Autacoids
Greek: autos--- self,
akos—healing substance or remedy
Autacoids ---"**local hormones**"
Produced by a wide variety of cells.
Act locally at the site of synthesis & release.
Short half life --- seconds to minutes.
Have no or limited clinical application as a drug.
Autacoids Agonists / Antagonists are used as drugs.

Classical Autacoids are
Amine autocoids;
Histamine
5-hydroxytryptamine (serotonin)
Lipid derived autocoids;
-- Prostanoids (Prostaglandins, prostacyclines, thromboxane)
Leukotrienes
Peptide autocoids (Plasma kinins);
(bradykinin, kallidin), Angiotensin
Histamine --- tissue amine
Physiologically active **amine** found in plant and animal tissues.
Synthesized in mast cells, basophils, enterocytes (parietal cells of gastric mucosa) and CNS.
Storage granules of mast cells
Inactive complex composed of histamine, polysulphated anions, heparin and proteases.
If not stored it is rapidly inactivated by amine oxidase enzyme.
Non mast cell histamine
Brain, epidermis, **gastric mucosa.**
Histamine -- Occurs in all tissues
High amounts at sites where the "inside" of the body meets the " out side"------ at sites of potential tissue injury.

Lungs, skin and GIT
Venoms and insect strings.
Inactive orally as it is completely metabolized in the liver.
Histamine does not penetrate BBB.
Histamine receptors (H_1, H_2, H_3 & H_4)
(family of G-Protein coupled receptors)
H_1receptors -- **Smooth muscles,**
Endothelium, Brain
G_q --- ↑ IP3, DAG
H_2 receptors -- **Gastric mucosa (parietal cells)**
Cardiac muscle.
G_s --- ↑ cAMP
H_3 receptors -- CNS
H_4 receptors GIT, basophils, and bone marrow cells
Actions of histamine
Contraction of **smooth muscles**
--- Intestine --- cramps and diarrhoea
--- Airway – bronchospasm
CVS
--- Vasodilation (via NO) & ↑ed permeability of the capillaries --- edema
--- ↓ peripheral resistance – hypotension
--- + ve chronotropism (H_2 receptors)
--- + ve inotropism (H_1 and H_2 receptors)
Actions of histamine
Stimulation of **secretions**
↑ production of nasal and bronchial mucus
Powerful stimulation of **sensory nerve endings** --- **pain, itching --- urticaria**
Skin – **triple response; Red line**(capillary dilatation), **flare** (arteriolar dilatation) and **wheal** (local edema due to escape of fluid from the capillaries)

Gastric glands -- ↑ gastric acid secretion (H_2 receptors)
Release of Histamine (Allergies)
Allergies are caused by a hypersensitivity reaction of the antibody class **IgE** (which are located on mast cells in the tissues and basophils in the blood)
When an allergen is encountered, it binds to IgE, which excessively activates the mast cells or basophils, leading them to release massive amounts of histamines.
These histamines lead to inflammatory responses ranging from runny nose to anaphylactic shock

Uses of histamine
No therapeutic use
As a diagnostic agent (in the past)
Histamine aerosol used as **provocative test of bronchial hypersensitivity** in pulmonary function laboratories.
To test acid secreting capacity of stomach. (Now pentagastrin is used for this purpose).
For diagnosis of pheochromocytoma (Obsolete).

Betahistine (Serc)
H_1 selective histamine analogue.
Orally active.
Used to control vertigo in **Meniere's disease**
Reduce endolymphatic pressure by improving the microcirculation (vasodilatation in internal ear)
Contraindicated in **asthmatics & ulcer patients.**
Antagonism of actions of histamine
Physiological antagonism ---- **Adrenaline**
Adrenaline act on different receptors but have smooth muscle actions opposite to those of histamine -- Life saving in **anaphylaxis.**

Release inhibitors; Cromolyn and Nedocromil

Reduce the degranulation of mast cells.

Act by stabilizing the mast cells & inhibit the release of histamine & other mediators of inflammation.

CROMOLYN nasal solution used for the prevention & treatment of **allergic rhinitis.**

Orally used to treat the histaminic symptoms of mastocytosis.

β_2 agonists also reduce histamine release.

Classification

Receptor antagonists (H_1 and H_2)

H_1 receptor antagonists (Antihistamines);

First generation antihistamines.

Second generation (non sedating) antihistamines.

H_2 receptors antagonists;

First generation antihistamines

ETHANOLAMINES;

Diphenhydramine

Dimenhydrinate

Doxylamine.

Clemastine

Carbinoxamine

ETHYLENEDIAMINES;

Pyrilamine

Phenbenzamine

Methapyriline.

Thonzylamine.

Alkyl amines;

Chlorphenamine

Bromopheniramine

Pheniramine (Avil)

Triprolidine

Piperazines

Cyclizine
Chlorcyclizine
Hydroxyzine
Meclizine
Cetirizine (Zyrtec)

Second Generation Antihistamines
More selective for peripheral H1 receptors
Examples:
terfenadine
loratadine
cetirizine
mizolastine
Astemizole
Third generation H_1-receptor antagonists;
Fexofenadine
Desloratadine
Levocetirizine

These are active metabolite derivatives of second generation drugs intended to have increased efficacy with fewer adverse drug reactions.

Antihistamines
(H_1 receptor antagonists)

Act as **competitive antagonists** of histamine and therefore may be ineffective at high levels of histamine. The term antihistamine **only refers to H_1 receptor antagonists** (actually inverse agonists). Antihistamines compete with histamine for binding sites at the receptors and cannot remove the histamine if it is already bound. All require hepatic metabolism.

Several of 2nd generation agents are metabolized by the CYP3A4 --- drug interaction e.g., ketoconazole.

Oral – rapidly absorbed.
Peak blood concentration 1-2 hrs
1st generation are mostly short acting (4 - 6hrs).
Long acting meclizine & several 2nd generation (12-24 hrs).

Differences between 1st and 2nd Generation antihistamines

1st generation
Penetrate the CNS and cause sedation

2nd generation
Do not penetrate the BBB, less CNS toxicity.
Non sedating—desloratadine, **fexofenadine**, loratadine
Mild sedation –cetrizine, acrivastine

1st generation
Tend to interact with other receptors, producing a variety of unwanted adverse effects, Ach
Serotonin,
α-adrenergic
Inexpensive

2nd generation
Specific for H_1 receptors.
No anticholinergic side effects.
They have poor antipruritic, antiemetic and antitussive actions.
Expensive

Clinical Uses of Antihistamines

Anti-allergic actions due to H_1 receptor blockade (All H_1 antihistamines)
Suppresses many manifestations of type I hypersensitivity reactions (Allergic reactions).
Used for prevention and treatment of symptoms of
Allergic rhinitis,
Allergic conjunctivitis,
Hay fever,
Allergic dermatological conditions
urticaria, pruritus, allergic skin rashes & angioedema
Sneezing and rhinorrhea.
Cough suppressant.

Clinical Uses of Antihistamines

Anaphylactic fall in BP is only partially prevented
Injectable formulation may be useful **as adjunct to adrenaline** for severe drug hypersensitivities and emergency treatment of anaphylaxis.
Asthma is unaffected (other mediators , Leukotrienes)
Used in the treatment of **insomnia (**Hypnotic**)**
as **"sleep aids",** compulsive use not reported (first generation)
Children occasionally (adults rarely) manifest **excitation rather than sedation**

Clinical Uses of Antihistamines
Actions not caused by histamine receptor blockade;
Motion sickness (**Antinausea and antiemetic action)**

Less effective against an episode of motion sickness already present.
Dimenhydrinate, diphenhydramine, cyclizine, meclizine
Antiemetic --- **promethazine**
Preanesthetic medication– sedation, anticholinergic and antiemetic properties– promethazine.
Clinical Uses of Antihistamines
Actions not caused by histamine receptor blockade;
Extrapyramidal Syndrome (**Antiparkinsonism effects);**
Acute suppressant effects on the (EPS) extrapyramidal symptoms associated with certain antipsychotic drugs.
Diphenhydramine --- used parenterally for acute dystonic reactions to antipsychotics.
Anorexia; Cyproheptadine – (antiserotonin action,↑ appetite).

Clinical Uses of Antihistamines

Actions not caused by histamine receptor blockade;
Local anesthesia (not used clinically)
Diphenhydramine and promethazine
Block Na+ channel in excitable membrane, action similar to procaine and lidocain.
Other actions (H_4 receptor blockade effect)
Cetrizine --- inhibit mast cell release of histamine and some mediator of inflammation.

Side effects
Associated with the first generation H_1-antihistamines due to their ease of crossing BBB and lack of selectivity for the H_1 receptors and anti-cholinergic activity.
Side effects due to CNS depression are;
↑ Sedation, Fatigue, Dizziness, Lassitude
↓ cognitive and psychomotor performance.

Incoordination , blurred vision, Tinnitus, and tremors.
Side effects
Intensity of sedation varies
Marked sedation – dimenhydrinate, promethazine
Moderate sedation -- cyprohepatidine
Slight sedation – cyclizine
No sedation - fexofenadine (2nd generation)
Individual susceptibility to different agents varies considerably.
Children occasionally (adults rarely) manifest **excitation rather than sedation.**
Driving and handling of machinery must be avoided.

Side effects
Due to anticholinergic actions;
Dry mouth
Urinary retention
Sinus tachycardia
Diphenhydramine and promethazine
Due to α-Adrenoceptor blocking actions;
Alpha receptor blocking action may cause orthostatic hypotension, dizziness ,reflex tachycardia
Phenothiazine -- promethazine
Side effects
Anti-cholinergic actions;
Dryness of mouth and nasal passage, Blurred vision, Urinary retention;
High
Promethazine, Diphenhydramine, Dimenhydrinate, Carbinoxamine
Low
Chlorpheniramine Hydroxyzine
Triprolidine Cyclizine
Minimal/absent

Clemastine Terfenadine Astemizole
Loratadine cetrizine

Newer **second generation H1-antihistamines** are more selective for the peripheral histamine receptors and have far less side effects **(drowsiness, fatigue, headache, nausea and dry mouth.**

Why Terfenadine is withdrawn from the market;

Certain 2nd generation antihistamine can precipitate lethal arrhythmias.

Block K+ channels in heart resulting in prolonged action potential and excessive prolongation leads to arrhythmias.

Terfenadine (withdrawn from the market) –prolong QT interval.

Drug interactions;

Potentiation of all other **CNS depressants.**

MAO inhibitors exacerbates the **anticholinergic effects.**

Anticholinergic effects of antihistamine adds up if used concurrently with -- **Atropine, Phenothiazines, TCAs.**

Azole antifungal drugs and other CYP3A4 inhibitors interfere with metabolism of **astemizole and terfenadine** --- dangerous high levels – Cardiotoxicity including arrhythmias.

Drug interactions

Terfenadine and astemizole with **ketoconazole** and macrolide antibiotic such as **erythromycin**.

Overdose

Relatively high margin of safety and chronic toxicity is rare

Acute poisoning ----- Young children

CNS --- Hallucinations., excitement, ataxia, and convulsions,

Coma and collapse of CVS

Clinical classification

First generation antihistamines

Second generation antihistamines

Terfenadine Fexofenadine Astemizole

Loratadine Desloratadine Cetrizine Azelastine
Mizolastine Ebastine

H_2 receptors antagonists

Cimetidine ranitidine famotidine nizatidine

H_2 receptor antagonists

Antagonize the **gastric acid** stimulating activity of the histamine

Selective H_3 and H_4 antagonists are not yet available for clinical use.

H_2 - Receptor Antagonists

Cimetidine.

Ranitidine

Famotidine

Nizatidine.