- Hypersensitivity (not immunologic but due to PG inhibition)

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

THERAPEUTICS USES OF ASPIRIN

ANALGESIA

- Most frequently used analgesic
- For mild to moderate pain
- Severe pain is not controlled by aspirin

a. Used alone in pain like:

- Headache, myalgia, arthralgia, neuralgia, osteomyelitis, osteoarthritis, toothache, dysmenorrhea

b. With opioids – synergistic action

- In pain of cancer metastases in bone
- Post-operative pain requirement

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

URICOSURIC AGENT (large doses >4 gm /d)

CLOSURE OF PDA

LOWERS INCIDENCE OF COLON CANCER

Niacin- flushing

Systemic mastocycosis

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

Aspirin Toxicity

- Salicylism

Management of aspirin/salicylate overdose toxicity/poisoning

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

DRUG INTERACTIONS

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

NON-SELECTIVE COX INHIBITORS

DICLOFENAC

- 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

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

ACETAMINOPHEN

- Active metabolite of phenacetin
- Weak COX-I and COX-2 inhibitor
- Inhibits COX-3 centrally
- No significant anti-inflammatory effects

Pharmacokinetics:

- Peak blood level is reached in 30-60 min
- Metabolized by hepatic microsomal enzymes and form acetaminophen sulfate and glucronide
- N-acetyl-*p*-benzo-quinoneimine (NAPQI)-Toxic to liver and kidneys

Indications

- 325 – 1000mg (total dose not > 4000mg)
- Headache, myalgia, postpartum pain
- In rheumatoid arthritis with anti-inflammatory agent
- Preferred to aspirin in peptic ulcer, in children with viral infections, hemophilia, bronchospasm

Adverse effects

- Mild increase in hepatic enzymes
- Dizziness, excitement & disorientation at larger doses
- Dose greater than 4-6 g/d is not recommended - cause liver damage
- 15-20gm potentially fatal (30tablets)
- NAPQI reacts with sulfhydryl gps in GSH normally & then excreted as mercapturic acid in urine but in toxic dose GSH is depleted and toxic metabolite accumulates

Treatment

- Supportive therapy
- *N*-Acetylcysteine

COX-2 SELECTIVE INHIBITORS

- Celecoxib, rofecoxib, valdecoxib, parecoxib, etoricoxib, lumaricixib
- Inhibit prostaglandin synthesis by the COX-2 isozyme
- Analgesic, antipyretic and anti inflammatory effects
- No effect on platelet aggregation
- No cardioprotective effect

CELECOXIB

- Highly selective COX- 2 inhibitor.
- Half life is 11 hrs
- Metabolized mainly in the liver
- Effective in rheumatoid arthritis and osteoarthritis.
- Less production of peptic ulcer
- Inhibit COX 2 mediated prostacyclin synthesis in vascular endothelium-platelet aggregation