Nonsteroidal Anti-inflammatory Drugs (NSAIDs) and Analgesics

Dr. Alia Shatanawi

Pain

- 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

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.

NSAIDs

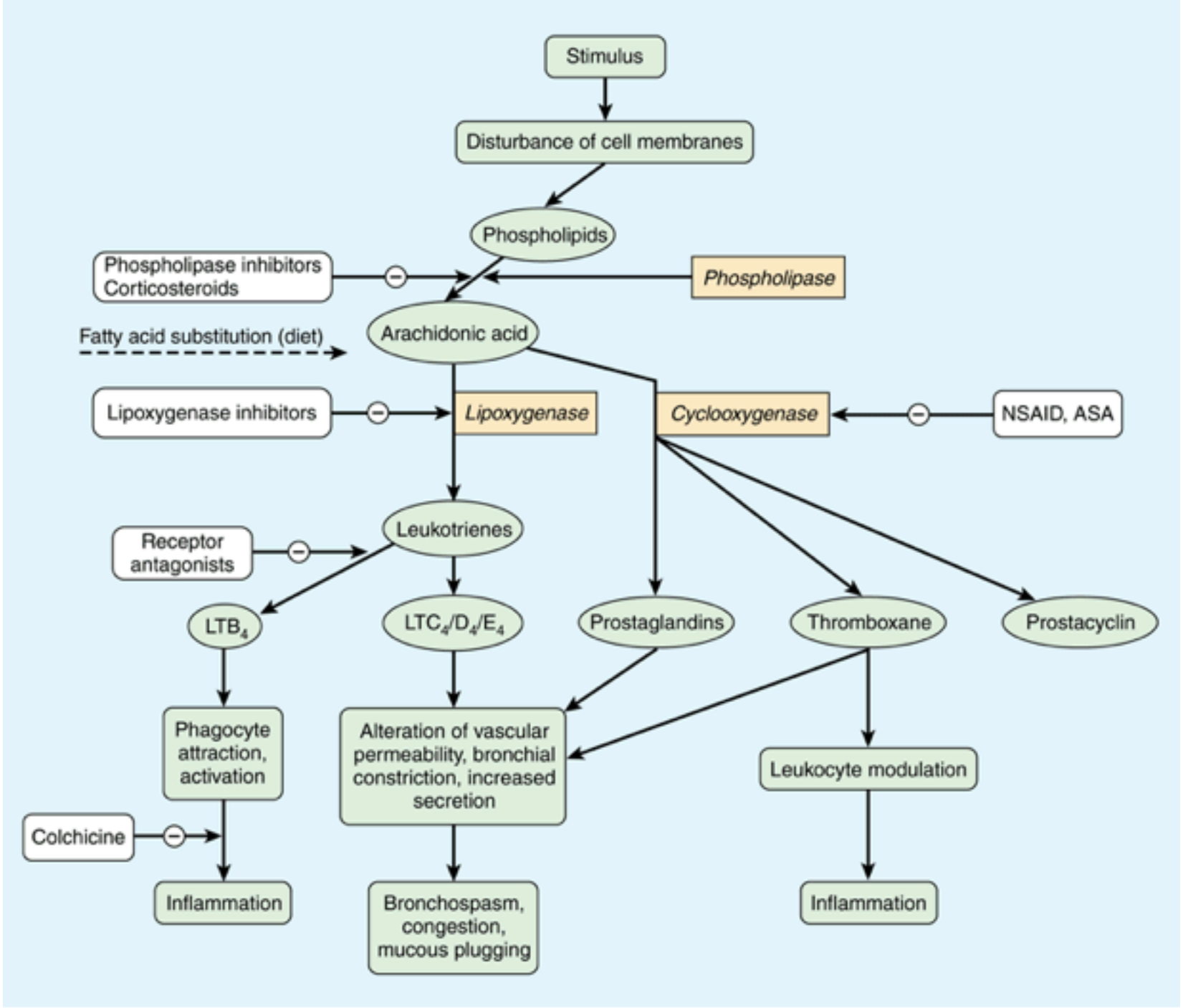
- The NSAIDs are a group of chemically dissimilar agents that differ in their **antipyretic**, **analgesic**, and **anti-inflammatory** activities.

- **inhibiting** the **cyclooxygenase** enzymes that catalyze the first step in prostanoid biosynthesis.

>>>> decreased prostaglandin synthesis with both **beneficial** and **unwanted** effects.

Comparison of Analgesics

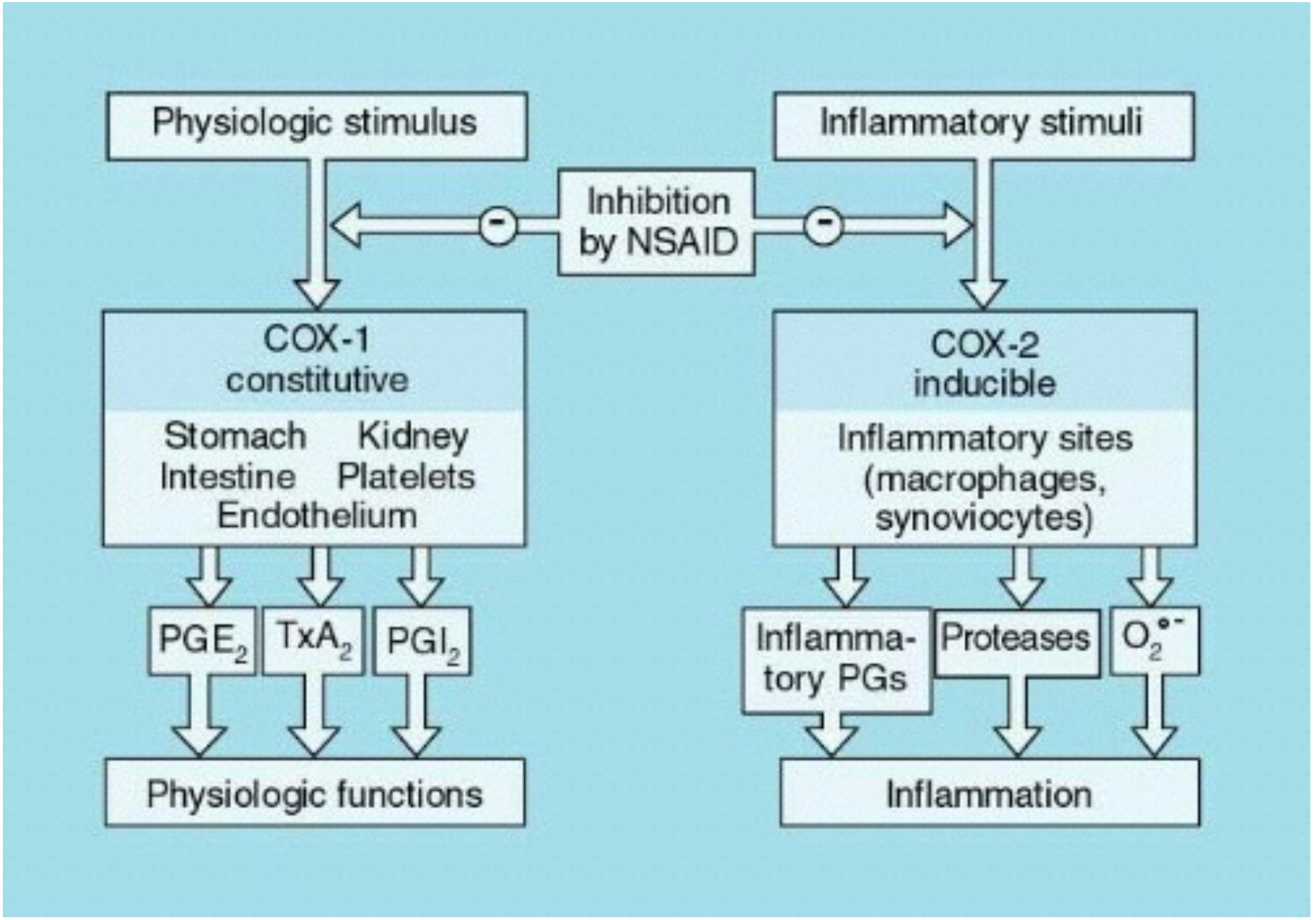
Feature	Narcotic (Opioids)	Nonnarcotic (nonopioid)
Efficacy	Strong	Weak
Prototype	Morphine	Aspirin
Pain Relieved	Any Type	Musculoskeletal
Site of Action	Central	Peripheral and Central
Mechanism	Specific Receptors	PG Synthesis
Danger	Tolerance & Dependence	G.I irritation
Anti-inflammatory	No	Yes
Antipyretic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



Source: Katzung BG, Masters SB, Trevor AJ: Basic & Clinical Pharmacology, 12th edition:

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.


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

Non-steroidal anti-inflammatory drugs (NSAIDs)

pain

fever

Inflammation

By inhibition of cyclo-oxygenase enzymes COX1 & COX2.

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 sensitivity 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.

NSAIDs

An antipyretic effect:

this is partly due to a decrease in the mediator prostaglandin that is responsible for elevating the hypothalamic set-point for temperature control in fever.

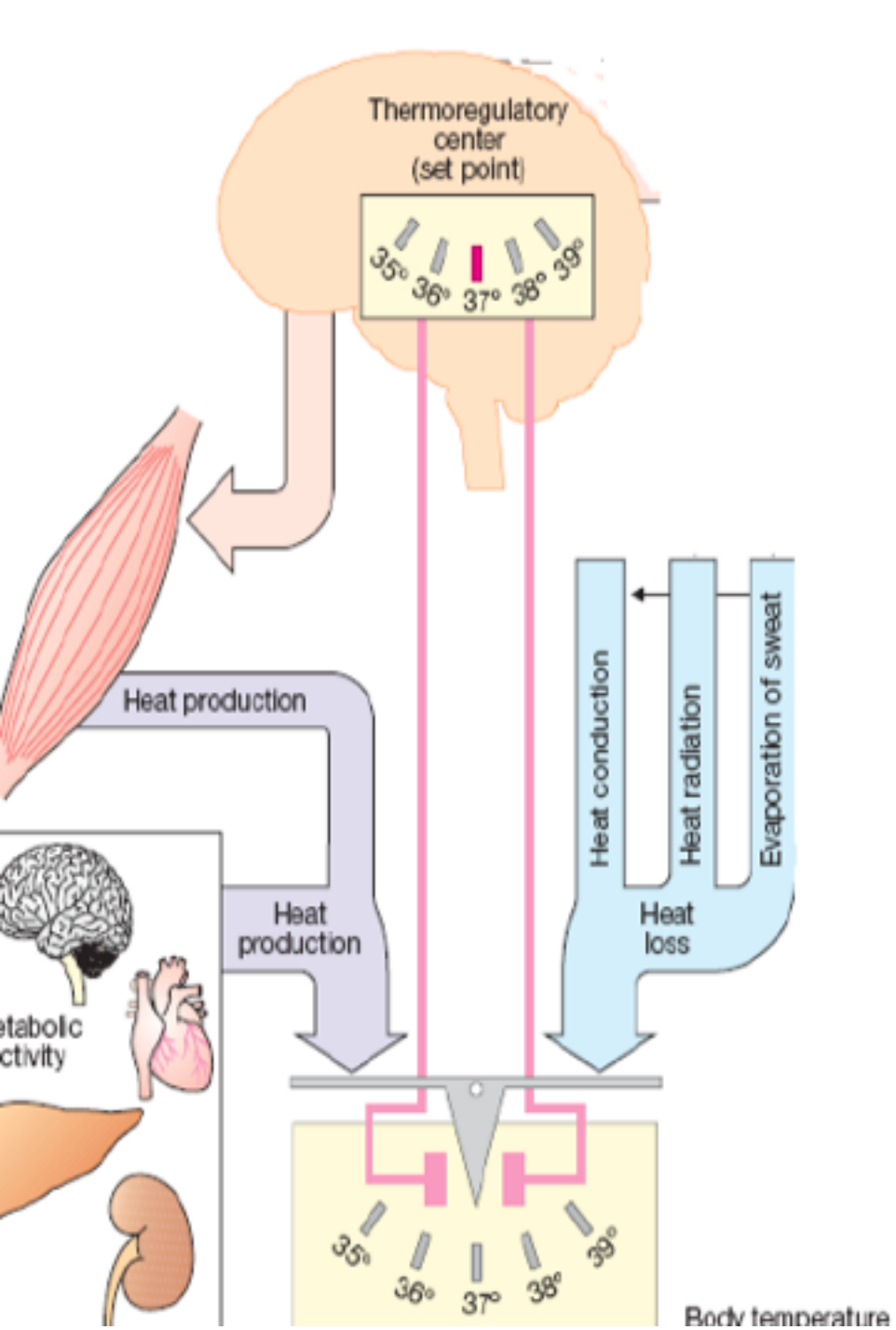
Antipyretic actions – Fever, incr T° are hypothalamic problems.

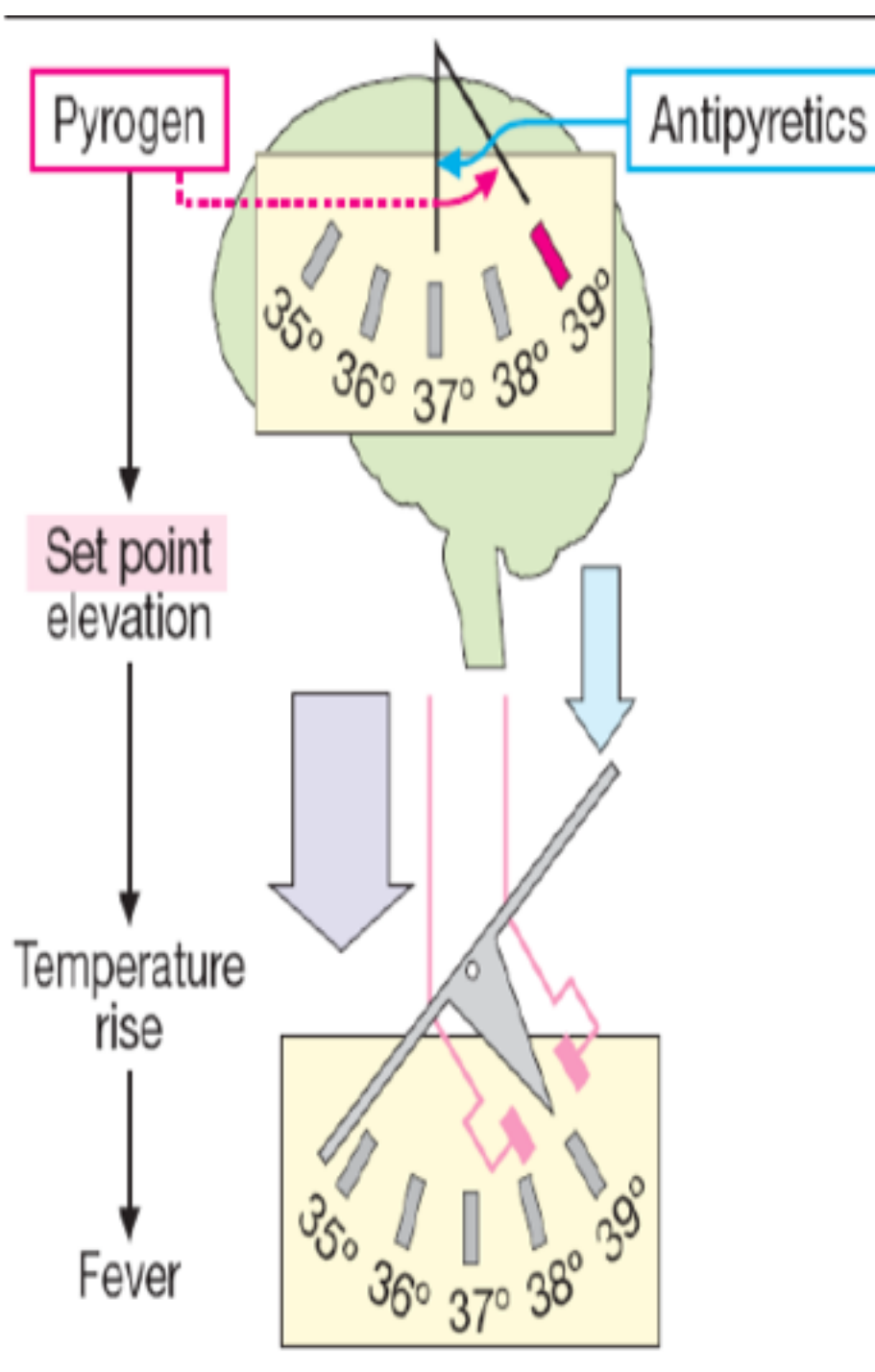
- So, NSAIDs do not decrease body T°.

- Fever :release of endogenous pyrogens (e.g., interleukin-1) released from leucocytes that acts directly on the thermoregulatory centers in hypothalamus to increase body T°.

- This is associated with increase in brain PGs (pyrogenic).

- Aspirin prevents the T°-rising effects of interleukin-1 by preventing the increase in brain PGs.


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°

Pharmacological Effects (cont'd)

- Diverse group of chemicals, but all inhibit cyclooxygenase.
- Resultant inhibition of PG synthesis is largely responsible for their therapeutic effects.
- But, inhibition of PG synthase in gastric mucosa → GIT damage (dyspepsia, gastritis).

NSAID

Mechanism of Action:

- **Inhibition of PG synthesis**
  - **Cyclooxygenase (COX) Enzyme:**
    - **COX-1 or Constitutional form of COX.**
    - **COX-2 or Induced form of COX.**

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

Cardiovascular

- Platelets: Inhibition of platelet COX-1-derived TxA_2 with the net effect of increasing bleeding time (inhibition of platelet aggregation)
- Endothelial COX-2 derived PGI_2 can inhibit platelet aggregation (inhibition augments aggregation by TxA_2).

Aspirin (acetylsalicylic acid) covalently modifies and, irreversibly inhibits platelet COX. The enzyme is inhibited for the lifetime of the platelet (~8 -11 days). Effect achieved at very low dose.

- *Basis of therapeutic efficacy in stroke and MI (reduces mortality and prevents recurrent events).*

Additional Cardiovascular Considerations

- *Blood vessels/smooth muscle*

COX-2 derived PGI_2 can antagonize catecholamine- and angiotensin II-induced vasoconstriction (NSAIDs can elevate bp).

- *Atherosclerosis*

Inhibition of COX-2 can destabilize atherosclerotic plaques (due to its anti-inflammatory actions)

Renal

- COX-1 and COX-2 – generated PGs (TxA_2, PGF_2 , PGI_2 (glom), PGE_2 (medulla), powerful vasodilators).
- NSAIDs tend to promote Na^+ retention and can therefore increase bp. Can counteract effects of many anti-hypertensives (diuretics, ACE inhibitors and -AR antagonists).
- PGs have minimal impact on normal renal blood flow, but become important in the compromised kidney.
- Patients (particularly elderly and volume depleted) are at risk of renal ischemia with NSAIDs.

Gastrointestinal

- PGs (generated via COX-1)

  1) inhibit stomach acid secretion,

  2) stimulate mucus and HCO_3^- secretion, vasodilation and therefore,

  3) are cytoprotective for the gastric mucosa.
- Therefore, NSAIDs with COX-1 inhibitory activity will produce opposite effects, leading to:
- Gastric distress, gastric bleeding, sudden acute hemorrhage (*effects are dose-dependent)*

Gestation

PGs (generated from COX-2) are involved in the initiation and progression of labor and delivery. Therefore, inhibition of their production by NSAIDs can prolong gestation.

Respiratory system

High doses (salicylates) cause partial uncoupling of oxidative phosphorylation with increased CO_2 production (COX-independent effects). Increase in plasma CO_2 → hyperventilation. Even higher doses cause depression of respiration.

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.

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

- Furthermore, by decreasing **prostaglandin** synthesis, salicylate also prevents the sensitization of pain receptors to both mechanical and chemical stimuli.

- Aspirin may also depress pain stimuli at **subcortical** sites

Aspirin (salicylate)

• 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.

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.

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
- it rapidly lowers the body temperature of febrile patients by increasing heat dissipation as a result of peripheral vasodilation and sweating.
- Aspirin has no effect on normal body temperature.

Respiratory actions:

- At therapeutic doses, aspirin increases alveolar ventilation. uncouple oxidative phosphorylation, which leads to **elevated CO2** and increased respiration.

- Higher doses work directly on the **respiratory center** in the medulla, resulting in hyperventilation and respiratory alkalosis

- At **toxic** levels, central respiratory paralysis >> **acidosis**

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:

- **TXA2** enhances platelet aggregation >> **Low doses 81 mg** daily of aspirin can irreversibly **inhibit** thromboxane production in platelets via inhibition of cyclooxygenase.

- Because platelets lack nuclei, they cannot synthesize new enzyme, and the lack of thromboxane persists for the lifetime of the platelet (7 days)>> As a result prolonged **bleeding time.**

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.
- **Interstitial nephritis** can also occur with all NSAIDs except aspirin

Therapeutic uses

Anti-inflammatory, antipyretic, and analgesic uses:

- The salicylic acid derivatives are used in the treatment of gout, rheumatic fever, osteoarthritis, and RA.
- Commonly treated conditions requiring **analgesia** include headache, arthralgia, and myalgia.

External applications:

- Salicylic acid is used topically to treat corns and warts.

Cardiovascular applications:

- Aspirin is used to inhibit platelet aggregation. Low doses are used **prophylactically** to

1) reduce the risk of recurring transient ischemic attacks (**TIAs**) and stroke or death

2) reduce the risk of death in those having an acute **myocardial infarction** . ,,, **angina**

pharmacokinetics

Administration and distribution:

- After oral administration, the un-ionized salicylates are passively absorbed from the **stomach** and the **small intestine**

- **Rectal** absorption of the salicylates is **slow** and unreliable, but it is a useful route for administration to vomiting children.

- Salicylates must be avoided in children and teenagers (<15 years old) with varicella (chickenpox) or influenza to prevent **Reye's** syndrome.

Dosage:

- The salicylates exhibit analgesic activity at low doses; only at higher doses do these drugs show anti-inflammatory activity .

- For example, two 325-mg aspirin tablets administered four times daily produce **analgesia**, whereas higher dose produce both analgesic and **anti-inflammatory** activity.

- For long-term **myocardial infarction prophylaxis**, the dose is 81 to 162 mg/day
- for those with **RA or osteoarthritis**, the initial dose is 3 grams/ day

- for **stroke prophylaxis**, the dose is 50 to 325 mg/day

Fate:

- At dosages of 650 mg/day, aspirin is hydrolyzed to salicylate and acetic acid by esterases in tissues and blood .
- Salicylate is converted by the **liver** to water-soluble conjugates that are rapidly cleared by the **kidney**
- Both **hepatic** and **renal** function should be monitored periodically in those receiving long-term, high-dose aspirin therapy.
- aspirin should be avoided in patients with a creatinine clearance of less than 10 mL/min.

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.**

Blood:

- inhibition of **platelet** aggregation and a prolonged bleeding time. (1 week)

Respiration:

- In toxic doses, salicylates cause respiratory depression and a combination of uncompensated respiratory and metabolic **acidosis**.

Metabolic processes:

- Large doses of salicylates **uncouple oxidative phosphorylation**. The energy normally used for the production of adenosine triphosphate is dissipated as heat, which explains the **hyperthermia** caused by salicylates when taken in toxic quantities

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 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.

- In pregnancy: Aspirin is classified as FDA pregnancy category C risk during Trimesters 1 and 2
- Category D during Trimester 3.
- Because salicylates are excreted in breast milk, aspirin should be avoided during pregnancy and while breast-feeding.

FDA Pregnancy Categories

Category	Description
A	Controlled studies of pregnant women show no risk in first trimester
B	Animal studies show no risk, or animals show risk unconfirmed in humans
C	Animal studies show risk, caution is advised, benefits may outweigh risks
D	Evidence of risk to human fetus, benefits may outweigh risks in serious conditions
X	Risk outweighs benefit

Adapted from Dwosh E, et al. *Int MSJ*. 2003;10:52-59.

MedscapeCME

Toxicity:

- **The mild form is called salicylism**
- nausea, vomiting, marked hyperventilation, headache, mental confusion, dizziness, and tinnitus (ringing or roaring in the ears).
- Ingestion of as little as 10 g of *aspirin* can cause death in children.
- In serious cases, mandatory measures include the intravenous administration of **fluid**, **dialysis**
- correction of **acid-base** and electrolyte balances.

Propionic acid derivatives

- **Ibuprofen , naproxen, fenoprofe, ketoprofen , flurbiprofen**

- All these drugs possess anti-inflammatory, analgesic, and antipyretic activity
- their **GI** effects are generally less intense than those of aspirin.
- These drugs are **reversible** inhibitors of the cyclooxygenases

- All are well **absorbed** on oral administration and are almost totally bound to serum **albumin**.
- They undergo **hepatic** metabolism and are excreted by the **kidney**.
- The most common adverse effects are **GI**, ranging from dyspepsia to bleeding.
- Side effects involving the central nervous system (**CNS**), such as headache, tinnitus, and dizziness, have also been reported.

Naproxen and Ibuprofen

- Pregnancy : category C, category D
- 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 , sulindac , Etodolac**
- All have anti-inflammatory, analgesic, and antipyretic activity. They act by **reversibly** inhibiting cyclooxygenase.
- Despite its potency as an anti-inflammatory agent, the **toxicity** of **indomethacin** limits its use to the treatment of acute gouty arthritis, ankylosing spondylitis .
- The adverse reactions caused by **sulindac** are similar to, but less severe than, those of the other NSAIDs, including indomethacin.
- **Etodolac** has effects similar to those of the other NSAIDs

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**.

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*.

Fenamates

- ***Mefenamic***
- *have **no advantages** over other* NSAIDs as anti-inflammatory agents.
- Their side effects, such as **diarrhea**, can be severe, and they are associated with inflammation of the bowel.
- Cases of hemolytic anemia have been reported

Heteroaryl acetic acids

- ***Diclofenac and tolmetin , ketorlac***
- *are approved for long-term use in the treatment of RA*, osteoarthritis.
- ***Diclofenac*** *is more potent than indomethacin or naproxen.*
- *An* ***ophthalmic*** preparation is also available.
- *Diclofenac accumulates in synovial fluid, and the primary route of excretion for the* drug and its metabolites is the **kidney**.

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.
- Pregnancy: category C
- Toxicity similar to others

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

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.

Paracetamol = Acetaminophen

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

Pharmacokinetics

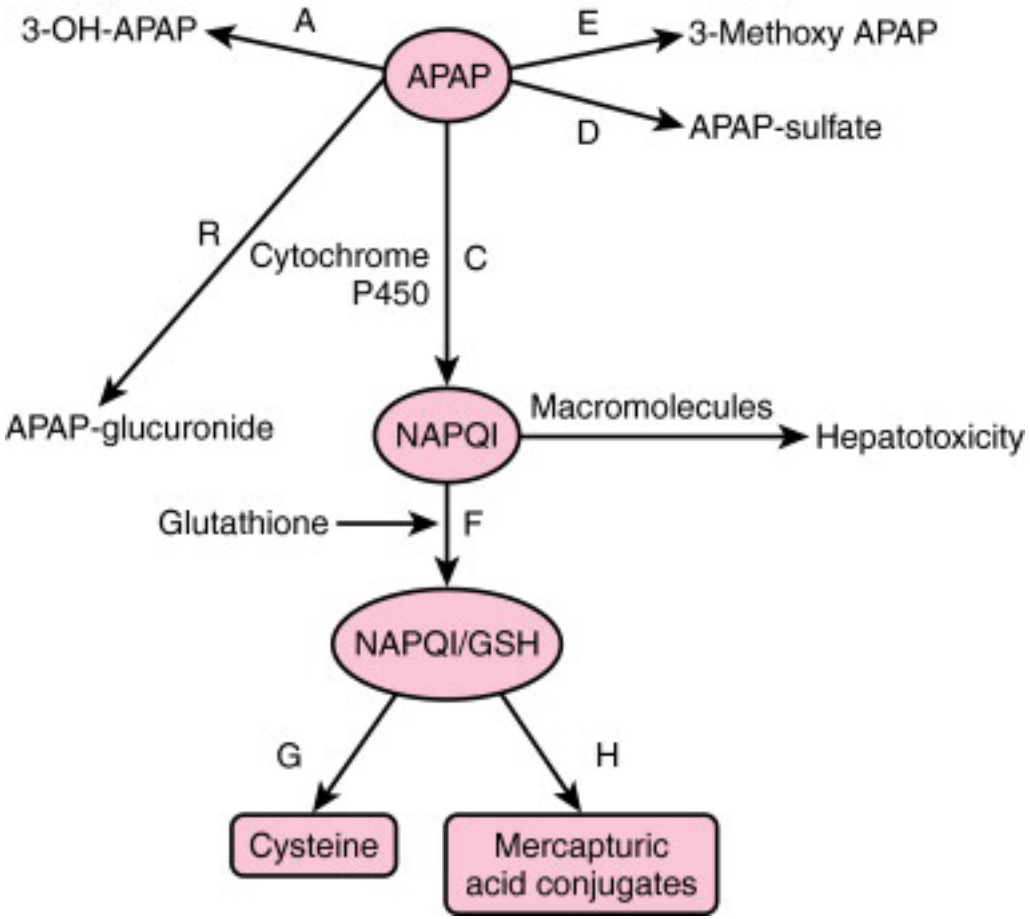
- Acetaminophen is rapidly **absorbed** from the GI tract. A significant first-pass metabolism occurs in the **luminal** cells of the intestine and in the **hepatocytes**.

- 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.


3-OH-APAP
A
APAP
E
3-Methoxy APAP
D
APAP-sulfate
R
Cytochrome
P450
C
APAP-glucuronide
NAPQI
Macromolecules
Hepatotoxicity
Glutathione
F
NAPQI/GSH
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Cysteine
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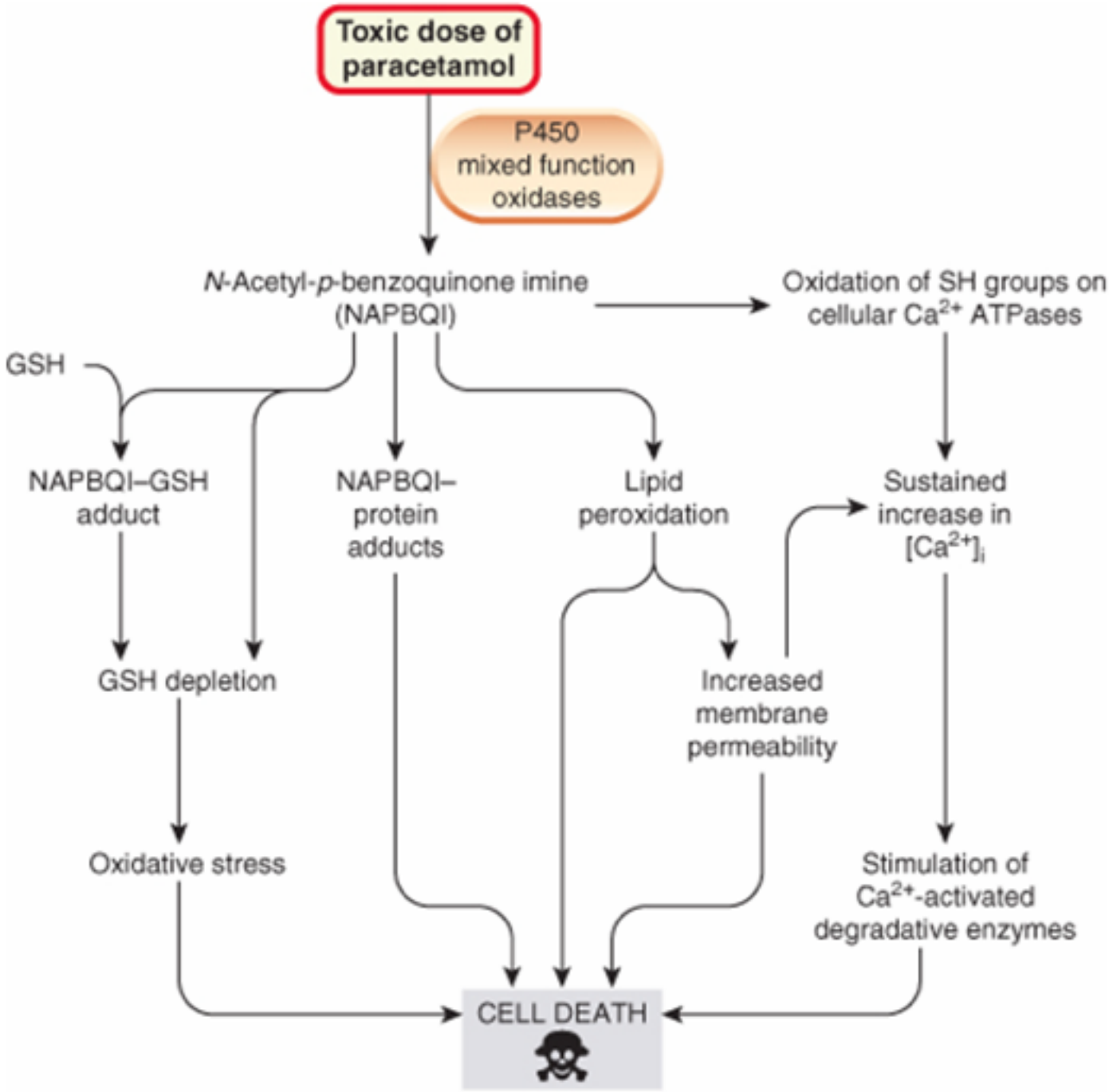
acid conjugates


Toxic dose of paracetamol
P450 mixed function oxidases
N-Acetyl-p-benzoquinone imine (NAPBQI)
Oxidation of SH groups on cellular Ca2+ ATPases
GSH
NAPBQI–GSH adduct
NAPBQI–protein adducts
Lipid peroxidation
Sustained increase in [Ca2+]i
GSH depletion
Increased membrane permeability
Oxidative stress
Stimulation of Ca2+-activated degradative enzymes
CELL DEATH

Paracetamol

- Toxicity
  - Severe hepatotoxicity with high doses
  - N- acetylcysteine is the antidote when given in the first 24hours.

Cyclooxygenase II Inhibitors

- Meloxicam
- Rofecoxib (WITHRDRAWN)
- Celocoxib

Cyclooxygenase II Inhibitors

- Do not affect platelet function.
- May increase the incidence of edema and hypertension.
- Less gastroirritant (half of COX2-non selective drugs).
- Higher incidence of cardiovascular thrombotic events.

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	(-)	(+) (+)