ZAPORIZHZHIA STATE MEDICAL UNIVERSITY

PHARMACOLOGY DEPARTMENT

LECTURE № 4

OPIOID (NARCOTIC) ANALGESICS and ANTAGONISTS. NON-OPIOID (NON-NARCOTIC) ANALGESICS.

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General mechanisms of pain reception

Nociceptive and antinociceptive systems:

➞ Nociceptive system

- is the system of pain reception and it s psychical appreciation with launching some defensive conditional and inconditional reflexes.

➞ Antinociceptive system

- is the system of excessive pain reception supression.

If feeling of pain reaches excessive level, pain from the distress signal turns into source of distress and may cause shock.

OPIOID AGONISTS and ANTAGONISTS

1. **FULL AGONISTS:**

   Morphine hydrochloride *Tab. 0.01 g; amp. 1% -1 ml*

   Omnopon – *amp. 1% solution - 1 ml*

   Promedole (*Trimeperidine*)-*amp. 1% - 1 ml, Tab. 0.025 g*

   Fentanyl – *amp. 0.005% - 1 ml*

2. **PARTIAL AGONISTS**, or **Agonists-Antagonists**:

   Pentazocine – *amp. 3%-1 ml, Tab. 0.05 g*

   Tramadol – *caps. 0.05; amp. 5%-1 ml*

   Nalorphine – *amp. 0.5%-1 ml and 0.05%-0.5 ml*

   Buprenorphine – *Tab. 0.0002*

3. **Antagonists**:

Naloxone – amp. 0.04% - 1 ml

Naltrexone – Tab. 0.01 ; 0.05 g

OPIATES (Opium Alkaloids)

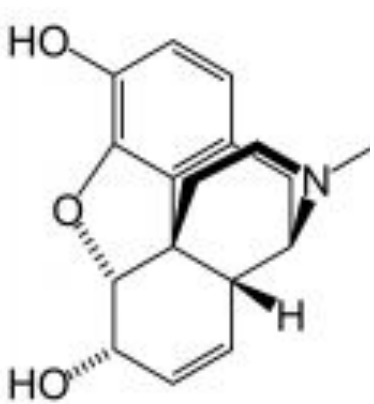
1. **Phenantrenes:**
   - **Morphine**
   - **Codeine**
   - **Omnopon**
   - **Aethylmorphine**
2. **Isoquinolines**:
   - **Papaverine hydrochloride**

Morphine

is the ancestor of the group of opioid analgesics derived from opium

Opium is the dried milky juice extracted from the unripe seed capsules of the opium poppy

Opium ∈ ~ 20 alkaloids such as ***Morphine*** ***and*** ***Codeine***



Papaver somniferum

OPIATE RECEPTORS

μ-Rs: Supraspinal Analgesia,
Euphoria / Sedation,
Respiratory Depression,
GIT Motility,
Smooth Muscle Spasm, Miosis

κ-Rs: Spinal Analgesia,
Sedation / Dysphoria, Miosis

σ-Rs: Dysphoria, Psychotomimetic effects,
Respiratory and Vasomotor Stimulation,
Mydriasis

δ-Rs: Euphoria, Convulsive activity

ε-Rs: **β**-endorphine-like Analgesia

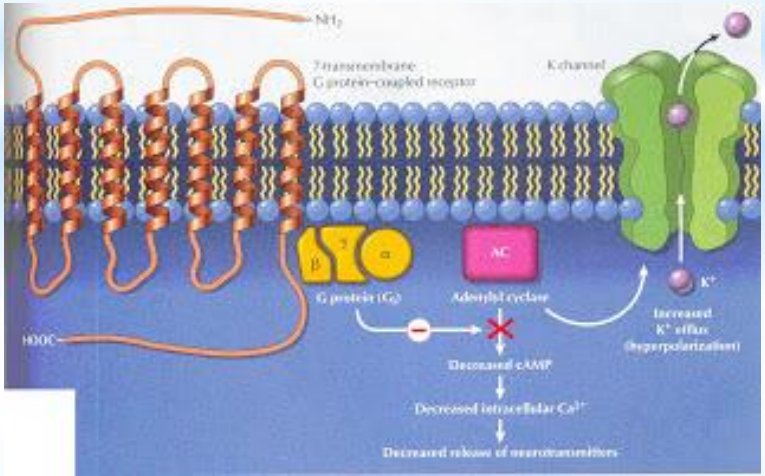
MECHANISM OF ACTION:

Stimulation of Opioid Receptors through G_i-Proteins =>

inhibition of Adenylyl Cyclase =>

- K^+ Efflux (Hyperpolarization)
- Ca^{2+} Influx

=> impeding Neuronal Firing and Transmitter Release



PHARMACOLOGICAL EFFECTS

- CNS: Euphoria, Drowsiness, Apathy, Mental Confusion, Nausea and Vomiting
- Respiratory:
  - Tidal Volume
  - Respiratory Rate
- Antitussive effects: a direct suppression of the Cough Reflex Center
- Cardiovascular: Peripheral Vasodilation
  - Total Peripheral Resistance
- *Histamine* Release => Flushing, Red Eyes, Sweating

GIT:

- Inhibition of peristalsis => Constipation
- Sphincter of Oddi spasm, nausea
- Gastric, Biliary, and Pancreatic Secretions
- Tone in the Biliary Tract => Biliary Spasm
- *Amylase* and *Lipase* levels up to 15 times

Urinary tract:

- Smooth Muscle tone and spasms

Clinicall uses of *MORPHINE*

- ANALGESIA:
  - Renal or Biliary Colic
  - Myocardial Infarction
  - Acute Trauma
  - Postoperative Pain
  - Terminal Cancer
- PULMONARY EDEMA

OVERDOSE with MORFINE

Respiratory and CNS Depression, Miosis

- ☐BP
- ☐HR
- ☐ t°

Skin is bluish and cold, face is pale,

Urine Retention, bladder overflowed,

Circulatory Collapse,

Pulmonary Edema, Convulsions,

Shock, Apnea, Cardiopulmonary Arrest

Treatment of overdose with Morphine

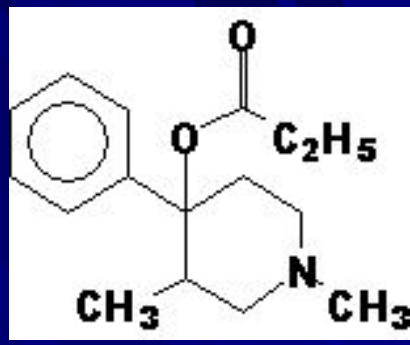
- **Narcotic antagonist: *NALOXONE*** 0.4 mg/ml
  IV bolus 0.8-2 mg (*2-5 ml*) q2-3 min to a total dose 10 mg
- **Symptomatic treatment:**

  Cordiamine, Sulfocamphocaine,
  Atropine, Coffeine

  - **Continued Respiratory Support**
  - **Correction of Fluid and Electrolyte Imbalance**
- **FORCED DIURESIS:**

  5% Glucose 500-800 ml
  0.9% NaCl isotonic solution
  4% $NaHCO_3$
  FUROCEMIDE 0.1% 4-8 ml

Promedole *amp. 1% -1 ml, Tab. 0.025 g,*
a synthetic opioid, *Piperidine Compound*



- *Binds to opioid Rs, particularly* ***κ-Rs***

It is preferred for analgesia during *LABOR* – *Neonatal Respiratory Depression* is less marked and it does not interfere with Uterine Contractility

It is often used in minor procedures like dilatation and curettage.

Fentanyl *amp.* 0.005%-1 ml

· is chemically related to *Promedole*,

· has 80 times the analgesic potency of *Morphine*.

· has a rapid onset and short duration of action (15-30 min)

FENTANYL + DROPERIDOL
produce a NEUROLEPTANALGESIA

Pentazocine amp. 3%-1 ml,Tab. 0.05

agonist - **κ**-Rs and **σ**-Rs

antagonist - **μ** and **δ**-Rs

- Activates Rs in the spinal cord, and is used to relieve moderate pain
- In angina:
  - *Aortic pressure*
  - Pulmonary AP => Heart Work
- *Renal plasma flow*

TRAMADOL caps. 0.05 g; amp. 5%-1 ml

a centrally acting weak synthetic opioid

with **μ** agonist effect and inhibitory action on

Noradrenaline and *Serotonin* reuptake in the CNS.

$T_{1/2}$ = 6 hours

- is only partially antagonized by *Naloxone*.

Adverse reactions: Dizziness, Headache, somnolence, CNS stimulation, euphoria, anxiety, coordination disturbance, seizures, vasodilation, anorexia, dry mouth, urine retention, respiratory depression.

Naloxone amp. 0.04%-1 ml - a pure Antagonist.

- antagonizes most of the opioid effects: respiratory depression, sedation, and hypotension
  Duration of action 1-4 hours

Clinical uses:

- Treatment of acute opioid overdose
- Postoperative narcotic depression
- Diagnosing opiate dependence
- Septic shock

Adversed effects: □HR, □AP, ventricular fibrillation, cardiac arrest; tremors and withdrawal symptoms in narcotic-dependent patients, diaphoresis, seizures, pulmonary edema.

Naltrexone **-** Tab. 0.05 g (50 mg)

$T_{1/2}$ = 10 hours.

A single oral dose of **100 mg** (2 tab.) blocks virtually all effects of a dose of heroin for up to 48 hours.

- PO 30-50 mg => minimal analgesia, only slight drowsiness, and no respiratory depression.
- Psychotomimetic effects, □AP

Clinical uses:

- Adjunct for maintenance of opioid-free state in detoxified individuals;
- Alcoholism.

Drugs from other groups with analgesic activity

- **α_2 – Adrenomimetics: *Clopheline***
- **Tricyclic antidepressants: *Amitriptyline***
  Imizine
- **Antiepileptic drugs: *Carbamazepine***
  Sodium Valproate
- **GABA-receptors' agonists: *Baclophene***
- **Hormones: *Somatostatin, Calcitonin***
- **Drugs for narcosis: *Nitrous oxide* (N_2O)**
  Ketamine

NON-OPIOID ANALGESICS

1. Para-Aminophenol Compounds
   - *Paracetamol* (*Acetaminophen, Panadol*)
   - *Phenacetin*
2. Salicylates – Salicylic Acid Compounds
   - *Acetylsalicylic Acid* (*Aspirin*)
   - *Sodium Salicylate*
3. Pyrazolone Compounds
   - *Analgin (Metamizole)*
   - *Butadione* (*Phenylbutazone*)

4. Antranil Acid Compounds

Mephenamic Acid

5. Indole-Acetic Acid Compounds

Indometacin

6. Phenyl-Acetic Acid Compounds

Diclofenac-Sodium

7. Phenyl-Propionic Acid Compounds

Ibuprophen

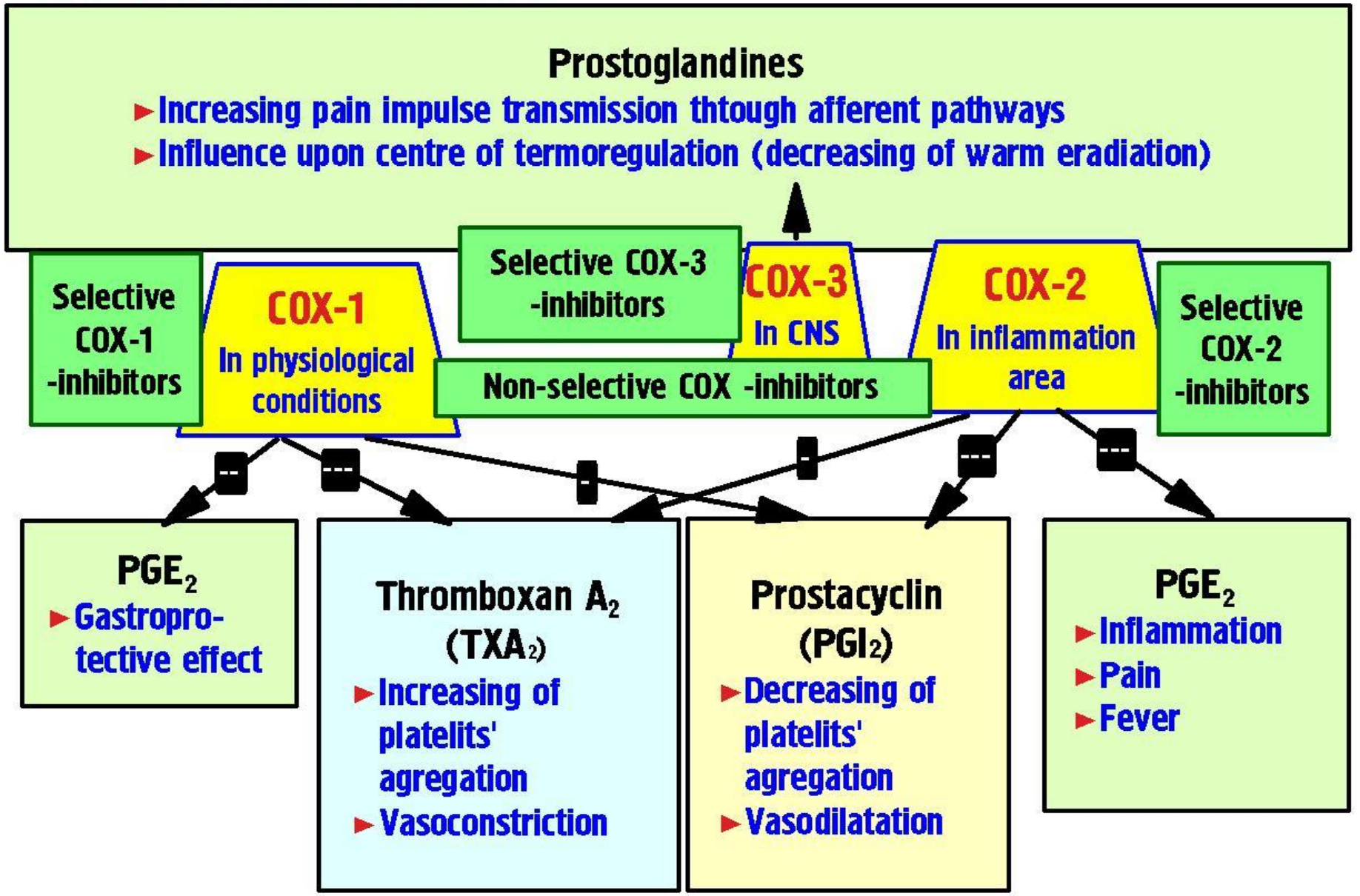
8. Naphtyl-Propionic Acid Compounds

Naproxen

- oxicams :

Piroxicam

Cyclooxygenase inhibitors



COX-2 inhibitors:

Meloxicam

Celecoxib

Nimesulide

- COX-1 is structural and responsible for PROTECTIVE PROPERTIES of GIT.
- COX-2 is induced and responsible for PG production by cells involved in INFLAMMATION.
- COX-3 is located in the CNS

Para-Aminophenol Compounds:

- *Paracetamol*
- *Phenacetin*

Mechanism of action: inhibition of COX-3

1) Antipyretic action:

Inhibition of COX-3 => **PG synthesis** in the **CNS**

2) Analgesic action:

is related to an elevation of the pain threshold.

Tab. «Citramon»:

Aspirin 0.2 g

Phenacetin 0.2 g

Caffeine 0.04 g

ADVERSE EFFECTS

Hemologic: hemolytic anemia, neutropenia, leukopenia, thrombocytopenia

Hepatic: Liver Damage (toxic doses), Rash, Hypoglycemia

- *Hepatic enzymes*

dizziness, excitement, disorientation.

Large doses of Paracetamol (7-10 g) =>

- Hepatocellular damage with central lobular necrosis
- Renal tubular necrosis

The liver toxicity: due to toxic metabolite

N-acetyl-P-benzoquinonamine, which normally turns harmless by Conjugation with Glutathione.

TREATMENT:

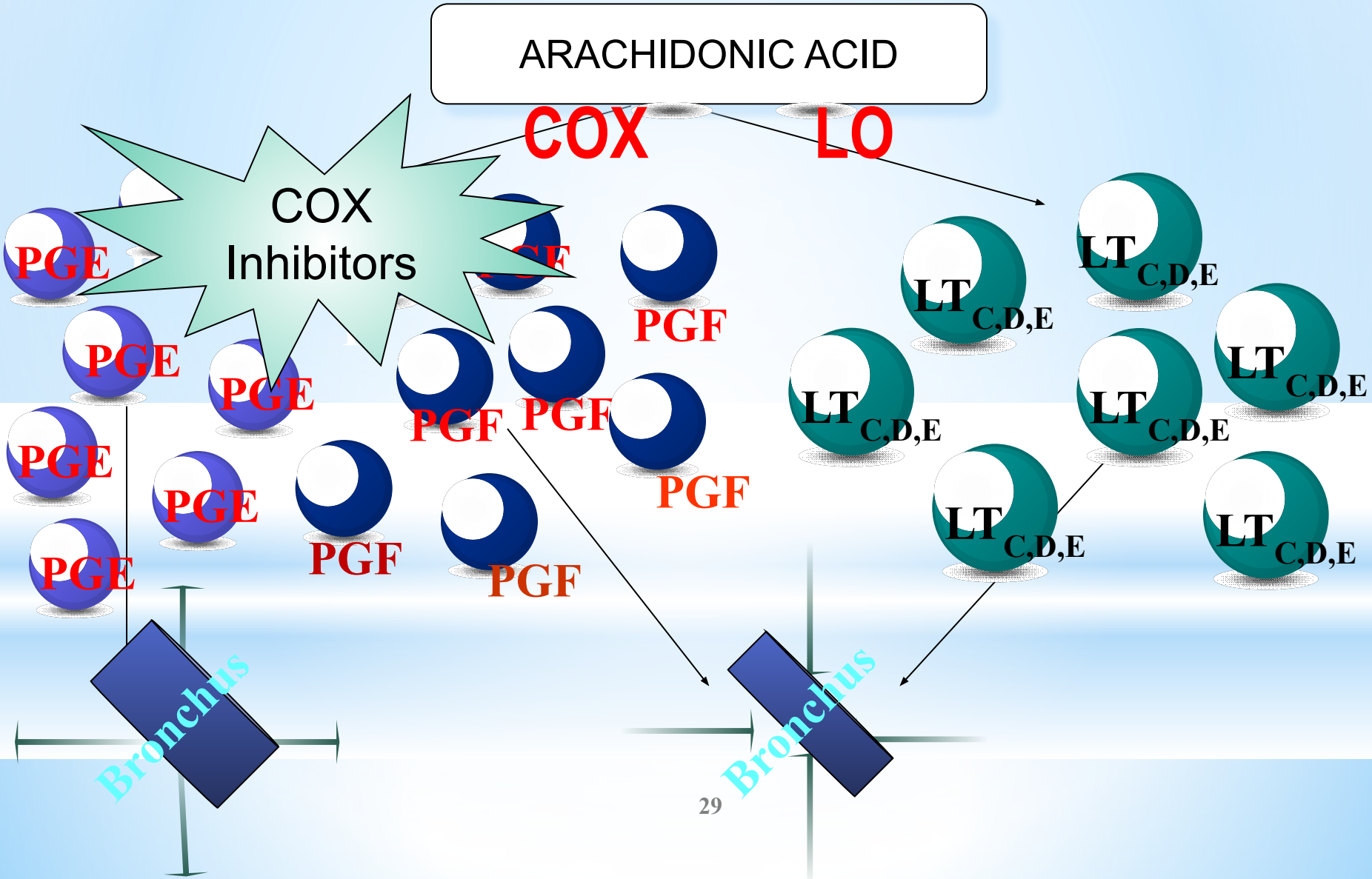
- Sulfhydryl SH- compounds:
  - Acetylcysteine (ACC)
  - Cystamine
  - Methionine

Aspirin is a weak organic acid that is unique among the *NSAIDs* in irreversibly acetylating (inactivating) ***COX-1*** and ***COX-2.***

NSAIDs **have 3 major therapeutic actions**:

- Antinflammatory
- Analgesic
- Antipyretic

MECHANISM OF ASPIRIN ASTHMA DEVELOPMENT



THERAPEUTIC USES of *SALICYLATES*

1. **Antipyretics and analgesics:**

Gout, Rheumatic Fever, Rheumatoid Arthritis.
headache, arthralgia, and myalgia.

2. **External applications:**

Salicylic acid is used topically to treat calluses and epidermophytosis

Methyl salicylate –

externally as a cutaneous **counterirritant**

3. **Cardiovascular applications:**

Aspirin *170-350 mg*

4. **Colon cancer**

ADVERSE EFFECTS of SALICYLATES

1. GIT: nausea, vomiting, bleeding, ulceration
2. Blood: ↓Prothrombin

Aspirin should not be taken for at least 1 week prior to surgery.

3. Respiration: Respiratory Alkalosis and true Metabolic Acidosis.
4. Metabolic processes: hyperthermia
5. Hypersensitivity: Urticaria, Bronchospasm, Lyell's syndrome (Epidermal Necrolysis), Angioneurotic Edema, Anaphylactic Shock
6. Reye's syndrome:

   HEPATITIS with CEREBRAL EDEMA

SALICYLISM - a condition of mild salicylate intoxication:
nausea, vomiting, hyperventilation,
headache, mental confusion,
dizziness, tinnitus (ringing in the ears),
tachypnoea and respiratory alkalosis

SEVERE SALICYLATE INTOXICATION :
restlessness, delirium, hallucinations,
convulsions, coma,
Respiratory Alkalosis + Metabolic Acidosis,
Death from respiratory failure.

Treatment: gastric lavage, correction of hyperthermia,

- IV fluids
- Dialysis (hemodialysis or peritoneal dialysis)
- Correction of acid-base and electrolyte balances:

Urinary Alkalinization: normal *0.9% NaCl* saline solution containing *2% glucose* solution and *2% Sodium Bicarbonate* solution at the rate of 2 liters/hour.

Analgin (*Metamizole*) Tab. 0.5 g, amp. 25%-2 ml

Antipyretic action - by direct action

on the hypothalamic heat-regulating center to block the effects of Endogenous Pyrogens IL1,TNF-α

=> heat dissipation through sweating and vasodilation

$T_{1/2}$ = 72 hours.

- Clinical uses: moderate to severe pain including headache, toothache, neuralgia, and myalgia

Analgin is a major cause of AGRANULOCYTOSIS

Phenylbutazone (Butadion)

Diclofenac-natrium

Indometacin

can cause APLASTIC ANEMIA.

=> Should be used ONLY when *ASPIRIN* and other safer NSAIDs are ineffective.

Indomethacin -

is more effective in relieving inflammation with acute gouty arthritis, osteoarthritis of the hip, ankylosing spondylitis, and uveitis,

postoperative ophthalmic procedures,

Indomethacin can delay labor by suppressing uterine contractions.

- *Indomethacin* has been recommended as a Tocolytic in Preterm Labour < 32 weeks of gestation.

Diclofenac-Natrium (*VOLTAREN*)

Tab. 0.025 g; amp. 2.5%-3 ml

- a Potent COX inhibitor with Antiinflammatory, Analgesic, and Antipyretic properties
- more potent than *Indomethacin*

Adverse effects: 20% of patients -

GIT distress,

Occult GIT Bleeding,

Gastric Ulceration,

 Hepatic Enzyme Levels

Ketorolac

Tab. 10 mg (0.01 g),
amp. 3%-1 ml IM,
ophthalmic drops: 0.5% solution

Effective Analgesic in patients with moderate to severe postoperative pain.

- *as effective as Morphine, and have fewer side effects, in surgical and chronic cancer pain.*
- *has longer duration of action* (T1/2 = 5 hours) and acts like the other NSAIDs
- *has less antinflammatory activity*

Clinical uses: *postoperative pain, cancer pain, topically for allergic conjunctivitis*

Selective COX-2 inhibitors

Meloxicam Tab. 0.015 g

Celecoxib Caps. 0.1 g

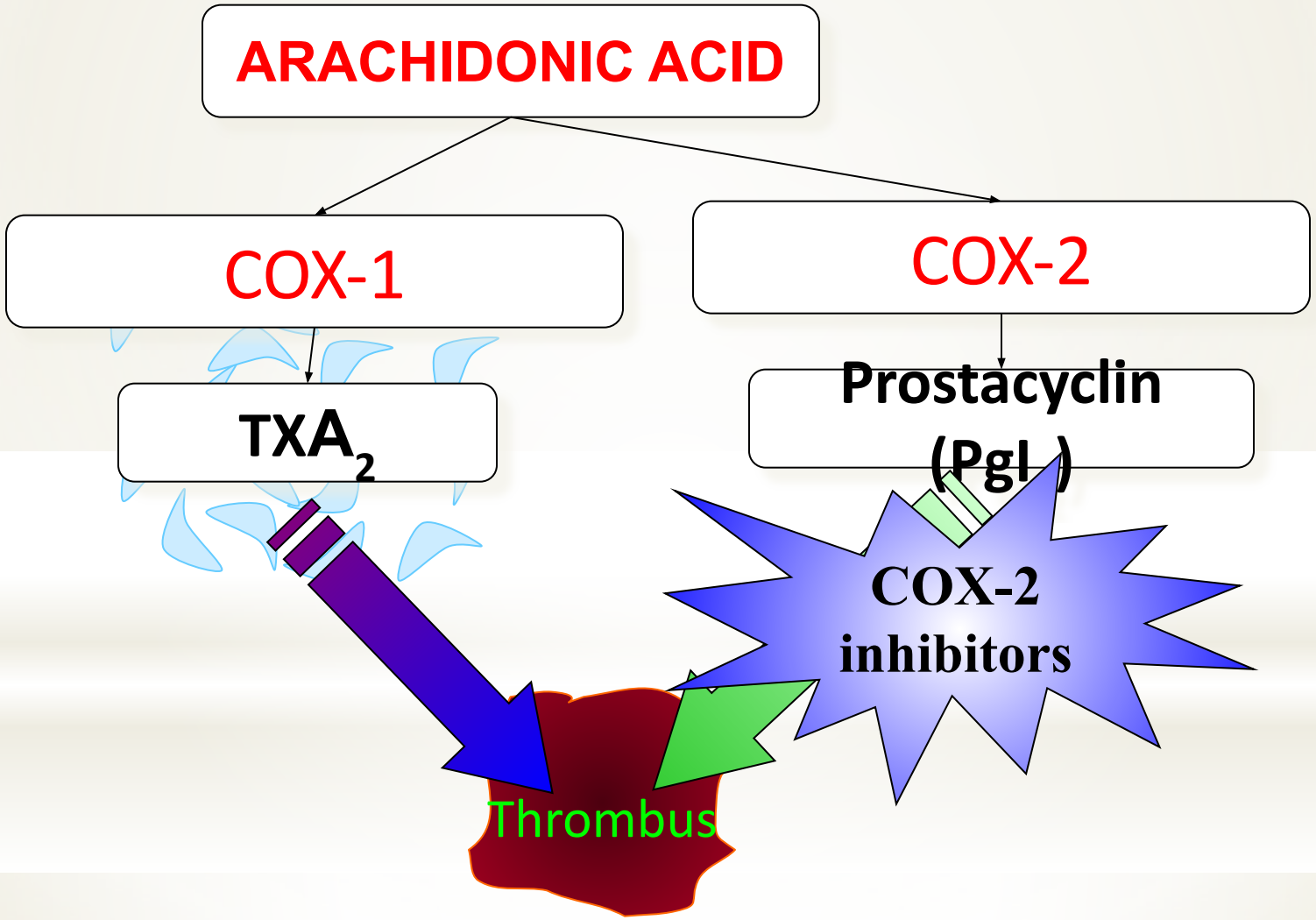
Advantage: fewer Gastric Ulcers and do not inhibit platelet aggregation

Disadvantage: may have prothrombotic effect, leading to a higher incidence of Cardiovascular Events.

Adverse reactions:

- Renal Toxicity – Renal blood flow, Edema, Hypertension
- Interfere with Wound (Ulcer) Healing, Bone Remodeling, Prenatal Renal Development

Mechanism of Cardiovascular Disorders Development



Rofecoxib, Valdecoxib, Nimesulide –

have been withdrawn from the pharmaceutical market:

- *Rofecoxib* and *Valdecoxib* have been reported to be associated with increased incidence of

  MYOCARDIAL INFARCTION and STROKE,

- Nimesulid - due to its high HEPATOTOXICITY.

THANK YOU for ATTENYION!