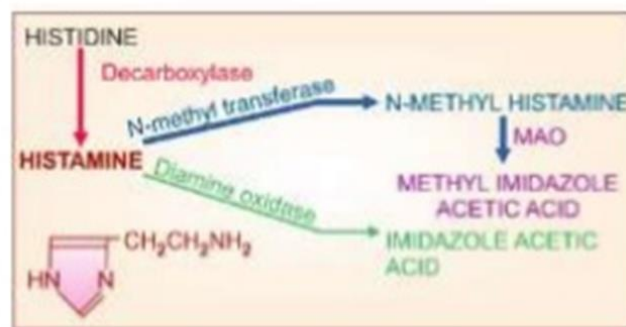
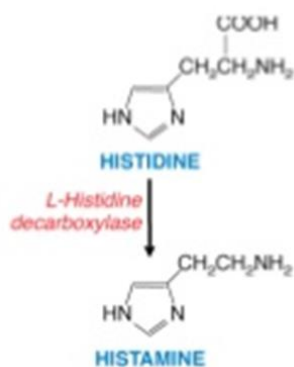


## HISTAMINE

- Histamine is a chemical messenger mostly generated in mast cells that mediates a wide range of cellular responses, including allergic and inflammatory reactions, gastric acid secretion, and neurotransmission in parts of the brain.
- Histamine has no clinical applications, but agents that interfere with the action of histamine (antihistamines) have important therapeutic applications.

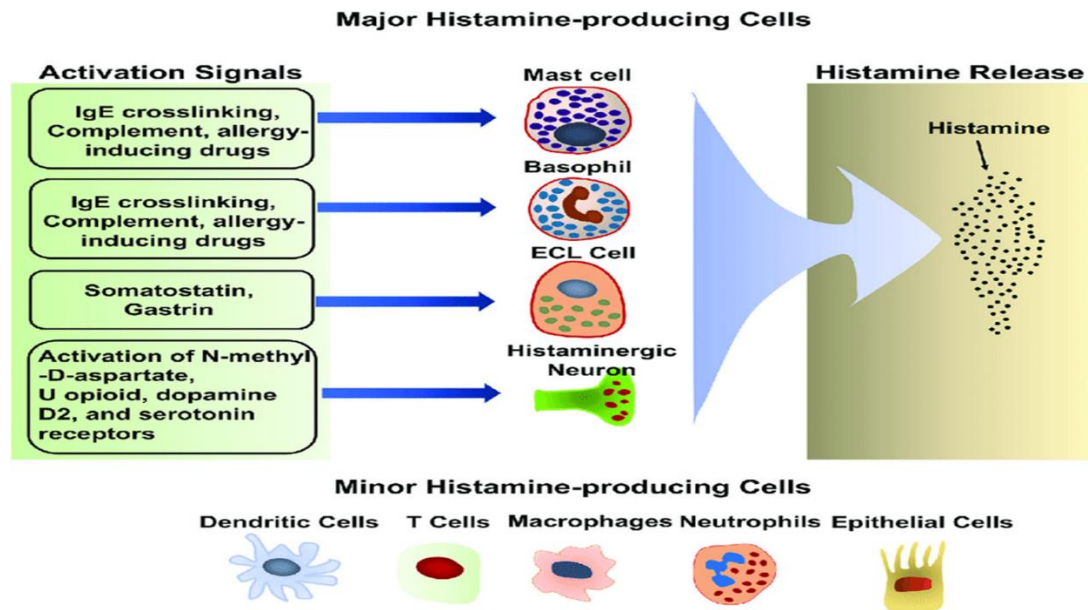
## Synthesis, storage & metabolism of histamine



- Synthesized by decarboxylation of amino acid histidine

### LOCATION:

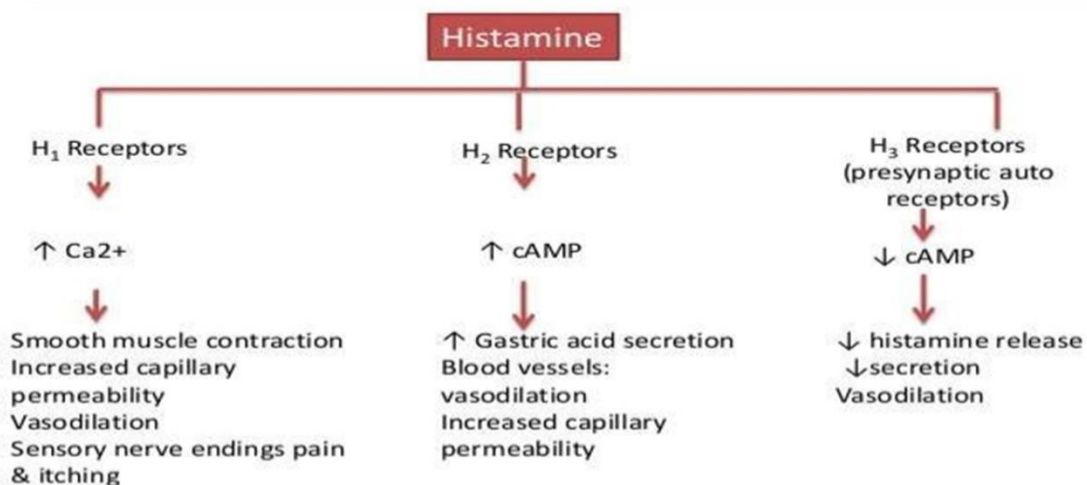
- Histamine occurs in practically all tissues, but it is unevenly distributed, with high amounts found in lung, skin, and the gastrointestinal tract (sites where the “inside” of the body meets the “outside”).
- It is found at high concentration in mast cells or basophils. Histamine also occurs as a component of venoms and in secretions from insect stings.



#### RELEASE OF HISTAMINE:

- The release of histamine may be the primary response to some stimuli, but, most often, histamine is just one of several chemical mediators released.
- The release of histamine from tissues is caused by the destruction of cells as a result of cold, bacterial toxins, bee sting venoms, or trauma.
- Allergies and anaphylaxis can also trigger release of histamine.

## Mechanism of Action of Histamine



	H <sub>1</sub>	H <sub>2</sub>	H <sub>3</sub>	H <sub>4</sub>
G protein coupling (2nd messengers)	G <sub>q/11</sub> (↑ Ca <sup>2+</sup> ; ↑ NO and ↑ cGMP)	G <sub>s</sub> (↑ cAMP)	G <sub>i/o</sub> (↓ cAMP; ↑ MAPK)	G <sub>i/o</sub> (↓ cAMP; ↑ Ca <sup>2+</sup> )
Distribution	Smooth muscle, endothelial cells, CNS	Gastric parietal cells, cardiac muscle, mast cells, CNS	CNS: presynaptic	Cells of hematopoietic origin
Representative agonist	2-CH <sub>3</sub> -histamine	Amthamine	(R)-α-CH <sub>3</sub> -histamine	4-CH <sub>3</sub> -histamine
Representative antagonist	Chlorpheniramine	Ranitidine	Tiprolisant	JNJ7777120

*cAMP, cyclic AMP; cGMP, cyclic GMP; CNS, central nervous system; MAPK, MAP kinase; NO, nitric oxide.*

Antihistamines - Classification	
Generation I	Examples
Most sedative, Most potent:	Diphenhydramine, Dimenhydrinate, Hydroxyzine, Promethazine
Moderate sedative, Moderate potent:	Pheniramine, Meclizine, Buclizine, Cyproheptadine, Cetrizine
Less sedative, Less potent:	Chlorpheniramine, Mebhydroline, Dimethindone, Clemastine
Generation II	Examples
Mainly antiallergic:	Levocetirizine, Loratadine, Desloratadine, Fexofenadine
Antivertigo, Antimigraine:	Flunarizine, Cinnarizine

# CLASSIFICATION OF ANTIHISTAMINES

## Histamine Receptors blockers

Type	Examples	Main functions
H1 receptor blockers	Diphenhydramine Mepyramine maleate Promethazine hydrochloride Pheniramine maleate Antazoline	To treat allergic reactions
H2 receptor blockers	Cimetidine Burimamide Metiamide Ranitidine	To reduce Gastric acid release
H3 receptor blockers	Burimamide Impromidine Theoperamide	To treat neurodegenerative conditions
H4 blockers	Thioperamide	UI

### PHARMACOLOGICAL PROPERTIES:

#### Smooth Muscle:

- H<sub>1</sub> antagonists inhibit most of the effects of histamine on smooth muscles, especially the constriction of respiratory smooth muscle.

#### Capillary Permeability:

- H<sub>1</sub> antagonists strongly block the increased capillary permeability and formation of edema and wheal brought about by histamine.

#### Flare and Itch :

- The flare component of the triple response and the itching caused by intradermal injection of histamine are two different manifestations of the action of histamine on nerve endings.

#### Exocrine Glands:

H<sub>1</sub> antagonists do not suppress gastric secretion, but they do suppress histamine-evoked salivary, lacrimal, and other exocrine secretions.

#### Immediate Hypersensitivity Reactions, Anaphylaxis and Allergy:

- During hypersensitivity reactions, histamine is one of the many potent autacoids released, types of H receptors and by effects of other mast cell mediators.
- These include those derived from arachidonic acid (released from membranes by PLA<sub>2</sub>), which is converted by cyclooxygenases and lipoxygenases to prostaglandins, eicosatetraenoic acid derivatives, leukotrienes, and other mediators



## Central Nervous System

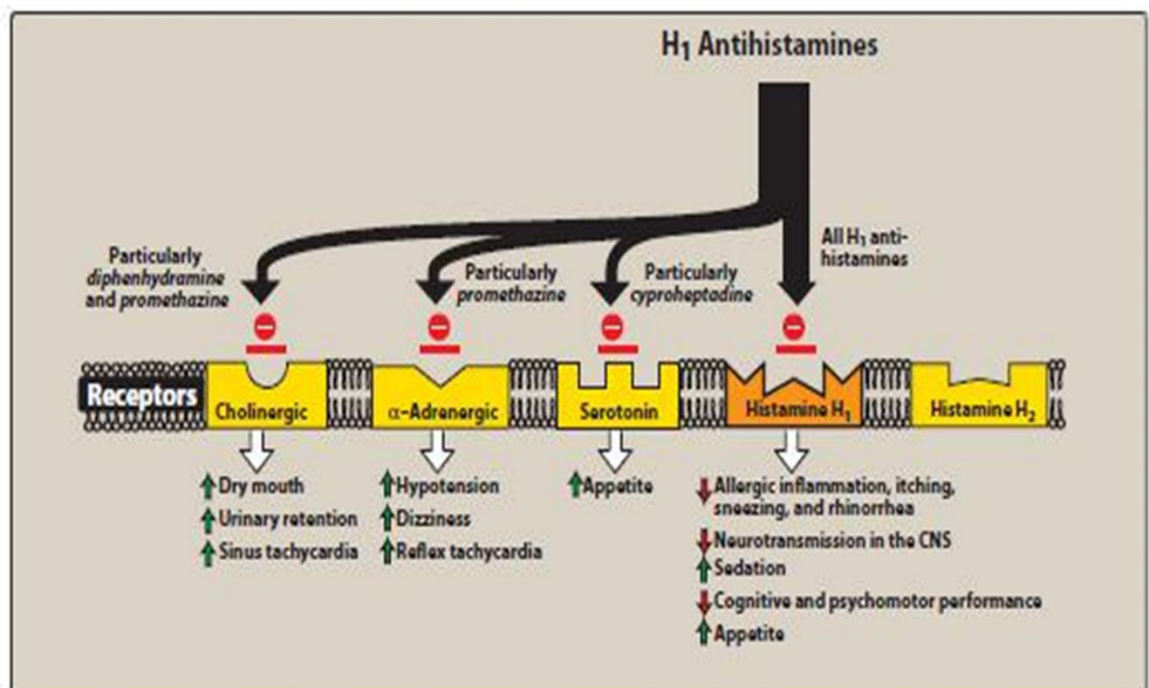
- The first-generation H<sub>1</sub> antagonists can both stimulate and depress the CNS

## Anticholinergic Effects

- Many of the first-generation H<sub>1</sub> antagonists tend to inhibit responses to acetylcholine that are mediated by muscarinic receptors.
- These atropine-like actions are sufficiently prominent in some of the drugs, Promethazine

## Local Anesthetic Effect:

- Some H<sub>1</sub> antagonists have local anesthetic activity, and a few are more potent than procaine e.g Promethazine
- has perhaps the strongest muscarinic-blocking activity



## THERAPEUTIC USES:

### Allergic and inflammatory conditions:

- ▶ H<sub>1</sub>-receptor blockers are useful in treating allergies caused by antigens acting on immunoglobulin E antibody-sensitized mast cells.

### Motion sickness and nausea:

- ▶ Along with the antimuscarinic agent scopolamine, certain H<sub>1</sub>-receptor blockers, such as diphenhydramine, dimenhydrinate (a chemical combination of diphenhydramine and a theophylline derivative), cyclizine and meclizine are the most effective agents for prevention of the symptoms of motion sickness

### Somnifacients:

- ▶ Although they are not the medications of choice, many first-generation antihistamines, such as diphenhydramine and doxylamine, have strong sedative properties and are used in the treatment of insomnia.

#### **PHARMACOKINETICS:**

- ▶ H1-receptor blockers are well absorbed after oral administration,
- ▶ The average plasma half-life is 4 to 6 hours, except for that of meclizine, which is 12 to 24 hours.
- ▶ H1-receptor blockers have high bioavailability and are distributed in all tissues, including the CNS.
- ▶ All first-generation H1 antihistamines and some second-generation H1 antihistamines, such as desloratadine and loratadine, are metabolized by the hepatic cytochrome P450 system.

#### **ADVERSE EFFECTS:**

- ▶ Drowsiness
- ▶ Tachycardia
- ▶ BP
- ▶ Hypotension
- ▶ Vertigo
- ▶ Increased appetite
- ▶ Dry mouth

*NOREENA MASOOD*

*Roll# 3*

*Pharmacology IV*