

**Anti-inflammatory drugs
Anti-allergic drugs
Immunomodulators**

**3th Year Pharmacology and
Toxicology
School of Health Sciences UNZA**

Andrew M Bambala

bambalaandrew@gmail.com

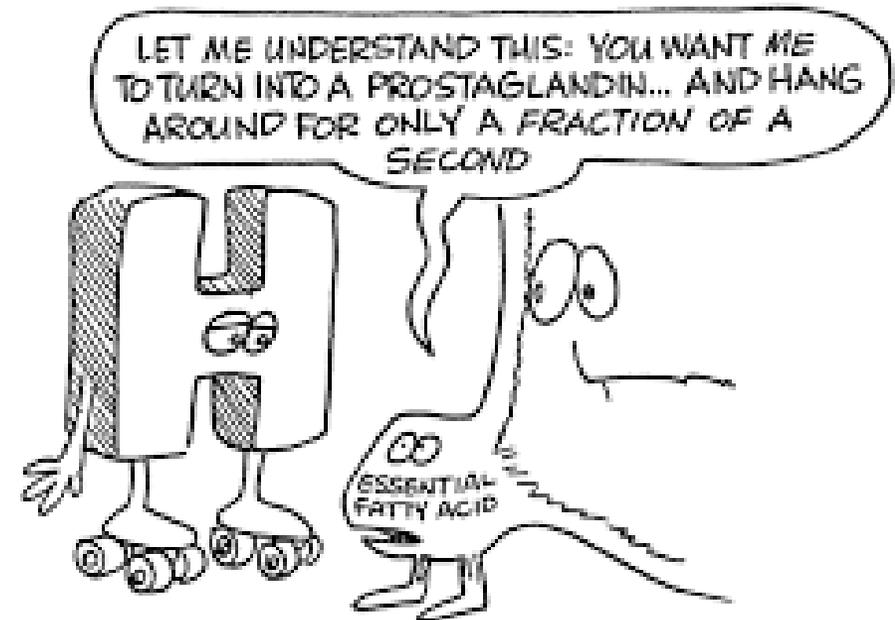
Inflammation

- Inflammation is a complex protective response of the organism to injury caused by damaging agents.
- It is aimed at inactivation or removal of these agents and promoting healing.
- The traditional names for signs of inflammation come from Latin:
 - Dolor (pain)
 - Calor (heat)
 - Rubor (redness)
 - Tumor (swelling)
 - Functio laesa (loss of function)

Mediators of inflammation

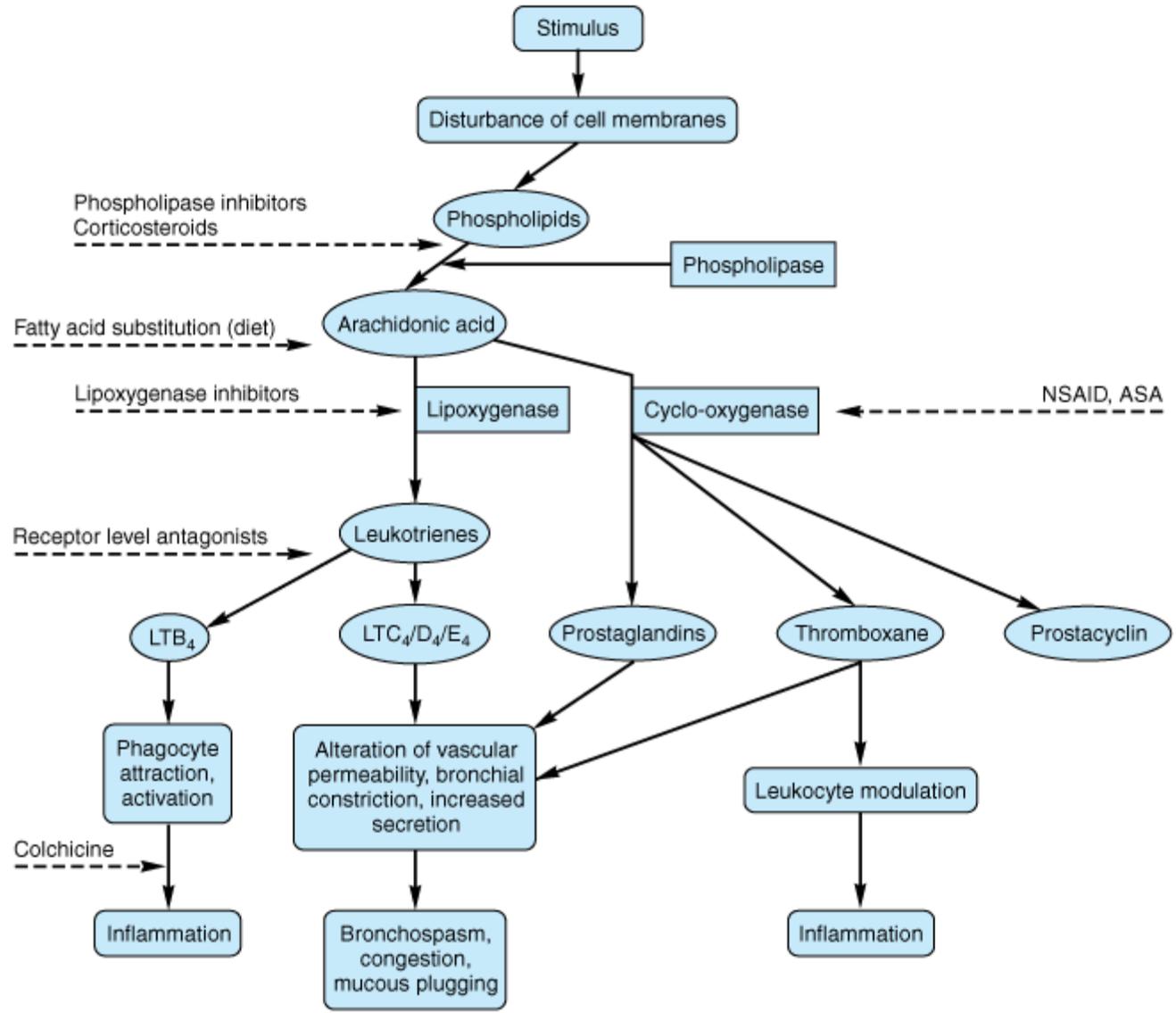
- Prostaglandins
- Bradykinin
- Serotonin
- Histamine
- Interleukins-2 – 6, 10, 12,13
- Platelet activating factor

- Gamma-Interferon
- Tumor Necrosis Factor
- Transforming Growth Factor
- Lymphotoxin



The role of some prostaglandins in the body

- **PGE 2** – vasodilation, bronchodilation, inhibition of gastric acid secretion, stimulation of gastric mucus secretion, sensitization of pain receptors to chemical and mechanical stimuli, promotion of anterior pituitary hormones release;
- **PGF2 α** - uterus contraction, bronchoconstriction, decrease in intraocular tension;
- **TXA2 (thromboxane)**, produced by platelets, - induction of platelet aggregation, vasoconstriction;
- **PGI 2** - inhibition of platelet aggregation, potent vasodilation;



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me for mediators derived from arachidonic acid and sites of drug action (dashed arrows). (LTB₄, LTC₄, leukotrienes B₄, C₄.)

Non-steroidal anti-inflammatory drugs (NSAIDs)

Non-selective COX inhibitors

1. Salicylates

- *Acetylsalicylic acid (Aspirin)
- * Salicylamide

2. Pyrazolone derivatives

- *Phenylbutazone
- *Metamizol (Analginum)

3. Indole derivatives

- *Indomethacin

4. Propionic acid derivatives

- *Naproxen

5. Antranilic acid derivatives

- *Mephenamic acid

6. Aryl – acetic acid derivatives

- *Diclophenac sodium

7. Oxicam derivatives

- *Piroxicam

8. Dihydropyrrolizine carboxylic acid derivative

- *Ketorolac

Non-steroidal anti-inflammatory drugs (NSAIDs) **selective COX inhibitors**

Preferential COX-2 inhibitors

- Nimesulide
- Meloxicam
- Nabumeton

- **NB!!!** These drugs cause little gastric mucosa damage, they do not inhibit platelet aggregation!!!

Selective COX-2 inhibitors

- Celecoxib
- Parecoxib
- Rofecoxib

Mechanism of action of NSAIDs

- NSAIDs **inhibit cyclo-oxygenase (COX)** enzyme that catalyses conversion of Arachidonic acid to Endoperoxides that synthesize Eicosanoids (i.e. Prostaglandins, Prostacyclin & Thromboxanes)– mediators of inflammation

Cyclo-oxygenase (COX)

Three main types of COX enzymes:

- 1) **COX-1 is constitutive** ; responsible for synthesis of protective PGs in GIT and Kidney;
- 2) **COX-2 is inducible** (formed during inflammatory response);
- 3) **COX-3 is active in CNS**; target for Paracetamol

Pharmacological Actions & Clinical Uses.

- Anti-inflammatory:
- Decreases vasodilator PGE2 and PGI2 thus reducing vasodilatation and edema of inflammation;
- Clinical Uses:
 - Inflammatory disorders
 - Rheumatic fever
 - Rheumatoid arthritis

Pharmacological Actions & Clinical Uses.

- Analgesic effect;
- **Peripheral effect:** inhibits synthesis of PGs which sensitize nerve endings to Kinins, increases the pain threshold;
- **Central effect:** Decreases PGs that sensitize pain stimuli at sub-cortical sites.

Pharmacological Actions & Clinical Uses.

- Clinical Uses:

- Mild to moderate pain secondary to inflammation;
- Rheumatoid arthritis;
- Headache (decreases cerebral vasodilator effect of PGs);
- Dysmenorrhea and Postpartum pain.

Pharmacological Actions & Clinical Uses

- Anti pyretic effect:
- Decrease PGE2 (generated in response to inflammatory pyrogens e.g.IL-1) responsible for elevating hypothalamic set point for temperature control.

Clinical Uses:

- Antipyretic (Lower body temperature) in fever e.g. Aspirin

General Clinical uses of NSAIDs

1. **Pain**: headache, toothache, myalgia, backpain;
2. **Fever**;
3. **Reduction of inflammation** (especially ibuprofen);
4. **Dysmenorrhoea** (especially ibuprofen);
5. **Unclosure of ductus arteriosus** (especially aspirin);
6. **Prevention of MI**, stroke, (aspirin);

General Adverse Effects

- GIT side effects:
 - Dyspepsia,
 - N/V/D,
 - gastritis,
 - Ulceration with risk of haemorrhage;
- Renal tubular damage (Analgesic nephropathy);
- Hypersensitivity reactions;
- Hyper uricemia;

Selective COX-2 Inhibitors ('Coxibs')

- Colecoxib, Rofecoxib & Nimesulide
- Selective COX-2 inhibitors that spare COX-1, thus do not inhibit synthesis of gastro-protective PGs;
- Have less GIT side effects;
- A/E: Hypersensitivity rxns (with colecoxib), Risk of thrombosis, hypertension and accelerated arterogenesis

Selective COX-2 Inhibitors ('Coxibs')

Advantages:

1. Highly selective inhibitors to COX2 enzyme.
2. Potent anti-inflammatory.
3. Have analgesic & antipyretic properties.
4. Highly bound to plasma proteins.

Selective COX-2 Inhibitors ('Coxibs')

5. Lower incidence of gastric upset.
6. No effect on platelet aggregation (COX1).
7. Renal toxicities (they are not recommended for patients with severe renal insufficiency).
8. High incidence of cardiovascular thrombotic events with some of them as ROFECOXIB.

Selective COX-2 Inhibitors ('Coxibs')

9- They are recommended in postoperative patients undergoing bone repair.

10- Also, indicated in primary familial adenomatous polyposis, dysmenorrhea, acute gouty arthritis, acute musculoskeletal pain, ankylosing spondylitis

Contraindications

A) Pregnancy

B) Haemophilic patients

C) Hypersensitivity reactions

D) Viral infections mainly in children

E) Peptic ulcer



Drugs interaction

- Potentiates the gastric irritant effect of alcohol
- Potentiates the hypoglycemic effects of oral hypoglycemic drugs



Steroidal anti-inflammatory drugs

1. Short-acting glucocorticoids (natural)

- Hydrocortisone
- Cortisone

2. Intermediate-acting glucocorticoids

- Prednisone
- Prednisolone
- Methylprednisolone
- Triamcinolone

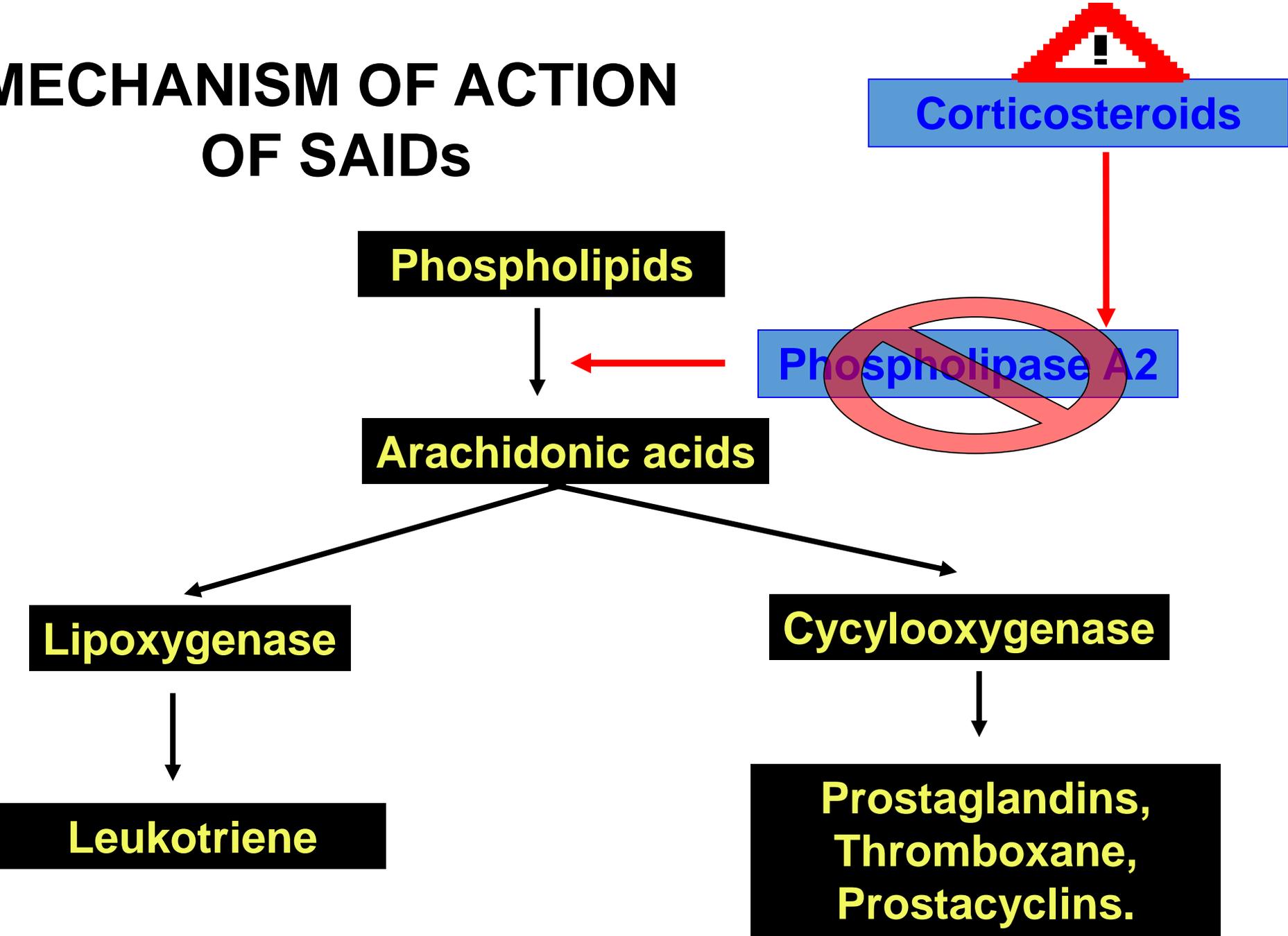
3. Long-acting

- Betamethasone
- Dexamethasone

4. Topically acting glucocorticoids

- Beclomethasone
- Budesonide
- Fluocinolone
- Fluocortolone

MECHANISM OF ACTION OF SAIDs



Corticosteroids

- **Anti-inflammatory effects:** inhibit phospholipase-A2, inhibiting formation of Arachidonic acid from membrane phospholipids with subsequent inhibition of PGs, PAF and LTs synthesis;
- **Ant allergic effects:** stabilize mast cell membranes; inhibit production of cytokines & decrease antibody production;

Clinical uses of SAIDs

- Bronchial asthma
- Severe allergic reactions
- Autoimmune diseases
- Skin diseases
- Cerebral edema
- Organ transplantation and skin allograft
- Septic shock



Main side effects of SAIDs

- Susceptibility to infections
- Delayed healing of wounds
- Osteoporosis
- Growth retardation in children
- Peptic ulceration
- Cushing habitus
- Hyperglycaemia
- Muscular weakness
- Psychiatric disorders
- Withdrawal syndrome

Allergy

- An allergy is a hypersensitivity disorder of the immune system.
- Allergic reactions occur when a person's immune system reacts to normally harmless substances in the environment.
- A substance that causes a reaction is called an allergen. These reactions are acquired, predictable, and rapid.



Allergy

- Allergy is one of **four forms of hypersensitivity** and is formally called type I (or immediate) hypersensitivity.
- Allergic reactions are distinctive because of excessive activation of certain white blood cells - lymphocytes called B cells, whose role is production of antibodies, called Immunoglobulin E (IgE).
- Mast cells are activated and release mediator of allergy (**HISTAMINE**) that results in an inflammatory response.

Allergic reactions

- **Allergic reactions** - Mediated by immune system, resulting from previous sensitization to a particular drug/ chemical or with a similar structural.
 - Type I: Anaphylactic Reactions,
 - Type II: Cytolytic Reactions.
 - Type III: Arthus Reactions.
 - Type IV: Delayed Hypersensitivity Reactions.

Antiallergic drugs

1. Antihistaminic
2. Corticosteroids
3. Mast cell stabilizers
4. Antileukotriene drugs

Anti-Allergic Agents

- For the treatment of Immediate –Type Reactions
 - Decrease the synthesis of histamines and active substances: **Cromlyn, Glucocorticoids, ketotifen**
 - H1 –Histaminoblockers – **Loratidine, Cetirizine**
 - Decrease manifestation of hypersensitivity- **Muscarinic blockers, Zafirlucast**
 - Decrease tissue alteration –**Steroids and Non-Steroid Inflammatory Agent**

Anti-Allergic Agents Continue

- For the treatment of Delayed –Type Reactions
- Immunosuppressant
 - Cyclosporine, Azathioprine
- Decrease Tissue alteration
 - Anti-Inflammatory Steroid and Non Steroid
 - Slow acting agents Chloroquine, Gold containing agents

Symptoms Associated With **Histamine** Release

- **Mild/cutaneous**

- Erythema, urticaria, and/or itching

- **Mild to moderate**

- Skin reactions, tachycardia, dysrhythmias, moderate hypotension,
- mild respiratory distress

- **Severe/anaphylactic**

- Severe hypotension, ventricular fibrillations, cardiac arrest, bronchospasm,
- respiratory arrest

Histamine Release

- Histamine stored as granules and released by degranulation in response to various stimuli;
 - **physical injuries**
 - **Antibodies mediated** – hypersensitivity reaction
 - **Complement products**- anaphyltoxin C3a, C5a.
 - **Neuropeptides** (e.g., substance P) and cytokines (IL1, IL8)

Pathophysiological Actions of Histamine

- Cellular mediator of immediate hypersensitivity reaction and acute inflammatory response
- Anaphylaxis
- Seasonal allergies
- Duodenal ulcers
- Systemic mastocytosis
- Gastrinoma (Zollinger-Elison Syndrome)

Histamine-related Drugs

- Mast Cell Stabilizers (Cromolyn Na, Nedocromil –Tilade -, Albuterol)
- H1 Receptor Antagonists (1st and 2nd generation)
- H2 Receptor Antagonists (Ranitidine, Cimetidine)
- H3 Receptor Agonist and Antagonists (potential new drugs being developed)

First Generation Agents

Uses:

- Adjunctive in anaphylaxis and other cases where histamine release can occur (H₂ antagonist, and epinephrine must also be used in anaphylaxis)
- Antiallergy (allergic rhinitis, allergic dermatoses, contact dermatitis)
- Sedative/sleep aid
- To prevent motion sickness (MECLIZINE, CYCLIZINE)

Histamine

Therapeutic Uses

- Allergic reactions (e.g. allergic rhinitis and urticaria)
- Motion sickness (for their anticholinergic and sedative effects)
- Parkinsonism (for their anticholinergic effects)

Adverse Effects:

- Sedation and drowsiness.
- Anticholinergic side effects e.g. dry mouth, urine retention, constipation, tachycardia, etc.

Drug interactions:

- Additive with classical antimuscarinics
- Potentiate CNS depressants
 - opioids
 - sedatives
 - general and narcotic analgesics
 - alcohol

2nd Generation Antihistamines

Have anti-allergic effects similar to 1st generation antihistamines but without sedation or anticholinergic effects

- Terfenidine
- Astemizole
- Loratadine
- Cetirizine

Advantages of 2nd generation antihistaminics

- Higher H1 selectivity, absence of anticholinergic side effects
- Absence of inhibitory action on CNS
- Additional antiallergic mechanisms: some of them are acting on leukotrienes or by antiplatelet activating factor

Third-generation antihistamines

- **Third-generation antihistamines** are defined as **metabolites or enantiomers** of previously available drugs and can therefore lead to an increase in efficacy and/or safety
 - **Levocetirizine**- Metabolite of Cetirizine
 - **Desloratadine** – Metabolite of Loratadine
 - **Fexofenadine**- Metabolite of terfenadine



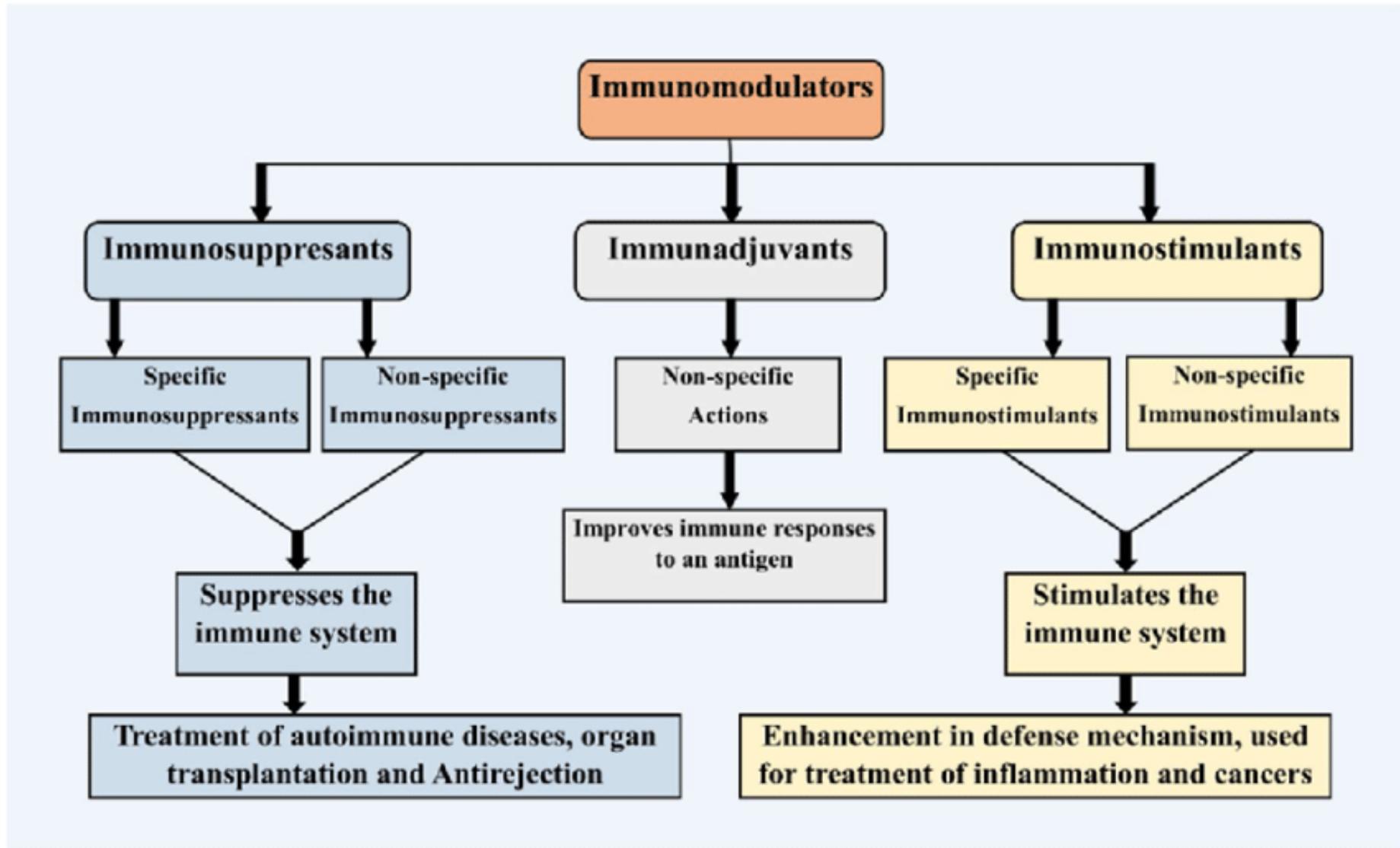
Mast cell stabilisers

- **Cromolyn sodium, Nedocromil sodium**
 - Inhibits mast cell release of histamines and Leukotrienes
 - Uses: Bronchospasm Prevention
- **Ketotifen**
 - Acts like cromolyn and blocks H1- receptors
 - Uses: Allergic bronchitis, Hay fever, Allergic Dermatitis

Antileukotriene drugs

- **Examples:**
 - Montelukast
 - Zafirlukast
- **MoA:** competitive block of LT1 receptors
- **Clinical use:** bronchial asthma





CLASSIFICATION OF IMMUNOSTIMULANTS

GROUP	AGENTS
Mainly Stimulate (Non-specific Immunity)	Derivatives Purines and Pyrimidines (Methyluracil, Pentoxly)
Mainly Stimulate (Monocyte and Macrophages)	Vaccines (BCG), Sodium Nucleinate, Zymoza
Mainly Stimulate (T-Lymphocytes)	Thymalin, Zinc agents, Interleukin (IL-2)
Mainly Stimulate (B-Lymphocytes)	Myelopid, Rigin, Amastinb
Mainly Stimulate (NK and K Cells)	Interferons, Filgrastim, Placenta Extracts
(Plant Origins, hormones, Vitamins)	Adaptogens, Vitamins C, E and A, Anabolic Steroids and Non- Steroid

1. Stimulators of Non-specific Immunity; **Methyluracil and Pentoxly**

- **Effects:** Hasten cellular regeneration, wound cleaning, stimulate cellular and humoral immunity
- **Indication:** Mild leukemia, poorly closed wound, burns, bone crush
- **Adverse Effects:** Usually well tolerated

2. Stimulators of Macrophages and T-Lymphocytes;

- **Sodium nucleate-** Different diseases of Leucopenia
- **BCG-** Leukemia, Carcinoma of the breast, Urinary bladder Intestine
- **Pyrogenal** –Chronic prostatitis, chronic inflammation of the female reproductive system

3. Stimulate NK and K Cells

Interferons –Possess antimicrobial, ant proliferative and anticancer activity

There are 3 types of interferons

- ❖ Alpha (Leukocytes) -
- ❖ Beta (Fibroblasts)
- ❖ Gamma (T-Lymphocytes)

Uses

- Natural Alpha Interferons are used locally for common cold herpes keratitis
- Recombinant Alpha Interferons (Reaferon and Laferon)
 - are used for hepatitis B&C, Carcinoma of the Urinary bladder and Intestine
- Recombinant Beta Interferons (Betaferons)- For multiple sclerosis

Cytokines with colony stimulating properties

- Granulocyte colony-stimulating factor (**Filgrastim**)
- Granulocyte macrophages colony-stimulating factor (**Molgrastim**)
- **Filgrastim** stimulate the formation of granulocytes
- **Molgrastim** –Mixed granulocyte-macrophages colony
- They hasten the recovery from neutropenia in patients after chemotherapy and bone marrow transplant

Classification of Immunosuppressant and Cytotoxic Agents

- **Antimetabolites** :Mecartopurines, Azathioprine, Methotrexate
- **Alkylating agents** :Chlorambucil, Cisplatin, Cyclophosphamide
- **Antibiotics**: Cyclosporine A, Actinomycine -D, Doxorubicin
- **Hormones and their antagonist** : Prednisolone, Dexamethasone
- **Antibodies**: Ant lymphocytic Globulin (ALG)
- **NSAIDS**: Butadion, Indomethacin
- **Miscellaneous** : Vincristine, Vinblastine , Asparaginase

1. Antimetabolites

- **MoA-** Analogs of the Physiological metabolites
 - Mecartopurines, Azathioprine Analogs of Purines
 - Methotrexate and 5FU –Analogs of pyrimidines
 - Inhibit DNA and Protein synthesis
- **Indication:** Leukemia, Breast and Gastric Cancer, Organ Transplant and Autoimmune Diseases

- **2. ALKYLATING AGENTS**

- **MoA:** Alkylation of the DNA within the Nucleus
- **Indications:** Hodgkin's disease, Ovarian and Breast Cancers, Leukemia

- **3. ANTIBIOTICS**

- **MOA-** Inhibits DNA synthesis, Cyclosporine inhibits T-Lymphocytes differentiation caused antigen action
- **Indication:** Breast, Endometrial and Thyroid Carcinoma, Cancer of the lungs and Kidneys, Organ Transplantation and Autoimmune Diseases

- **4. PERIWINKLE ALKALOIDS** (Vincristine, Vinblastine)
 - **MoA:** Mitosis inhibition
 - **Indication:** Hodgkins disease, Leukemia
- **5. ENZYMES-** L-asparaginase
 - **MoA:** Splitting asparagine
 - **Indication:** Lymphosarcoma, Leukemia

ADVERSE EFFECTS OF IMMUNOSUPPRESSANTS

initial:

- disturbance of bone marrow function
- disturbance of GIT function
- predisposition to infections
- allergic reactions

postponed:

- cancerogenic (cytotoxic agents)
- disturbance of reproductive system (10-70%) and teratogenic effect
- growth retardation in children
- others: hyperpigmentation, lungs fibrosis, hemorrhagic cystitis, alopecia; hepatotoxicity (antimetabolites)



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Thank You!!!

