# Histamine and antihistamines

- It is an autacoid and is a biological amine, act locally in the vicinity of tissue by which it is released.
- It is called as a local hormone
- Autacoids:
- Amines- histamine, serotonin
- Lipid derived-prostaglandins and leukotrienes
- Kinins-plasma kinin and angiotensin

# Histamine

- Biological amine present in animal and plant tissue. It is one of the mediators involved in inflammatory and hypersensitivity reactions.
- It is synthesized by  decarboxylation of amino acid histidine.
- Histamine is βimidazolylethylamine.
- Histamine is present in storage granules of mast cells and found in the skin, lungs, liver and gastric mucosa.

- Immunologic release
- Mast cell sensitized by IgE antibodies attached to their surface membrane,degranulate when exposed to appropriate antigen.
- Degranulation leads to simultaneous release of histamine,ATP and other mediators stored in the granules.

- Distribution
- Tissue rich in histamine- skin, gastric and intestinal mucosa, lungs, liver and placenta
- Nonmast cell hitamine occurs in brain,epidermis and gastric mucosa

- Storage & Release:

Immunological stimulus

↓

- in mast cells, if sensitized by surface IgE antibodies, degranulate when exposed to specific antigen.
- Degranulation is involved in the immediate (type 1) allergic reactions.

# Mechanism of action

Histamine

Its actions are mediated by histamine receptors(H1,H2,H3).

H1 Receptors

↓

Phospholipase C

↓

IP3+DAG release

↓

Calcium release

↓

smooth muscle contraction, vasodilation, increased vascular permeability(H1 receptor located in smooth )

H2 receptors

↓

Adenylate cyclase

↓

Increased cAMP

↓

Activation of Protein Kinase A

↓

Stimulation of gastric acid secretion

H3 receptors

↓

Adenylate cyclase

↓

decreased cAMP

↓

reduced activation of Protein Kinase A

↓

inhibition of histamine release

Actions

- Triple response: red, flare and wheal.
- Increases gastric acid secretion by mediating through stimulation of H2 receptors.
- Initiates the sensation of itch and pain at sensory nerve endings
- Produce vasodilation in inflammation
- Increase the vascular permeability in inflammation.

- Produce bronchoconstriction
- Increase the heart rate
- Urticaria
- Hypersensitive reactions, Flushing
- No CNS effects since histamine do not cross BBB.

Antihistamines

These drugs competitively antagonise the actions of histamine at H1 receptors

- Drugs that block H1 receptors and reduce H1 receptor mediated actions are called antihistamines
- First antihistamine discovered in 1933 by Jeff Forneau and daniel Bovent is piperoxan.

Classification

First generation

Highly sedative:

Ex: Diphenhydramine, dimenhydrinate, promethazine

Moderately sedative:

Ex: Pheniramine,meclizine,cyproheptadine

Mild sedative:

Ex: Chlorpheniramine, triprolidine, clemastine

Second generation

Ex: Fixofenadine, loratadine, azelastine, mizolastine

Classification

Ethylenediamines: Mepyramine

Ethanolamine: Diphenhydramine, clemastine

Alkylamines: Chlorphenramine

Piperazines: Cyclazine, meclizine

Tricyclics: Promethazine, cyproheptadine

Butyrophenones: terfenadine,fexofinadine

- PHARMACOLOGICAL ACTIONS
- Qualitatively all H1 antihistaminics have similar
- actions, but there are quantitative differences,
- especially in the sedative property.

- **Antagonism of histamine They effectively**
- block histamine induced bronchoconstriction,
- contraction of intestinal and other smooth muscle
- and triple response—especially wheal, flare and
- itch. Fall in BP produced by low doses of histamine
- is blocked.

- **Antiallergic action Many manifestations of**
- immediate hypersensitivity (type I reactions) are

suppressed. Urticaria, itching and angioedema

are well controlled. Anaphylactic fall in BP is only

partially prevented. Asthma in man is practically

- unaffected though anaphylactic bronchoconstrictionin guinea pig is largely prevented. Thistissue and species dependence of response probablyreflects extent of involvement of histamine in the reaction.

**CNS The older antihistamines produce**

- Variable degree of CNS depression. This appears to depend on the compound's ability to penetrate blood-brain barrier and its affinity for the central (compared to peripheral) H1 receptors.
- Certain *H1 antihistamines are* effective in preventing motion sickness.

- Promethazine and few other antihistaminics

reduce tremor, rigidity and sialorrhoea of parkinsonism.

- Anticholinergic and sedative properties underlie the benefit.
- Some H1 antihistamines are also effective

antitussives

- **Anticholinergic action**
- **Many H1 blockers** in addition antagonize muscarinic actions of ACh. The anticholinergic action can be graded
- as:
- *High, Low,Minimal/Absent*
- If used concurrently with atropine or its substitutes,
- phenothiazines, tricyclic antidepressants

or disopyramide, the anticholinergic action adds up.

- **Local anaesthetic Some drugs like pheniramine,** have strong while others have weak membrane stabilizing property. However, they are not used clinically as local anaesthetic because they cause irritation when injected s.c.
- Membrane stabilizing activity also confers
- antiarrhythmic property to these compounds.

- **BP Most antihistaminics cause a fall in BP**

on i.v. injection (direct smooth muscle relaxation).

- However, this is not evident on oral administration.

## SIDE EFFECTS AND TOXICITY

- Side effects with first generation H1 antihistaminics are frequent, but are generally mild. Individuals show marked differences in susceptibility to side effects with different drugs. Some tolerance to side effects develops on repeated use.
- Sedation, diminished alertness and concentration, light headedness, motor incoordination, fatigue and tendency to fall asleep are the most common.

- Dryness of mouth, alteration of bowel movement, urinary hesitancy and blurring of vision can be ascribed to anticholinergic property.
- Epigastric distress and headache are also common.
- Local application can cause contact dermatitis.

USES

- *Allergic disorders Antihistaminics do not* suppress AG: AB reaction, but block the effects of released histamine—are only palliative. They
- effectively control certain immediate type of allergies, e.g. itching, urticaria, seasonal hay fever, allergic conjunctivitis and angioedema of lips, eyelids, etc.

- *Pruritides Many conventional antihistamines* have antipruritic action independent of H1antagonism. Though relief is often incomplete, older antihistaminics remain the first choice drugs for idiopathic pruritus.

- *Common cold: Antihistaminics do not affect* the course of the illness but may afford symptomatic relief by anticholinergic (reduce rhinorrhoea) and sedative actions. The newer nonsedating antihistamines are less effective in this respect.
- 5. *Motion sickness Promethazine, diphenhydramine,* dimenhydrinate and cyclizine have prophylactic value in milder types of motion sickness; should be taken one hour before starting journey. Promethazine can also be used in morning sickness, drug induced and postoperative vomiting, radiation sickness.

- *Vertigo: Cinnarizine is the H1 antihistamine* having additional anticholinergic, anti-5-HT, sedative and vasodilator properties which has been widely used in vertigo. It modulates Ca2+ fluxes and attenuates vasoconstrictor action of many endogenous substances. Cinnarizine inhibits vestibular sensory nuclei in the inner ear, suppresses postrotatory
- labyrinthine reflexes, possibly by reducing stimulated influx of Ca2+ from endolymph into the vestibular sensory cells. Beneficial effects have been reported in Méniére's disease and other types of vertigo.

- *As sedative, hypnotic, anxiolytic Antihistamines* with CNS depressant action have been usedas sedative and to induce sleep, especially in children.

.Ex:Diphenhydramine

- *Cough :Antihistaminics like chlorpheniramine,*
- diphenhydramine and promethazine are constituents of many popular cough remedies.
- They have no selective cough suppressant action, but may afford symptomatic relief by sedative and anticholinergic property