Histamine

- meaning 'tissue amine' **(histos-** tissue)
- present mostly within storage granules of mast cells.
- Tissues rich in histamine are skin, gastric and intestinal mucosa, lungs, liver and placenta. Nonmast cell histamine occurs in brain, epidermis, gastric mucosa.

Synthesis, storage and destruction

- It is synthesized locally from the amino acid histidine and degraded rapidly by oxidation and methylation.

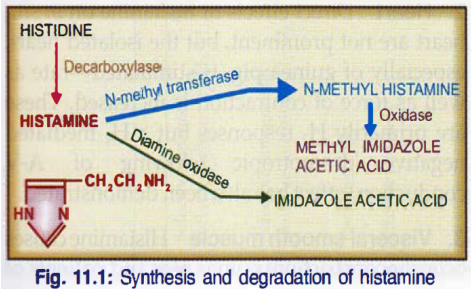

Fig. 11.1: Synthesis and degradation of histamine

Release of Histamine

- The stores of histamine in Mast cells can be released by-
  - ✓ Immunologic release
  - ✓ Inflammation and immune response
- The important pathophysiologic mechanism of mast cell release histamine is immunologic.
- Mast cell if sensitized by IgE attached to their surface membrane, degranulate when exposed to antigen.
- Degranulation leads to release of histamine, ATP and other mediators that are stored in the granules
- Non antigen mediated histamine release: Drugs (tubocurarine, morphine, atropine), venoms, other substances that damage or disrupt cell membrane.

MOA

- Histamine exerts its biologic action by combining with specific cellular receptor located on the surface membrane.
- Four different histamine receptor (H1, H2, H3 and H4) have been identified.
- Only H1,H2 and H3 blockers are in clinically used.

Pharmacological Action

- *Blood vessel*: vasodilation
- *Heart*: H1: increase force of contraction; H2- slowing down AV conduction
- *Visceral Smooth muscle*: H1: bronchoconstriction
- *Glands*: H2: increase gastric secretion
- *Sensory nerve ending*: itching
- *Brain*: don't cross blood brain barrier- no effect
- Intracerebroventricular injection: rise in BP, cardiac stimulation, behavioral arousal, hypothermia, vomiting and ADH release.

Pathophysiological action

1. Gastric secretion:
   - Secretion of HCl in stomach.
   - H2 blockers (Ranitidine) suppress acid secretion induced by histamine.
2. Allergic phenomena
   - Histamine is causative in urticarial, angioedema, bronchoconstriction and anaphylactic shock.
   - H1 antagonist are effective in controlling these manisfestations.
3. As transmitter
   - Initiate sensation of itch and pain at sensory nerve ending
   - Maintain wakefulness
   - Suppress appetite
4. Inflammation
   - Vasodilation
   - Increase capillary permeability

Clinical Uses

- No therapeutic use.
- Sometimes used as a provactive test of bronchial hyperractivity.

Adverse effect

- Dose related
- Flushing, hypotension, tachycardia, headache, wheals, bronchoconstriction and GI upset.

H1 Antihistamines

- These drugs competitively antagonize actions of histamine at the H1 receptors.
- Can be divided into first and second generation drugs.
- First generation drugs
  - ✓ Penetrate the CNS and cause sedation
  - ✓ Interact with other receptors (cholinergic, adrenergic or serotonin Receptors), producing a variety of unwanted adverse effects.
- Second generation drugs
  - ✓ Specific for peripheral H1 receptors
  - ✓ Do not cross the BBB thus less CNS depression than first generation drugs and shows less sedative. (cetirizine are partially sedating)

	Drug	Dose and route
I.	*HIGHLY SEDATIVE*	
	Diphenhydramine	25–50 mg oral
	Dimenhydrinate	25–50 mg oral,
	Promethazine	25–50 mg oral, i.m. (1 mg/kg)
	Hydroxyzine	25–50 mg oral, i.m.
II.	*MODERATELY SEDATIVE*	
	Pheniramine	20–50 mg oral, i.m.
	Cyproheptadine	4 mg oral
	Meclizine	25–50 mg oral
	Buclizine	25–50 mg oral
	Cinnarizine	25–50 mg oral
III.	*MILD SEDATIVE*	
	Chlorpheniramine	2–4 mg (0.1 mg/kg) oral, i.m.
	Dexchlorpheniramine	2 mg oral
	Dimethindene	1 mg oral
	Triprolidine	2.5–5 mg oral
	Mebhydroline	100–300 mg oral
	Cyclizine	50 mg oral
	Clemastine	1–2 mg oral

SECOND GENERATION ANTIHISTAMINICS	
Fexofenadine	120–180 mg oral
Loratadine	10 mg oral
Desloratadine	5 mg oral
Cetirizine	10 mg oral
Levocetirizine	5–10 mg oral
Azelastine	4 mg oral 0.28 mg intranasal
Mizolastine	10 mg oral
Ebastine	10 mg oral
Rupatadine	10 mg oral

Pharmacological Action

1. Antagonism of histamine: block histamine induced bronchoconstriction

2. Antiallergic action:

- Histamine mediate Type 1 hypersensitivity reaction.
- Urticarial, itching, angioedema are suppressed.
- Anaphylactic fall in BP is only partially prevented.

3. CNS:

- Produces various degree of CNS depression (sedation). Second generations are practically non-sedating.
- Certain H1 antihistamines are effective in preventing motion sickness.
- Promethazine also controls vomiting of pregnancy.

Pharmacological Action

- 4. Anticholinergic action: Block action of acetylcholine.

High	*Low*	*Minimal/Absent*
Promethazine	Chlorpheniramine	Fexofenadine
Diphenhydramine	Hydroxyzine	Astemizole
Dimenhydrinate	Triprolidine	Loratadine
Pheniramine	Cyclizine	Cetirizine
Cyproheptadine		Mizolastine

- 5. BP: cause fall in BP

Side effect

- Common: Sedation, diminished alertness and concentration, fatigue and tendency to fall asleep,
- Anticholinergic effect: dryness of mouth, constriction of pupil, blurred vision, urinary retention

Precaution

- Patients should be cautioned not to operate motor vehicle or machinery requiring constant attention.

Second Generation antihistamines

- Higher H1 selectivitiy: no anticholinergic side effects.
- Absence of CNS depressant property.
- Additional antiallergic mechanisms

Advantages

- Don't impair psychomotor performance
- No sedation

Disadvantages

- Poor antipruritic, antiemetic and antitussive action

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Uses

1. Allergic disorders
2. Common cold
3. Motion sickness: promethazine, cyclizine, diphenhydramine

Promethazine can also be used in morning sickness, drug induced and postoperative vomiting, radiation sickness.

(Cyproheptadine has appetite stimulating effect)

4. Vertigo: cinnarizine
5. Preanaesthetic medication: Promethazine (anticholinergic and sedative properties)
6. Cough: chlorpheniramine, diphenhydramine and promethazine may afford symptomatic relief by sedative and anticholinergic property.
7. Parkinsonism: Promethazine and some others afford mild symptomatic relief in early cases based on anticholinergic and sedative property.

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Betahistine

- It is an orally active, strong antagonist of H3 receptor and weak agonist of H1 receptor.
- used to control vertigo in patients of Meniere's disease: possibly acts by causing vasodilatation in the inner ear.
- It is contraindicated in pheochromocytoma, asthmatics and ulcer patients.