Athar Batch

Pharmacology

Lecture: 24

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there are some drugs that do the same action as the autacoids or the other drugs can do the opposite and are called the antagonists/blockers.

AUTACOIDS & RELATED DRUGS

they are similar to the normal hormones but they're not secreted from the glands.

- Autacoids are biologically active substances of heterogenous chemical structures, which may be involved in some pathological conditions, and are known as "Locally- acting hormones". because they are secreted from some cells and act locally on some organs like the skin/GIT/Heart.

Classification:

- Autacoids are classified chemically into:

a) Amino Acid derivatives:

1. Histamine (derived from histidine).
2. Serotonin = 5-Hydroxytryptamine (5-HT; derived from tryptophan).

will be discussed later in the GI and the CNS systems.

b) Vasoactive Peptides: chain of the amino acids.

in the CVS

1. Angiotensin.
2. Kinins
3. Substance P.
4. Endothelin.
5. Vasoactive Intestinal Peptide (VIP). mainly found in the gastrointestinal tract.
6. Atrial Natriuretic Peptide (ANP). mainly found in the atrium of the heart.

c) (Fatty acid derivatives):

1. Eicosanoids: Prostaglandins & Leukotrienes.
2. Platelet Activating Factor (PAF).

d) Others: Cytokines as interferons found in the inflammatory cells like the white blood cells and the lymphocytes.

HISTAMINE (HI)

Synthesis: by decraboxylation of the amino acid L-histidine with L-aromatic amino acid decarboxylase enzyme.

one of the important places to find mast cells is the lungs "Bronchi".

amino acid **L-histidine** —**Decarboxylase**→ **Histamine**

Storage: in storage granules inside mast cells (with heparin), in basophils, and other cells (in most tissues e.g. lung, skin & GIT). when there's a stimulous/pathogenic condition, then it will be produced from the cells and initiates a response.

Release:

- **Histamine liberation:** ***HI liberators*** are basic drugs (e.g. morphine, atropine, curare, hydralazine) that replace HI in storage granules without degranulation.

- **Immunogenic release:** interaction of antigenic drugs (e.g. **penicillin**) with IgE on surface of sensitized mast cells →↑ intracellular calcium & release of the whole histamine- containing granules (exocytosis).

Mechanism of action:

- **Histamine stimulates specific G-protein coupled receptors:**

Receptor	Signal transduction	Sites	Actions
H_1	Gq→ activation PLC→ ↑DAG and IP3→↑ Ca^{2+}.	1. Smooth muscle fibers as bronchi, GIT, uterus. 2. Endothelium of Bl.vessel 3. Skin & sensory nerve end. 4. CNS (post-synaptic). 5. Vestibular system	1. Spasmogenic effect. 2. Vasodilatation & ↑ capillary permeability. 3. Itching, urticaria, pain. 4. Alertness. 5. Vomiting
H_2	Gs→ activation of A.C.→ ↑c-AMP.	1. Gastric Parietal cells 2. Heart. 3. Blood vessels. 4. CNS (post-synaptic).	1. ↑ secretion of HCl and pepsin. 2. ↑ cardiac properties (+ve inotropic & chronotropic). 3. Vasodilatation. 4. Alertness.
H_3		CNS (pre-synaptic)	↓ Release of neurotransmitters
H_4	Gi → inhibition of A.C.→↓ c-AMP	Inflammatory cells as: T-lymphocytes, Neutrophils, Esinophils.	Modulation of cytokines.

Role of histamine

1. Allergy: immediate hypersensitivity reactions:

a. Local allergic response: localized H_1 receptors stimulation on blood vessels & nerve endings →

i. Redness.

ii. Edema.

iii. Pain & itching.

spreading to all the tissues.

b. Anaphylactic shock: generalized H_1 receptors stimulation → marked hypotension.

c. Bronchospasm.

2. Vomiting of vestibular origin (e.g. motion sickness) is H_1-receptor mediated.

3. Peptic ulcer: H_2 receptors mediate more than 70% of HCl secretion.

so if this secretion exceeds the normal limits, then I have to decrease the H_2 receptors/Blocking them.

4. Heart: myocardial stimulation, ↑ heart rate

5. CNS: alertness

decreasing the role of histamine

Drugs that antagonize the action of histamine

1. Pharmacological Antagonists:

A drug that blocks the same receptor that the antiagonist works on.

a) H1-Antagonists (blockers) = Antihistaminics = Antiallergic drugs.

will be taken in the GI system.

b) H2-Antagonists (blockers): Cimetidine-Famotidine → treatment of peptic ulcer.

2. Physiological Antagonist:

Two drugs and each drug works on different receptors and its action is against the receptor's action.

works on:
1. alpha → vasoconstriction
2. Beta 2 → Broncho-dilatation

Adrenaline is the physiological antagonist of histamine

works on the H_1 and H_2 and causes vasodilatation & Bronchospasm.

Histamine يعكس action عملت بـ receptors ثانية.

adrenaline is given to cases of the anaphylactic shock.

3. Inhibitors of Histamine release:

a) Glucocorticoids: inhibit antibody formation and antigen-antibody reaction, → inhibit histamine release.

those are the reason behind the release of histamine.

b) Mast Cell Stabilizers = Degranulation inhibitors (inhibits the exocytosis): as cromolyn, nedocromil

Ba stabalizes the mast cells.

4. Desensitization.

the injection of the antigens in theraputic corses.

في مراكز علاج التحسس.

it's like the adaptation/tolerance by exposing the hypersensitive body naturally to the allergic material, thus making the body able to adapt to it and preventing the allergic reaction to occur in the second time of exposing.

كل ما يتعرض لهاي المادة اللي بتعمل حساسية، فالجسم ج يبطّل يفرز الهستامين وما ج يتولد وينفرز عندي الـ antigen - antibody و بس

H_1-ANTAGONISTS (ANTIHISTAMINICS-ANTIALLERGICS)

- All antihistaminics are **competitive antagonists** with histamine on H_1-receptors.
- All antihistaminics are **"Antiallergic drugs"** used in treatment of allergic conditions such as: skin rash- urticaria- angioneurotic edema-anaphylactic shock ***(Adrenaline is life-saving in anaphylactic shock).***

an edema in the face that may be severe and affects the tounge, larynx and leading to chocking.

important.

Pharmacokinetics:

1. They can be given **orally, parenterally, and topically** as skin ointment, eye drops, nasal drops and ear drops.

IV or IM

2. **"First generation"** antihistaminics can **pass easily B.B.B**. whereas "Second generation" drugs poorly penetrate B.B.B.

more lipophilic

3. **Pass placental barrier** and (may be teratogenic in experimental animals "Cyclizine & Meclizine").

تُفضّل المرأة الحامل إنها تبتعد عنهم وفي حال أخذت فتأخذ في كميات صغيرة.

they cause teratogenic effects in the animals but still don't cause teratogenics in the human.

4. Metabolized by **the liver** and excreted **in urine, and** are **partly** excreted **in breast milk.**

may affect the newborns.
* sedation.
* drowsiness.

دائم النوم مع عدم الانتظام في الرضاعة و تناول الطعام.

Classification:

causing sedation by crossing the BBB

1st Generation = Sedating Antihistaminics	**2nd Generation= less sedating Antihist.**
●Pass B.B.B. → sedation and drowsiness, but toxic doses → hallucination, excitation and convulsions. تشنجات	●Poor passage through B.B.B. → No CNS actions, i.e. No sedation & No antiemetic.
●They block H_1 and M receptors in the medullary vomiting center → anti-emetic	● Long duration (24 hours) due to slower metabolism by hepatic microsomal enzymes.
● They block M receptors in basal ganglia → anti-parkinsonian action	
● Short duration (6 hours) due to rapid metabolism by hepatic microsomal enzymes.	

like atropine

those two receptors are found in the vestibular pathway thus causing vomiting

atropine-like effect.

extrapyramidal tract.

thus decreasing the acetylcholine in the BG and the return of the normal ratio of acetylcholine to dopamine.

balance between the acetylcholine and the dopamine to balance the movement of the human.

the patient with the parkinson will have less dopamine and high acetylcholine.

more lipophilic
more metabolism.
less duration.
more penteration.

thus meaning that i have to take it more than one time aday.

will block more in the peripheral rather than in the central.

it may be taken once a day or twice aday "each 12 hours".

BPH: Beningn prostate hypertrophy.
IOP: Intraocular pressure.

the first generation of histamine has atropinic effects and is contraindicated in BPH & glaucoma.

Actions:	Actions:
1. Antihistaminic action: antagonize the actions of histamine on H1-receptors in blood vessels, bronchi, GIT, and skin. (vasodilatation X, bronchospasm X, GIT spasm X, redness X, the inhibition through the blockage of H1.)	**1. Antihistaminic action.** it blocks the H1 receptors found in the peripheral. (the only function/action.)
2. Antimuscarinic (Atropine-like) action → (anti-vomiting)	**2. NO** Atropine-like action →
a) Antiemetic action including motion sickness.	a) **NOT** Antiemetic
b) Antiparkinsonian action. (Because the muscranic receptors leads to stimulation of the wall and relaxation of the sphincter. + constipation)	b) **NOT** Antiparkinsonian action.
c) Urine retention (contraindicated in BPH). (closure of the sphincter. عكس الوظيفة)	c) **NOT** contraindicated in BPH.
d) ↑IOP (contraindicated in glaucoma). (when i block the muscarinic receptors then mydriasis will occur leading to the increase in the IOP.)	d) **NOT** contraindicated in glaucoma.
3. Some have **Antiserotonin action** → ↑appetite; e.g. Cyproheptadine.	**3. NO** Antiserotonin action
4. Some block Na^+-channels **(Membrane stabilizing action) →** ***Local anaesthetic*** and ***Antiarrhythmic action (Quinidine-like action);*** e.g: Antazoline. (an antiarrythmic drug that blocks the Na^+ channel.)	**4. NO** block Na^+-channels
5. α-blocking action. (through the α receptors → vaso-dilatation)	**5. NO** α-blocking action
Examples:	**Examples:**
• **Diphenhydramine** (antiemetics and antiparkinsonian).	• Cetrizine
• **Meclizine and Cyclizine** (antiemetic but contraindicated in pregnancy, may teratogenic).	• Loratadine.
• **Chlorpheniramine (common cold medication)** (analgesic + vasoconstriction, α1 antagonist) (عشان الناس اللي وجعلها برد بكتجعراتي عندهم كتير ضد البرد.)	• Fexofenadine
• **Antazoline** (antiarrhythmic).	يقال في الاختبار و الشرح. day: analgesic + vasoconstriction. night: analgesic + vasoconstriction + antihistaminic.
• **Cyproheptadine** (antiserotonin→ appetizer) (فاتح للشهية)	
• Ketotifen (antiserotonin & mast cell stabilizer)	
Therapeutic uses:	**Therapeutic uses:**
1. Treatment of **allergic conditions** (allergic rhinitis, rash, urticaria, angioneurotic edeme, and anaphylactic shock).	1. Treatment of **allergic conditions** (allergic rhinitis, rash, urticaria, angioneurotic edeme, and anaphylactic shock). (we give * adrenaline. * Corticosteroids. * antihistamine.) (حالة طوارئ)

"الأدوية حفظ يا شباب وياهبايا"

عدم الاتزان / الدوار

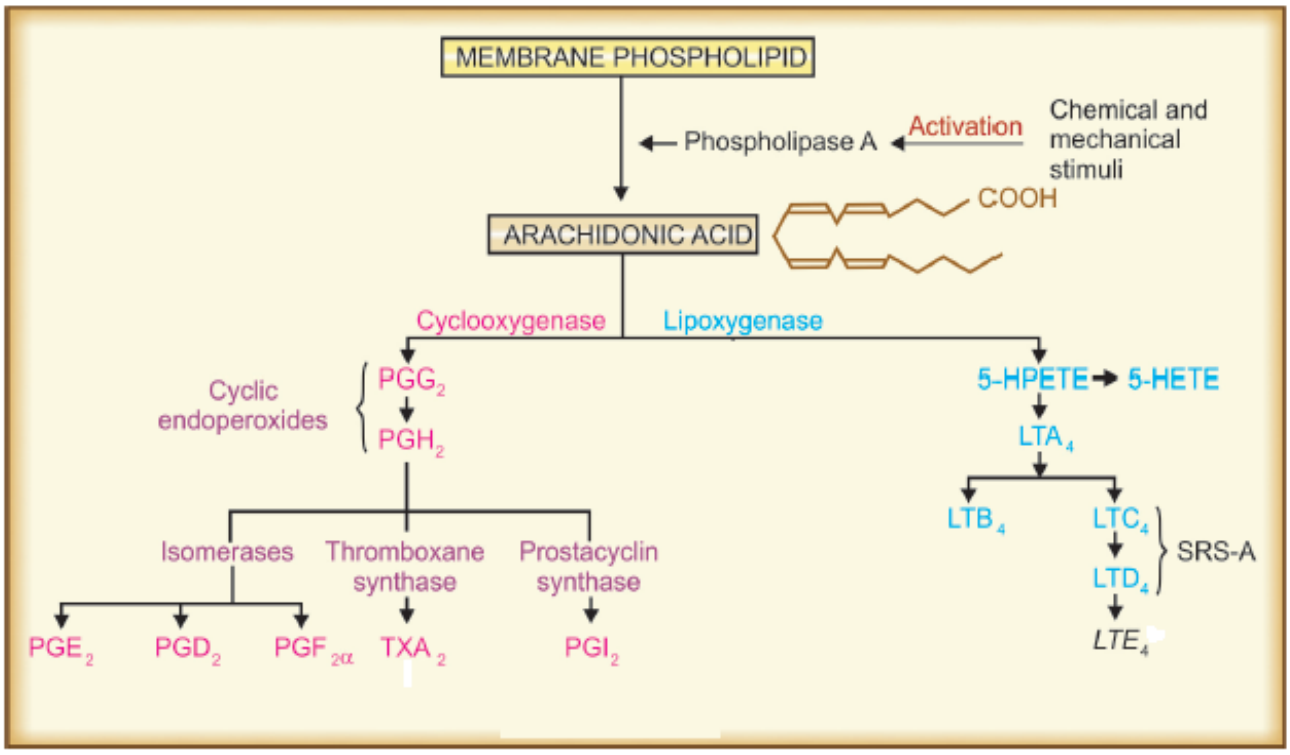
2. Antiemetics in **motion sickness, vertigo and Meniere's disease**. affects the middle ear, thus leading to the vomiting. 3. **Parkinsonism** (Diphenhydramine). 4. **Arrhythmias** (Antazoline). 5. **Anxiety and insomnia** (situational). "sedation" أرقه	
Adverse effects: 1. Sedation and drowsiness. 2. Excitation is more common in children 3. Teratogenicity (Cyclizine and Meclizine). 4. Allergic reactions. because the body will deal with the drug as a chemical substance, thus may be as an "antigen" to the body. (باحتمالات قليلة طبعًا) 5. Atropine-like adverse effects as dry mouth, constipation, urine retention, tachycardia, and elevation of IOP. 2. Acute toxicity: excitement, hallucinations, convulsions, and may be coma. Contraindications: 1-Car drivers. because they cause sedation. 2-Pregnancy. because of the possible teratogenics. 3-Glaucoma. because of the increase in the IOP. 4-BPH because of the urine retention.	Adverse effects: Cardiac arrhythmias especially in overdose or if given with HME inhibitors as erythromycin & ketoconazole. by the overdose, the selectivity may be lost الجسم رح يكون حساس شوي للدواء اللي عم ياخذ لانه الدواء حبسم غريب. يدخل للجسم فعشان هيك يقبل الدواء حبسم غريب. عشان هيك ممكن رح يصير بين الـ H1 والـ H2 ويروح يأثر على القلب. 1. increase the dose. 2. decrease the metabolism.

EICOSANOIDS

- They are endogenous 20-C (eicosanoid) fatty acid derivatives with profound physiological effects.
- They include:
  1. Prostaglandins (PGs) & Thromboxanes (TXs)
  2. Leukotienes (LTs)
- They are not stored in the body but are synthesized and rapidly metabolized, they have very short duration

1. Prostaglandins (PGs) and Thromboxanes (TXs)

- **Synthesis:** they are synthesized from arachidonic acid by cyclooxygenase enzyme **(COX)**



Biosynthesis of prostaglandins (PG) and leukotrienes (LT).

TX—Thromboxane, PGI—Prostacyclin; HPETE—Hydroperoxy eicosatetraenoic acid (Hydroperoxy arachidonic acid); HETE—Hydroxyeicosatetraenoic acid (Hydroxy arachidonic acid); SRS-A—Slow reacting substance of anaphylaxis

- **Mechanism of action:**

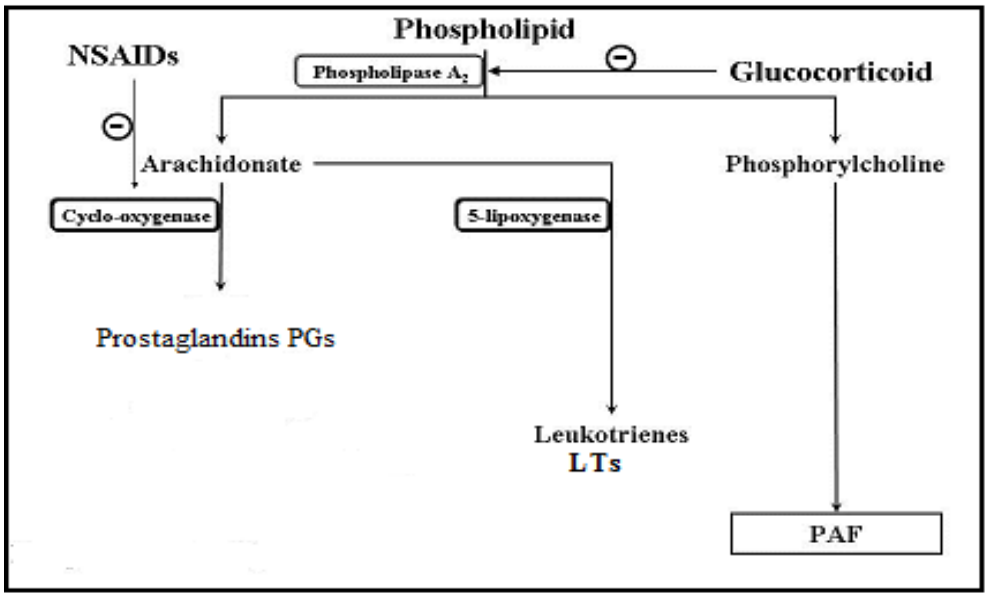
  PGs and TXA_2 act on specific G-protein coupled receptors:

  1. IP (Gs) receptors for PGI2 (prostacyclin).
  2. DP1 (Gs), DP2 (Gi) receptors for PGD.
  3. FP (Gq) receptors for PGF2α.
  4. EP1(Gq), EP2 (Gs), EP3 (Gi) and EP4 (Gs) receptors for PGE.
  5. TP receptors (Gq) for TXA2.

Physiological Role of PGs	Uses of PG Analogs
1. Role in Inflammation PGE, I_2 & D_2 released from mast cells in acute inflammation potentiate effects of histamine & bradykinin (BK)→ a. VD. b. ↑ capillary permeability. c. ↑ pain induced by BK	
2. Role in Pain (algesic action): a. PGs → ↑ pain transmission in the thalamus b. sensitize pain receptors to serotonin & kinins (pain mediators).	
3. Role in Fever (pyretic action): Pyrogens→ release of interleukin-1(IL-1) from inflammatory cells → Stimulates COX enz.→ ↑production of PGE2→ elevates the set point of hypothalamic heat regulating centre (HRC)	
4. Kidney (PGE) a. VD →↑ renal blood flow. b. Inhibits Na^+ reabsorption. c. ↑ renin secretion.	

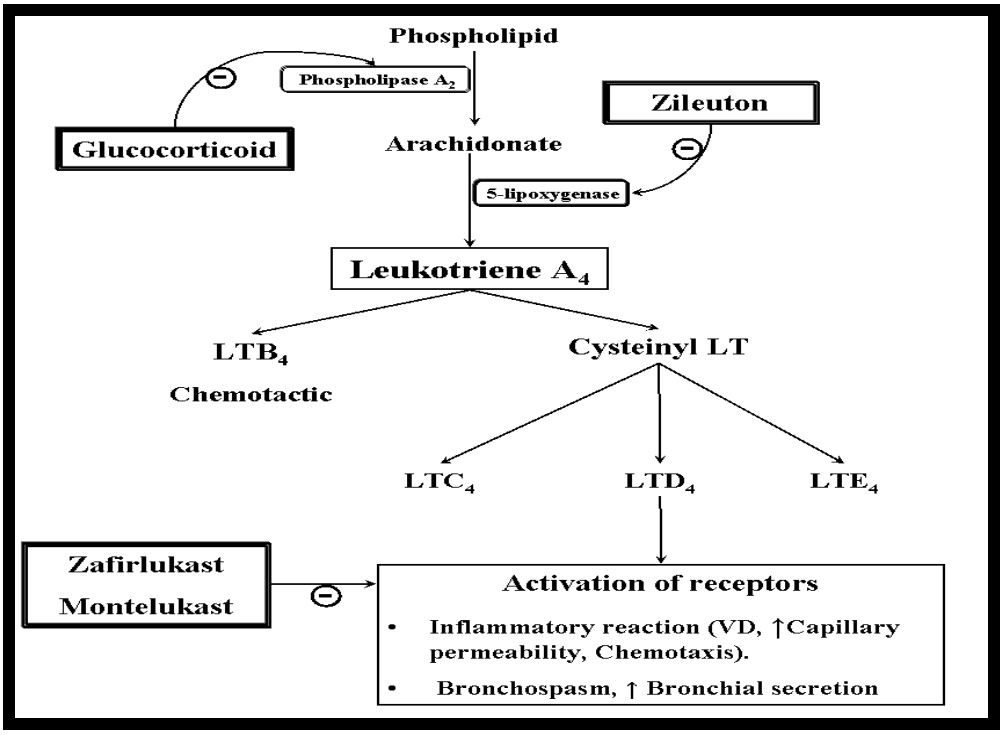
5. GIT: **a. Stomach: cytoprotective effects** PGE → - ↓ gastric HCl. - ↑ mucus secretion. - ↑ HCO_3 secretion - ↑blood flow →↑ healing of damaged mucosa **b. Intestine:** ↑ motility → colic, diarrhea	• **Misoprostol** (PGE): is given with NSAIDs or Steroids to ↓ their ulcerogenic effect • S/E: Misoprostol → colic , diarrhea
6. CVS: a. PGI_2 → ↓ platelet aggregation, VD b. TXA_2 → ↑ platelet aggregation, VC. c. PGE_2 and PGI_2 → maintain Patency of ductus arteriosus. d. PGE_2 recently, is assumed that it induces angiogenesis which may be the cause of cancer colon	• **Epoprostenol** (PGI_2) - Prevents platelet aggregation in dialysis machine - used in peripheral vascular disease & pulmonary hypertension. • **Alprostadil** (PGE_1): Maintains patency of ductus arteriosus in congenital pulmonary stenosis until surgery is performed.
7. Reproduction •**Male**: PGE → VD → erection & sperm motility •**Females:** $PGF_{2\alpha}$ & PGE → stimulate uterine contractions (oxytocic action) → induction of labor, abortion and control postpartum hemorrhage.	• **Alprostadil**: In erectile dysfunction (impotence). **Dinoprostone** (PGE_2): Induction of labor • **Dinoprost/ carboprost** ($PGF_{2\alpha}$):for induction of labor & abortion
8. Bronchial Tone a. PGI_2 - PGE → bronchodilation. b. $PGF_{2\alpha}$ - PGD_2 - TXA_2 → bronchospasm.	• $PGF_{2\alpha}$ induces bronchospasm thus
9. Eye: $PGF_{2\alpha}$ → ↑ aquous humor outflow →↓IOP	• **Latanoprost** ($PGF_{2\alpha}$) used locally in open angle glaucoma

Effects of PGs Inhibition:



1. **NSAIDs:** they inhibit COX enzymes→↓ PG synthesis → **Analgesic, Anti-inflammatory and Antipyretic effect**
2. **Corticosteroids:** induce inhibitory protein (Lipocortin) → inhibit phospholipase-A_2 → ↓ PGs, LTs & PAF synthesis → **- Anti-inflammatory** effects

2. Leukotrienes (LTs)



- **Synthesis:** LTs are synthesized from arachidonic acid by 5-lipooxygenase enzyme **(LOX).**
- **LTs include:**

1. LTB_4: powerful chemotactic agent → local accumulation of WBCs.

2. LTC_4, D_4 & E_4 (Cysteinyl LTs):

- Previously named as slowly reacting substances of anaphylaxis (SRSA)
- act on specific G_q-protein coupled receptors (LT receptors) →
  - potent bronchospasm
  - ↑ mucus
  - ↑ inflammatory reactions in bronchi

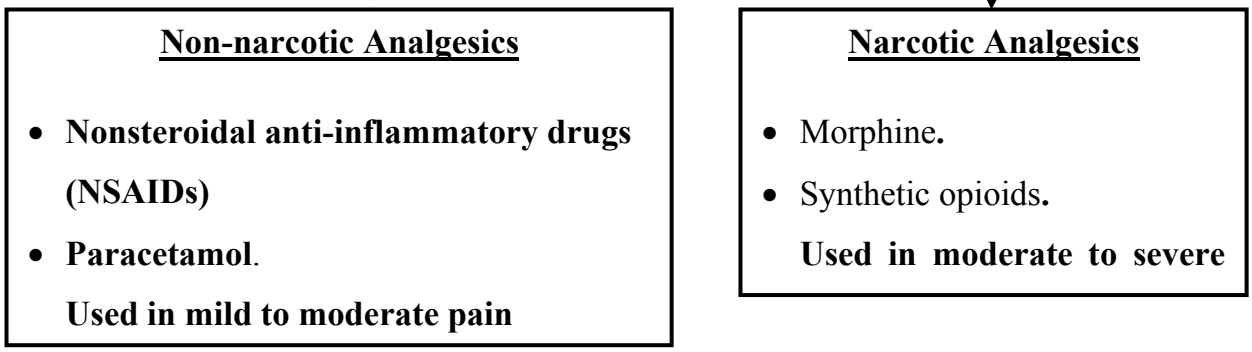
  } **Mediators of asthma**
- Present in sputum of patients with asthma, chronic bronchitis & allergic rhinitis.

- **<u>Inhibitors of LTs include:</u>**
  1. Lipooxygenase inhibitors: zileuton.
  2. LT receptor antagonists: zafir<u>lukast</u> and monte<u>lukast</u>.

NON-NARCOTIC ANALGESICS

- Analgesics are drugs that relieve pain due to multiple causes.

Classification of Analgesics



- **Non-steroidal anti-inflammatory drugs (NSAIDs)** are a heterogeneous group having anti-inflammatory, analgesic & antipyretic effects.

Cyclooxygenase Enzymes

- **COX-1:** constitutive (present normally in tissues regulating its physiologic functions), forming protective PGs involved in the essential physiological functions such as platelet aggregation, cytoprotection in the stomach and maintenance of normal kidney function.
- **COX-2:** inducible (only expressed by inflammatory mediators such as endotoxin and cytokines,forming PGs which exacerbate pain and inflammation)- [*constitutive in endothelium & kidney*].
- **COX-3 (COX-Ib):**present in the CNS??

Mechanism of Action of NSAIDs & Paracetamol:

They Inhibit cyclooxygenase enzymes ➔ inhibits conversion of arachidonic acid to endoperoxides ➔ inhibits PGs & TXA_2 production.

1. Non-selective COX inhibitors

1. Salicylic acid derivatives: Aspirin➔ **Irreversible** inhibition of COX enzymes

Other NSAIDs cause **reversible**inhibition of COX enzymes.

2- Pyrazolone derivatives: Phenylbutazone.

3- Acetic acid derivatives: Indomethacin & sulindac- Diclofenac

4- Fenamic acid derivatives: Mefenamic acid, flufenamic acid.

5-Propionic acid derivatives: Ibuprofen, ketoprofen, naproxene.

6- Oxicams: Piroxicarn, Meloxicam

2. **Selective COX-2 inhibitors:** Celecoxib, Rofecoxib

- **Inhibition of COX-1 is responsible for the adverse effects of NSAIDs.**
- **Inhibition of COX-2 is responsible for their therapeutic effects.**

I. ACETYLSALICYLIC ACID (ASPIRIN)

Mechanism: Aspirin → Irreversible inhibition of COX-1 & COX-2 enzymes

Pharmacological actions:

1- Analgesic action

2- Antipyretic action

3- Antiinflammatory action

4- GIT:

1. Gastric irritation, nausea and vomiting.
2. Hyperacidity, ulceration induced:
   - locally
   - systemically by ↓ PGs→↓ mucus secretion (No protection).

5- Blood:

1. Small dose (75-150mg/d) → Inhibit TXA_2→ ↓ platelet aggregation.
2. Large dose (5 g/d) → Hypoprothrombinemia: ↓synthesis of vit.K dependent factors (10,9,7,2)

6- Kidney:

1. Large dose (>5 g/day) → ↓ uric acid reabsorption by PCT→ treats gout
2. Nephropathy (large dose for prolonged time of combined NSAIDs)

Therapeutic uses:

1. Small (infantile)-Dose (75-150mg/d)

Prophylaxis for:

Transient ischemic attacks, unstable angina, acute myocardial infarction.

2. Intermediate dose (325 mg tab) 1-2 tab/4-6 hrs

- **Antipyretic** in fever.
- **Analgesic:**
    - Mild to moderate pain e.g. arthritis, dental pain.
    - Headache
    - dysmenorrhea.

3. High-Dose (4-8 g/d)

Anti-inflammatory

1. Rheumatic fever.
2. Rheumatoid arthritis
3. Other inflammatory joint diseases.

Adverse Effects:

A. Effects Common to all NSAIDs

1. GIT (most common; direct mucosal irritation &↓protective PGs)

- Epigastric pain, Nausea, vomiting, gastritis
- Acute & chronic peptic ulcers with ↑ risk of bleeding.

2. Nephrotoxicity (<u>less frequent with aspirin</u>)

*** Analgesic nephropathy:** irreversible chronic nephritis due to ***prolonged*** use of ***high*** doses of ***combinations*** of NSAIDs.

3. Hypersensitivity reactions

- Skin rash, rhinitis
- Asthma in susceptible patients

4. ↑ Bleeding tendency

- Displacement of warfarin from plasma proteins potentiating its effect.

B. <u>Effects Specific to Aspirin</u>

1. ↑ Bleeding tendency

1. Antiplatelet effect by small dose
2. Hypoprothrombinemia by large dose

2. Reye's syndrome: encephalopathy and liver damage in children with fever due to viral infection.

Contraindications:

1. GIT disorders: peptic ulcers, gastritis
2. Bleeding disorders: hemophilia, thrombocytopenia
3. Chronic renal impairment
4. Chronic liver diseases (bleeding tendency)
5. Hypersensitivity to aspirin
6. Children < 12 y

II.OTHER NON-SELECTIVE NSAIDs

- **Mechanism: Reversible** inhibition of COX enzymes
- **Action:** All have **analgesic, antipyretic & anti-inflammatory effects.**
- **Members: Ibuprofen - Piroxicam - Diclofenac**
- **Uses**:
  1. **Inflammatory joint diseases (osteoarthritis, rheumatoid arthritis, gout)**
  2. **Dysmenorrhea 3. Renal colic 4. postoperative pain**

Adverse effects: see before (common adverse effects of NSAIDs)

III. SELECTIVE COX-2 INHIBITORS

Celecoxib

- Selective COX-2 inhibitors were developed to avoid the adverse effects resulting from inhibition of constitutive COX-1 in GIT and kidney.

Uses:

1. Anti-inflammatory: chronic inflammatory musculoskeletal disorders (with less risk of gastric ulceration).
2. ↓ Progression of Alzheimer disease (anti-inflammatory effect).
3. ↓ Risk of colorectal cancer (COX-2 is responsible for tumor growth).

Adverse Effects of COX-2 Inhibitors

1. Nephrotoxicity (COX-2 is constitutive in kidney).
2. Stroke & infarction (COX-2 is responsible for endothelial PGI_2 synthesis).
3. Skin rash with celecoxib (structurally related to sulfonamides).

IV. PARACETAMOL (Acetaminophen)

- It is an **analgesic antipyretic** with **NO anti-inflammatory action**.
- **It is preferred to aspirin in**:
  1. Patients **A**llergic to aspirin.
  2. **B**leeding disorders (does not affect platelet function).
  3. **P**eptic ulcer (no GIT disturbances).
  4. **C**hildren with viral infections (to avoid Reye's syndrome with aspirin).
  5. **G**out (aspirin may cause hyperuricemia).

Dose: - Oral: 500 mg /4hrs or 6hrs/day

- Can be given **IV** or **rectal**

Kinetics

- Paracetamol is metabolized in liver by two pathways:
  1. Major pathway: 95 % undergoes sulphation and glucuronic acid conjugation → inactive metabolites
  2. Minor pathway: Only 5% is converted by CYP450 to a hepatotoxic metabolite N-acetyl-p-benzoquinone imine (NAPQI) ➔ deactivated by conjugation with glutathione (GSH).
- In toxic doses ➔ saturation of sulphation and conjugating enzymes ➔ ↑ conversion of the drug to the toxic metabolite(NAPQI) >> the capacity of liver to conjugate it with glutathione ➔ hepatotoxicity (centrilobular necrosis).

Adverse Effects and Toxicity

- Minimal adverse effects - well tolerated.
- **Nephrotoxicity: with high doses for long periods**.
- **Paracetamol hepatotoxicity in toxic doses [10 gm or 150 mg/kg]:** nausea and vomiting, followed in 24-48 h by liver damage

  Treatment: - Precursors for glutathione synthesis to prevent liver damage
  - should be given early within 7-14 hrs
  *** N-Acetylcysteine** (orally or IV) or **methionine** (orally)**.**