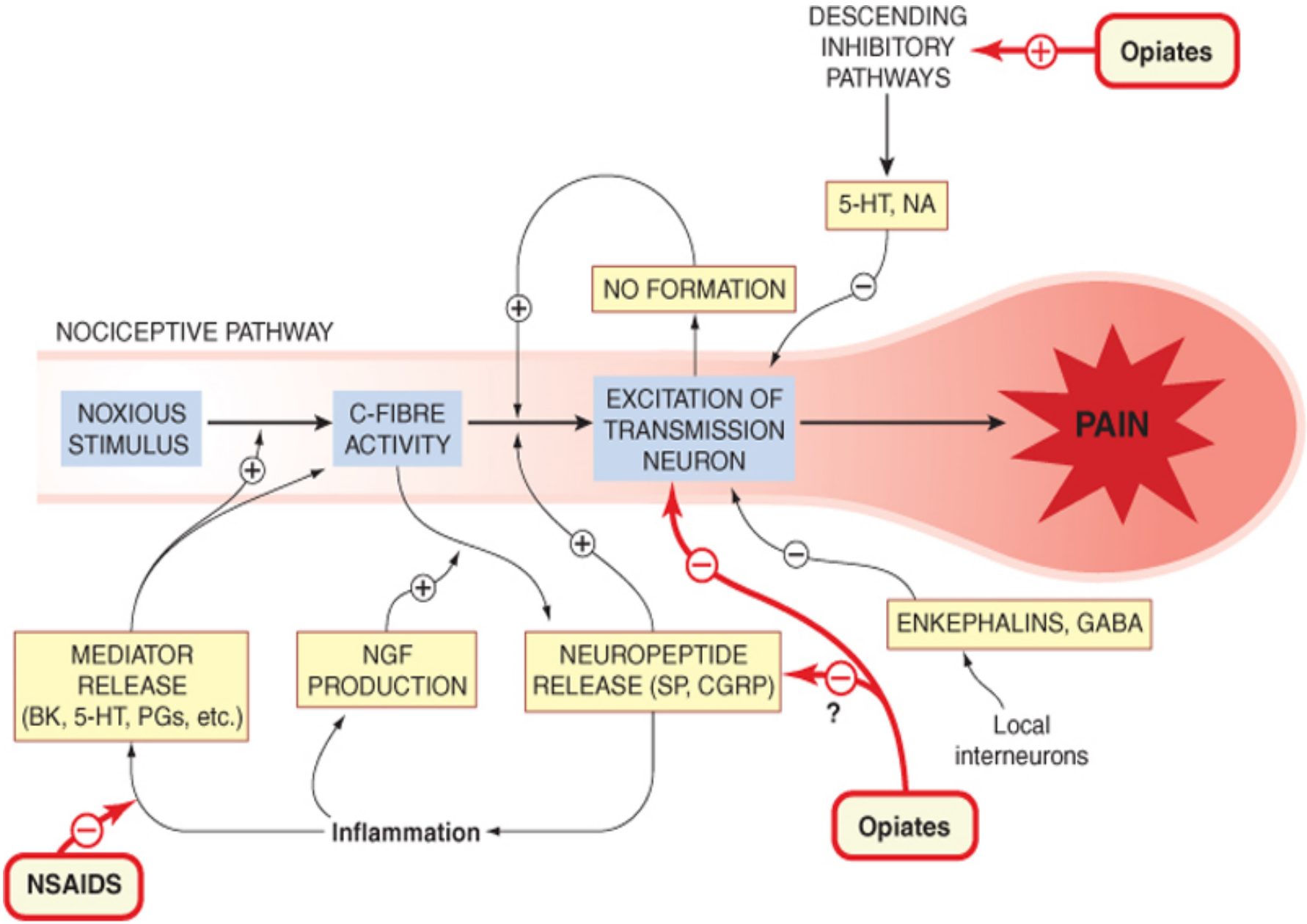
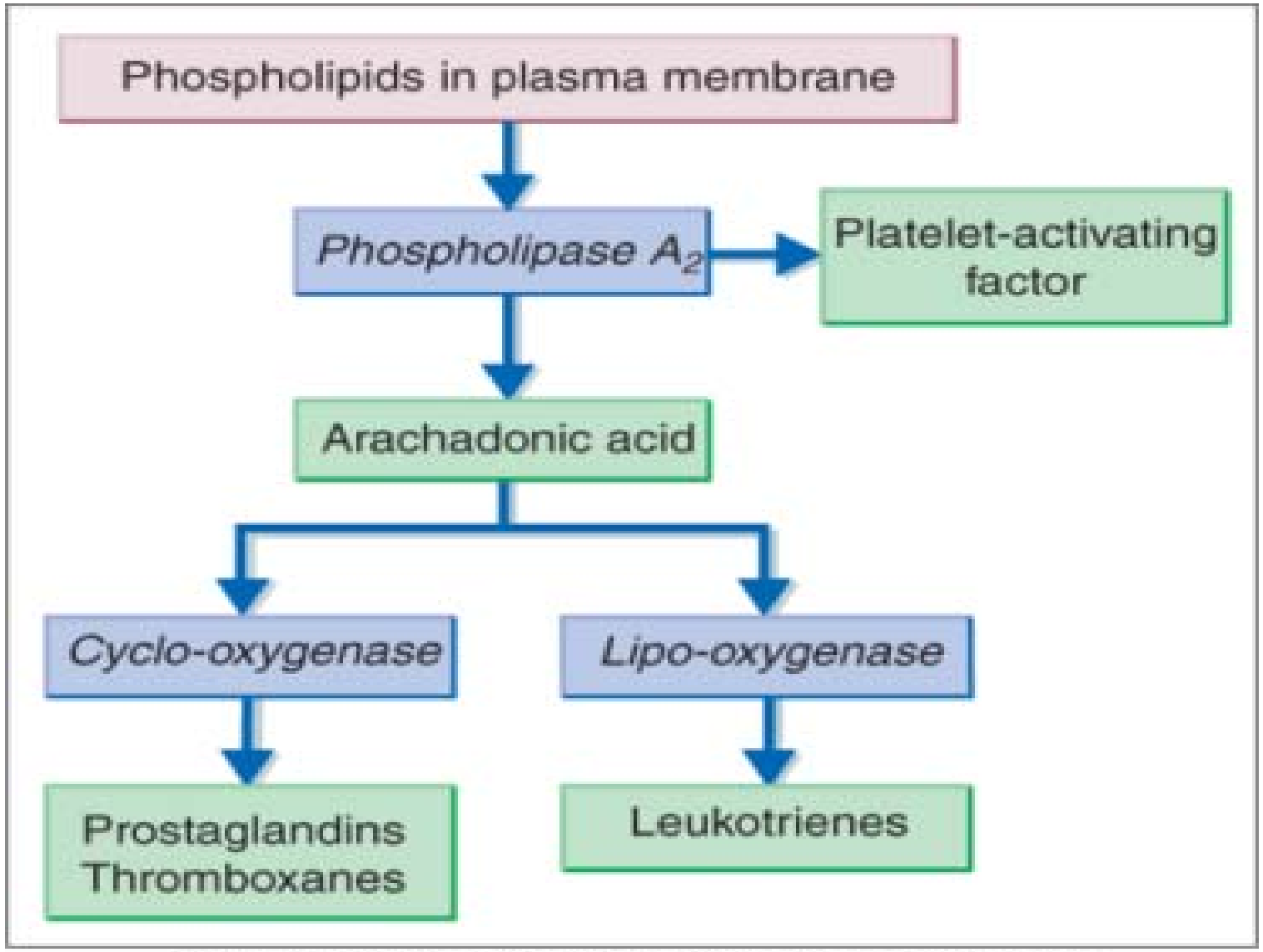
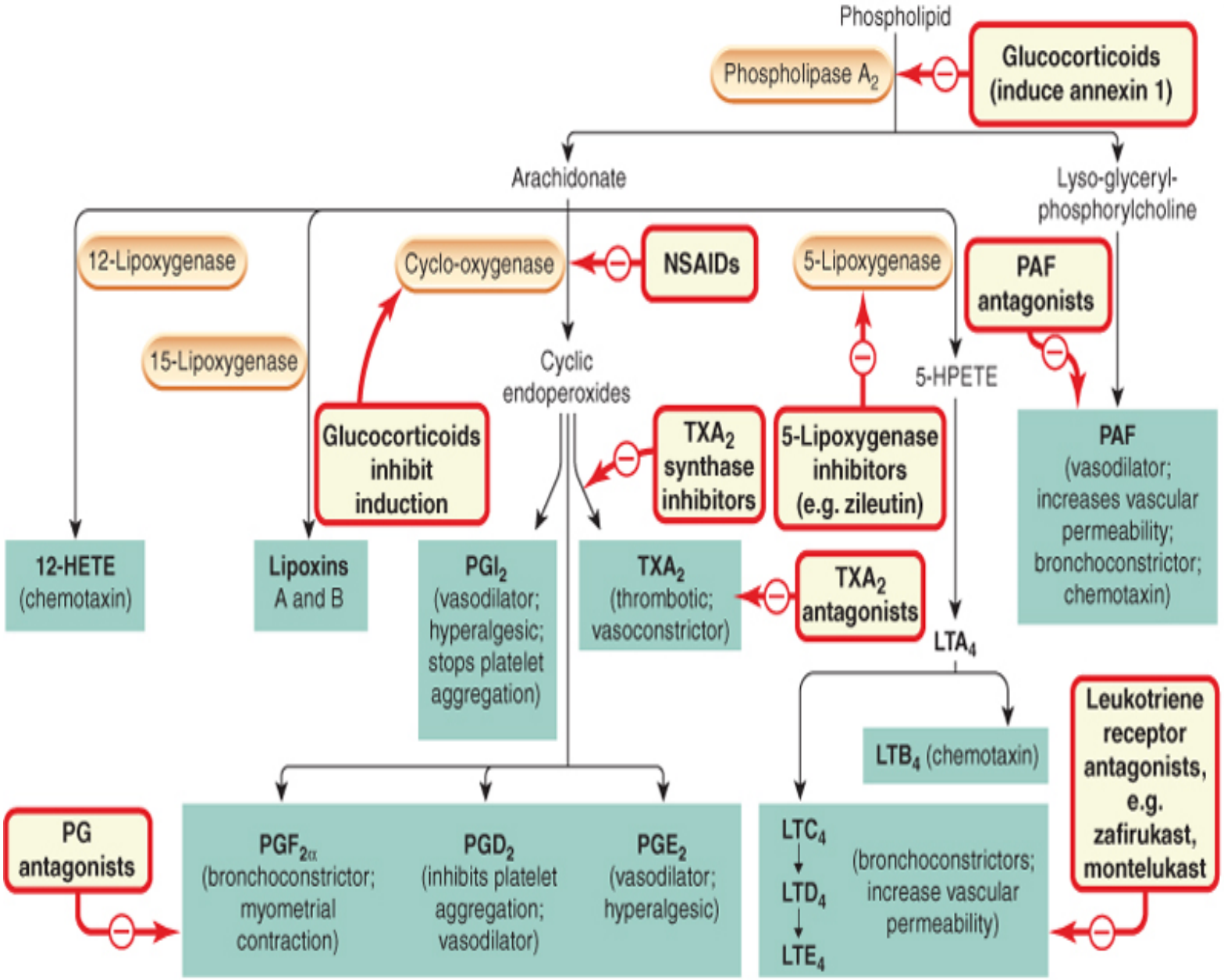
Non Steroidal Anti-inflammatory Drugs (NSAIDs)



4 signs of inflammation

- Redness - due to local vessel dilatation
- Heat - due to local vessel dilatation
- Swelling – due to influx of plasma proteins and phagocytic cells into the tissue spaces
- Pain – due to local release of enzymes and increased tissue pressure





NSAIDs

- Cause relief of pain -. analgesic
- Suppress the signs and symptoms of inflammation.
- Exert antipyretic action.
- Useful in pain related to inflammation.

Esp for superficial/integumental pain .

Classification of NSAIDs

- Salicylates: aspirin, Sodium salicylate & diflunisal.
- Propionic acid derivatives: ibuprofen, ketoprofen, naproxen.
- Aryl acetic acid derivatives: diclofenac, ketorolac
- Indole derivatives: indomethacin, sulindac
- Alkanones: Nabumetone.
- Oxicams: piroxicam, tenoxicam

Classification of NSAIDs .....

- Anthranilic acid derivatives (fenamates): mefenamic acid and flufenamic acid.
- Pyrazolone derivatives: phenylbutazone, oxyphenbutazone, azapropazone (apazone) & dipyrone (novalgine).
- Aniline derivatives (analgesic only): paracetamol.

Clinical Classif.

- Non selective Irreversible COX inhibitors
- Non slective Reversible COX inhibitors
- Preferential COX 2 inhibitors
- 10-20 fold cox 2 selective
- meloxicam, etodolac, nabumetone
- Selective COX 2 inhibitors
- > 50 fold COX -2 selective
- Celecoxib, Etoricoxib, Rofecoxib, Valdecoxib
- COX 3 Inhibitor? PCM

Cyclooxygenase-1 (COX-1):

-constitutively expressed in wide variety of cells all over the body.

-"housekeeping enzyme"

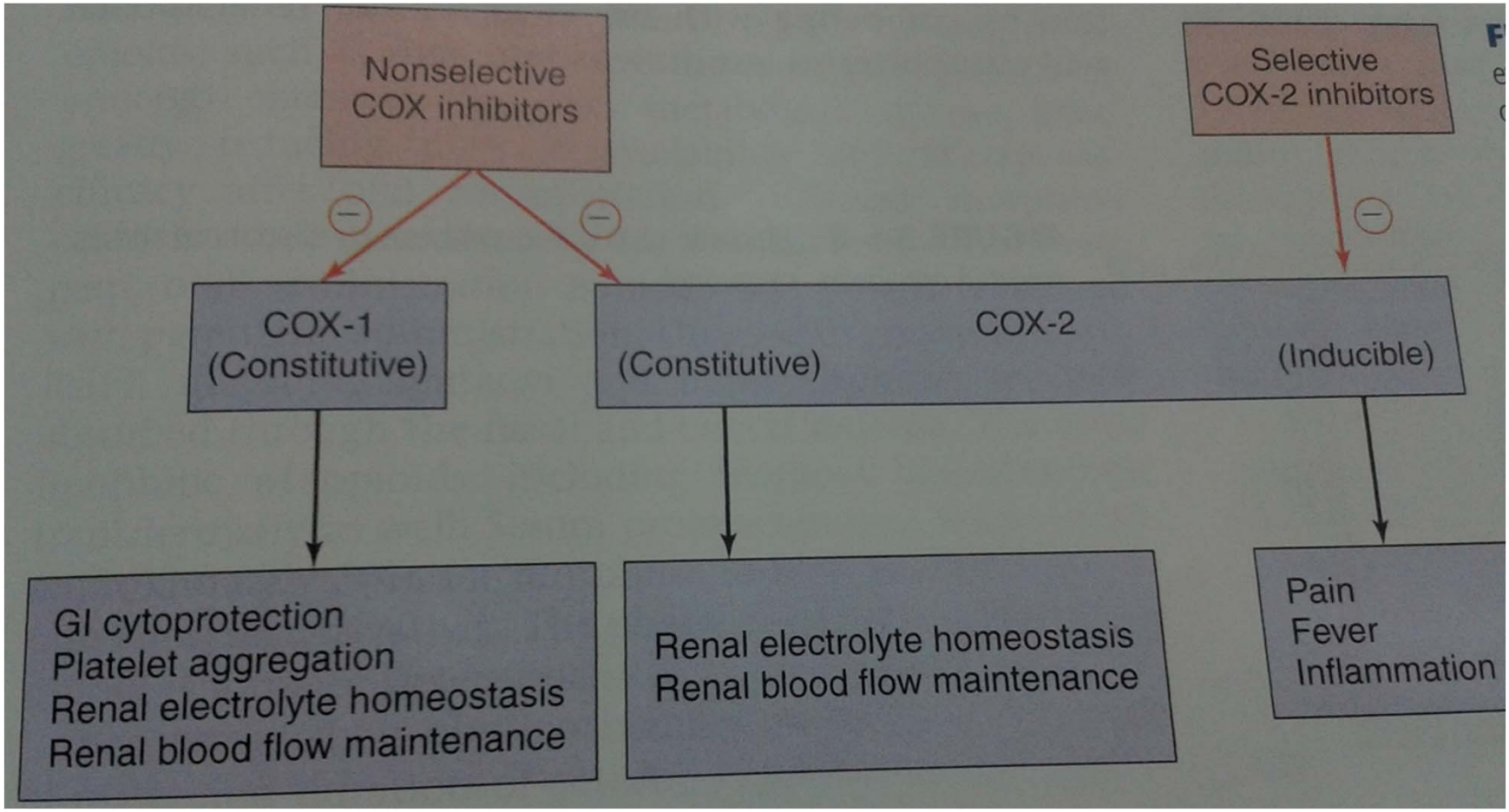
-ex. gastric cytoprotection, hemostasis

Cyclooxygenase-2 (COX-2):

-inducible enzyme

-dramatically up-regulated during inflammation (10-18X)

-constitutive : maintains renal blood flow and renal electrolyte homeostasis


Nonselective
COX inhibitors
Selective
COX-2 inhibitors
COX-1
(Constitutive)
COX-2
(Constitutive)
(Inducible)
GI cytoprotection
Platelet aggregation
Renal electrolyte homeostasis
Renal blood flow maintenance
Renal electrolyte homeostasis
Renal blood flow maintenance
Pain
Fever
Inflammation

Salicylates

Acetyl salicylic acid (aspirin).

Kinetics:

- Well absorbed from the stomach, more from upper small intestine.
- Distributed all over the body, 50-80% bound to plasma protein (albumin).
- Metabolized to acetic acid and salicylates (active metabolite).
- Salicylate is conjugated with glucuronic acid and glycine.
- Excreted by the kidney.
- Alkalinization of the urine increases the rate of salicylates excretion.

Aspirin….

- Low dose of aspirin 0.6 g is eliminated by 1st order kinetics and its t 1/2 is 3-5 h
- while high dose (more than 4 g/day) is eliminated by zero-order kinetics and its t 1/2 may increase up to 15 h.

Mechanism of action:

- Aspirin irreversibly inhibits cyclo-oxygenase enzyme, so blocks synthesis of prostaglandins and thromboxane A2.

Aspirin....*Pharmacological actions*

Anti-inflammatory actions:

Higher doses; 3-6 g/day, OA , RA, Rh fever

- Inhibits prostaglandin synthesis
- Blocks action of kinins which are mediated through prostaglandin synthesis.
- Inhibits granulocyte adherence to damaged vasculature.
- Stabilizes lysosomes.
- Inhibits migration of PMN leukocytes & macrophages into the site of inflammation.

Aspirin….

- **Analgesia**: inhib of PG :300-600mg ,6-8 hrly
- uses
- **Antipyretic** axn.: inhib of PG: resets the “hypothalamic thermostat”
- **Inhibition of platelet aggregation**: low doses: irreversibly inhibit platelet COX , antiplatelet effect lasts 8-10 days.(acts on TXA2 ,no effect on PGI2)

Aspirin…

- Uses:
- **Antiplatelet: M imp**
- Analgesic
- Antiinflammatory
- Antipyretic
- Misc.
- Colonic Ca
- Pre eclampsia
- Alzheimer’s Ds
- Familial polyposis
- Niacin induced flush

Adverse effects

- CNS: **Headache,** Tinnitus, dizziness,blurred vision, irritability, hyperventilation (Salicylism)
- Cardiovascular.: fluid retention, HT, edema, CHF(rarely)
- GIT upset: abd pain, nausea, vomiting, peptic ulceration & bleeding
- Hypersensitivity: bronchial asthma, angioedema & rashes,
- Thrombocytopenia, Hypoprothrombinemia and bleeding tendency as aspirin competes with vitamin K, so decreasing prothrombin synthesis.

Aspirin ADRs ….

- Renal effects: inhibition of PGE2 mediated vasodilation in response to ATII : renal insufficiency, renal failure,hyperkalemia, proteinuria. Analgesic nephropathy on chronic use
- Hepatic: Liver function abnormalities, rarely liver failure.

Reye's Syndrome

- Aspirin and derivatives may be a trigger.
- Hepato encephalopathy.
- Highly Lethal
- Do not give in children with chickenpox or influenza B infection.

Aspirin Overdose

- Acid-base disturbance.
- **Respiratory Alkalosis** (400-500microgm/ml).
- Direct stimul of the respiratory centers: salicylism ; renal mech compensate by increasing excretion of HCO3
- **Metabolic Acidosis** (**0.5-1mg/ml**)
- Medullary depression .Depletion of HCO3, accumulation of salicylic acid & deriv., absolute uncou[pling of oxidative phosp. >> accum of lactic acid, pyruvic & acetoacetic acid

Aspirin Overdose

TABLE 36–6 Relationship Between Blood Salicylate Level and Therapeutic and Toxic Effects

Blood Salicylate Level (μg/mL)	Effect	Consequence
50-100	Analgesia, antipyresis	
150-300	Antiinflammatory	
200-350	Salicylism	Tinnitus, dizziness, nausea
≤350	Hyperventilation	Respiratory alkalosis
450-800	Disrupted carbohydrate metabolism, sweating, vomiting, uncoupled oxidative phosphorylation, depressed respiration, increasing acidosis and body temperature	Metabolic acidosis, dehydration, hyperthermia, respiratory acidosis, delirium, convulsions, coma

Acute aspirin poisoning

S/S : Restlessness, tremors, convulsion, vomiting, dehydration, hypotension, hyperventilation, hyper reflexia, hyperpyrexia & coma.

Treatment:

- Activated charcoal 50g p.o to adsorb salicylates and prevents its absorption.
- Alkalinization of urine (to enhance excretion) by i.v Na HCO3 which also corrects acidosis.
- Anticonvulsant e.g. i.v diazepam.
- Cold fomentation and ice bags.

Acute aspirin poisoning…

- Correct dehydration by i.v fluids (5% dextrose).
- Correct acid / base balance (alkalosis or mixed alkalosis/acidosis need no specific treatment).
- Correct hypoprothrombinemia by i.v vitamin K.
- Hemodialysis may be needed.

Contraindications:

- Peptic ulcer,
- esophageal varices,
- bronchial asthma,
- idiosyncrasy, allergy,
- viral infection in children,
- bleeding tendency and
- small dose in gout (competes with uric acid excretion).

Interactions

- Aspirin displaces oral anticoagulants and oral hypoglycemics from their plasma protein binding sites, so increasing their activities and may lead to toxicity.
- inhibits the uricosuric effects of sulphinpyrazone and probenecid.
- Barbiturates increase the analgesic effect of aspirin.
- Alcohol:

.

Locally acting salicylates

- *Salicylic acid*: keratolytic, antiseptic & fungistatic.
- *Methyl salicylate* (wintergreen oil): used as counterirritant for muscle and joint pain.
- Sulfasalazine : it is a combination of sulfapyridine and 5-aminosalicylic acid (5-ASA). Sulfasalazine liberates 5-ASA in the colon where it blocks the synthesis of leukotriene B4 locally and used in ulcerative colitis.

PROPIONIC ACID DERIVATIVES

- Ibuprofen, Naproxen, Fenoprofen.
- Very similar in mechanism of action and effects (compared to aspirin).
- More effective as analgesics
- Ibuprofen and Fenoprofen half-life of 2 hrs.
- Naproxen has a longer half-life (13 hrs).
- Use: **Dysmenorrhea.**
- Adverse effects are similar: nephrotoxicity, jaundice, nausea, dyspepsia, edema, rash, pruritus, tinnitus.
- Interactions and contraindications: same as aspirin.

ACETIC ACIDS

- Indomethacin : indole AA :Most potent inhibitor of prostaglandin synthesis (COX-1) more effective but **more toxic** than aspirin. May also inhibit phospholipase A ,C
- Orally absorbed, highly bound to plasma proteins, half-life 2hrs.
- Metabolized in liver, excreted in bile and urine.
- A/E : GI, severe migraine (20-25%), dizziness, confusion and depression, risk of fluid retention, hyperkalemia and blood dyscrasias.
- Contraindicated in pregnancy and in patients with psychosis.
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Indomethacin

- Uses:Treatment of patent ductus arteriosus in premature babies.
- Acute gouty arthritis, ankylosing spondylitis, osteoarthritis.
- Sulindac:
- Is a pro-drug closely related to Indomethacin.
- Converted to the active form of the drug.
- Indications and toxicity similar to Indomethacin

Diclofenac

- Short half life (1-2 hrs), high 1st pass metab., accumulates in synovial fluid after oral admn..
- GI S/E : in about 20% pt. Severe effects like GI distress, GI bleeding, gastric ulceration less frequent than other NSAIDs and similar to celecoxib.
- High doses impairs renal function. Elevates liver enzymes.
- CI : children, pregnant women and nursing mothers

FENAMATES

- Mefenamic acid,
- Analgesic, anti-inflammatory properties less effective than aspirin ,more toxic.
- Short half-lives, should not be used for longer than one week and never in pregnancy and in children.
- Diarrhea and abdominal pain.
- Enhances oral anticoagulants.

PYRAZOLONE DERIVATIVES

- Phenylbutazone :Withdrawn from the market.
- Adverse effects : agranulocytosis, aplastic anemia, hemolytic anemia, severe gastric irritation
- Oxyphenbutazone: one of the metabolites of phenylbutazone. Apazone.- Similar to phenylbutazone, but less likely to cause agranulocytosis

OXICAMS

- Piroxicam.
- Half-life of 45 hrs. Once-daily dosing. Delay onset of action.
- High doses inhibits PMN migration, decrease oxygen radical production, inhibits lymphocyte function.
- Used in osteoarthritis, ankylosing spondylitis and rheumatoid arthritis.
- Adverse effects: GI symptoms, dizziness, tinnitus, headache, rash. **Peptic ulcer (9.5 higher).**

Ketorolac

- Analgesic, no anti-inflammatory effect.
- Can replace morphine in mild to moderate postsurgical pain.
- IM, IV.
- Similar toxicities. Renal toxicity common with chronic use.

Nimesulide

- Rel weak PG synth inhib , 5-10 COX 2 sel.
- Other mech – reduced SO prod , free radical scavenger, inhib of PAF synth & of metalloproteinase act in cartilage
- NOT FDA approved , Banned in many countries d/t hepatotoxicity
- NOT TO BE USED IN CHILDREN

Preferential COX 2 inhibitors

- 10-20 fold cox 2 selective
- meloxicam: longer acting
- etodolac: less GIT tox,
- nabumetone: non acidic , prodrug ,longer acting

Selective COX 2 inhibitors

- > 50 fold COX -2 selective
- Celecoxib, Etoricoxib, Rofecoxib, Valdecoxib, .

  Inhibit prostacyclin (**COX-2**) in sites of inflammation.
- Do not block “housekeeping” effect of COX-1.
- Antipyretic, analgesic and anti-inflammatory effect.
- Gastro –protective as compared to non selective NSAIDs ; BUT SAME potential for renal and hepatic dysfunction ,While INCREASED risk of thrombotic CVS disorders.

COX-2 Selective

- Celecoxib :
- Osteoarthritis (100-200mg BID) , rheumatoid arthritis, dysmenorrhea, acute gouty attacks, acute musculoskeletal pain.
- Being a sulphonamide can cause skin rash & hypersensitivity rxn ., occasional oedema & HT.
- A/E :

- Etoricoxib, parecoxib

Rofecoxib (Vioxx®) & Valdecoxib

- Withdrawn from the market.
- Higher incidence of cardiovascular thrombotic events.
- Inhibit prostacyclin (PGI2) in vascular endothelium , letting TXA_2 act freely and promote platelet aggregation.

Paracetamol /Acetaminophen

Analgesic and antipyretic actions equivalent aspirin.

- No anti-inflammatory effects---.can inhibit Cox 1 poorly in presence of superoxides at inflamm sites
- No occult bleeding or gastric irritation ,do not inhibit platelet aggregation, or affect prothrombin time.
- No relationship with Reye's syndrome.
- Does not antagonize the effects of uricosuric drugs.
- Proposed as COX 3 inhibitor – involved in pain perception & fever NOT in inflamm

Paracetamol Metabolism

Metabolized by liver glucoronyl transferase to form an inactive compound.

Minor CYP-dependent pathway produces a N-acetyl-para-benzoquinonimine (NAPQI) a reactive metabolite that is inactivated by glutathione.

In serious overdose glutathione becomes depleted, and metabolite damages hepatocytes.

Alcohol enhances liver toxicity via induction of CYP2E1 enzyme.

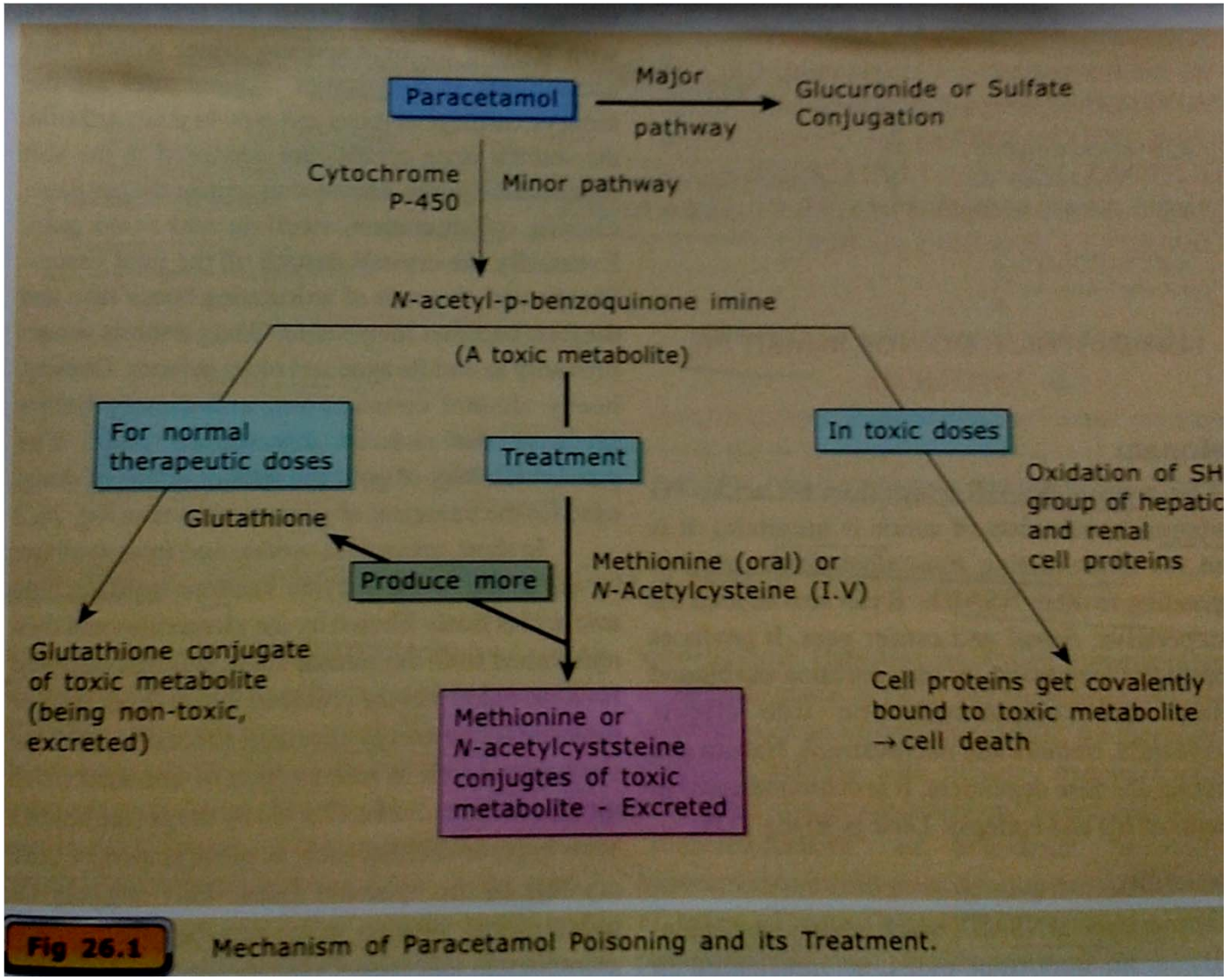

Fig 26.1 Mechanism of Paracetamol Poisoning and its Treatment.

Acute PCM Toxicity

- PCM usual doses - 325-650 TID –QID (Max 2.6 g/day -latest FDA ,) .
- Acute ingestion of > 7.5 g can result in toxicity--- severe liver damage .
- The signs & symptoms of toxicity start within 12-24 hrs: N, V, D, abdominal pain, dizziness, elevated plasma transaminases. Signs of hepatic damage appear over 2-4 days. Renal tubular necrosis may occur. .Onset of hepatic encephalopathy or worsening of coagulopathy beyond this pd. Indicates poor prognosis.

Management

- Severe liver damage with pl. conc>300 microgm/ml at 4 hrs or 45 microgm/ml at 15 hrs after ingestion.
- Activated charcoal- within 4hrs ↓PCM absb by 50-90%
- Antidote- N-acetylcysteine (NAC)- detoxifies NAPQI- both repletes glutathione store and may conjugate with NAPQI by serving as GSH substitute. Also has antioxidant and anti-inflamm properties.
- Oral loading dose of 140 mg/kg , followed by 70mg/kg q 4hrly for 17 doses. If available IV LD- 150mg/kg IV inf in200mlof 5%D over 1 hr, followed by 50 mg/kg in 500ml 5%D over 4hrs then 100mg/kg in 1000ml 5%D over 1