PHARMACOLOGY

HISTAMINE AND HISTAMINE RECEPTOR ANTAGONISTS

Histamine is an important mediator of immediate allergic (such as urticaria) and inflammatory reactions, although it plays only a modest role in anaphylaxis.

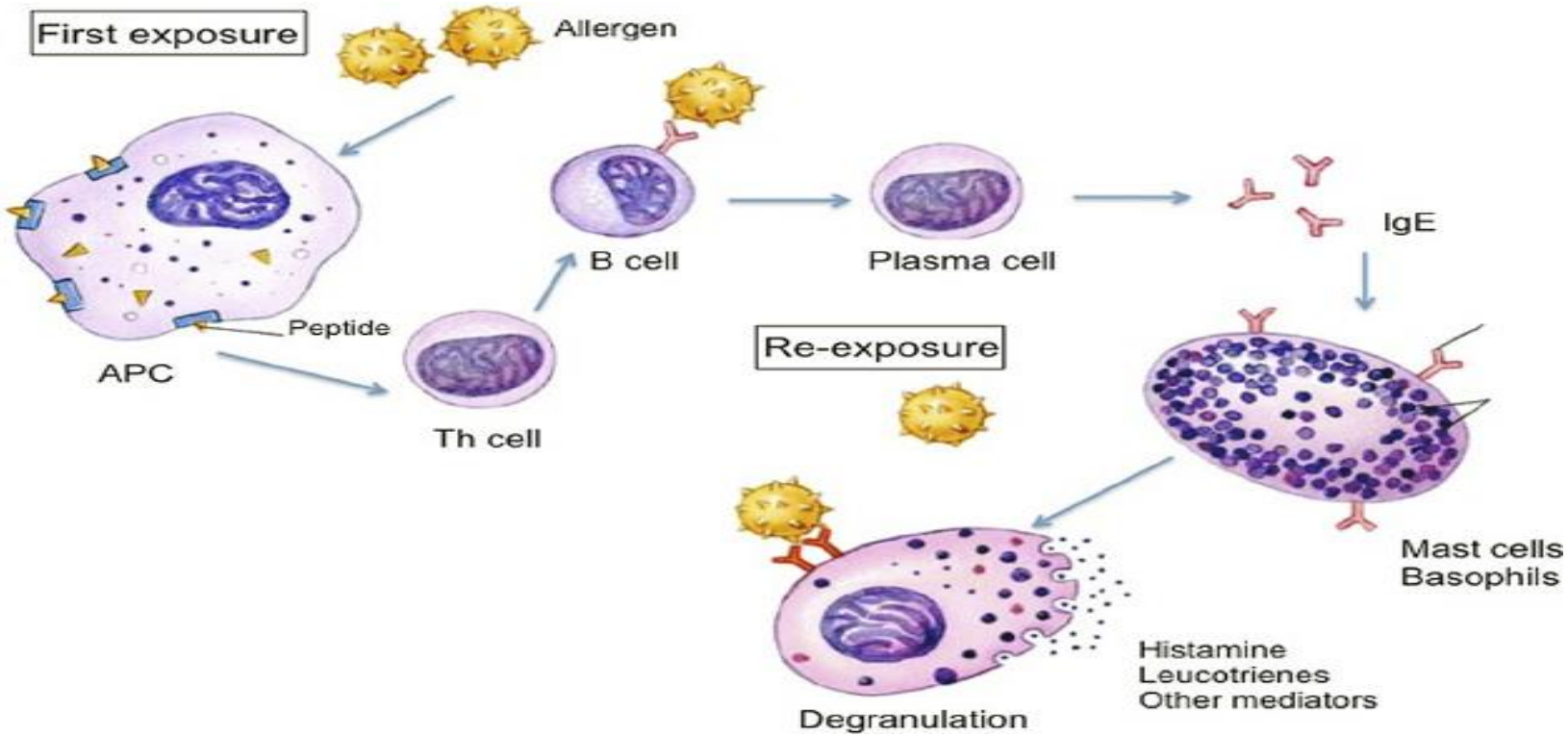
Histamine plays an important role in gastric acid secretion and functions as a neurotransmitter and neuromodulator. Newer evidence indicates that histamine also plays a role in chemotaxis of white blood cells.

Histamine has no clinical applications, but agents that interfere with the action of histamine (antihistamines) have important therapeutic applications.

Type I or anaphylactic reactions: Type I reactions are mediated by proteins called IgE antibodies produced by the immune system. These are produced in response to the allergens such as pollen, animal dander or dust mites, or even certain foods. This causes the release of histamine and other chemicals causing inflammation and swelling. Examples of type I allergic reactions include :

bronchial **asthma**, **allergic rhinitis**, allergic **dermatitis**, **food allergies**, **allergic conjunctivitis** (eye inflammation) and **anaphylaxis** (allergic **shock**).

Anaphylaxis is the most severe form and is a medical emergency because it can lead to a sudden, life-threatening respiratory failure. People with anaphylaxis have extreme difficulty in **breathing**, swelling, **low blood pressure**, bluish skin and shock.


First exposure
Allergen
B cell
Plasma cell
IgE
Peptide
APC
Th cell
Re-exposure
Mast cells
Basophils
Histamine
Leucotrienes
Other mediators
Degranulation

Location

Histamine is present in practically all tissues , with significant amounts in the lungs, skin, blood vessels and gastrointestinal tract. It is found in high concentrations in mast cells and basophils .

Most tissue histamine is sequestered and bound in granules (vesicles) in mast cells or basophils; the histamine content of many tissues is directly related to their mast cell content. The bound form of histamine is biologically inactive, but as noted, many stimuli can trigger the release of mast cell histamine, allowing the free amine to exert its actions on surrounding tissues. Mast cells are especially rich at sites of potential tissue injury—nose, mouth, and feet; internal body surfaces; and blood vessels.

histamine is found in several tissues, including the brain, where it functions as a neurotransmitter Strong evidence implicates endogenous neurotransmitter histamine in many brain functions such as neuroendocrine control, cardiovascular regulation, thermal and body weight regulation, and sleep and arousal.

other important site of histamine storage and release is the enterochromaffin-like (ECL) cells of the fundus of the stomach. ECL cells release histamine, one of the primary gastric acid secretagogues, to activate the acid-producing parietal cells of the mucosa.

Histamine is found in:

1.Tissues: It is found in most tissues but is present in high conc. In the lungs, skin and fundus of the stomach (Enterochromaffin-like ,ECL cells).
2.Cells: It is found largely in mast cells and basophils
3.Neurons: histaminergic neurons in the brain.

Synthesis:

Histamine is an amine formed by the decarboxylation of the amino acid histidine by histidine decarboxylase enzyme, an enzyme that is expressed in cells throughout the body, including central nervous system (CNS) neurons, gastric parietal cells, mast cells, and basophils . In mast cells, histamine is stored in granules. If histamine is not stored, it is rapidly inactivated by amine oxidase enzymes.

Release of histamine:

1. Immunological Release

Immunologic processes account for the most important pathophysiologic mechanism of mast cell and basophil histamine release. These cells, if sensitized by IgE antibodies attached to their surface membranes, degranulate explosively when exposed to the appropriate antigen . Histamine released by this mechanism is a mediator in immediate (type I) allergic reactions, such as hay fever and acute urticaria.

Endogenous histamine has a modulating role in a variety of inflammatory and immune responses. Upon injury to a tissue, released histamine causes local vasodilation and leakage of plasma-containing mediators of acute inflammation (complement, C-reactive protein) and antibodies. Histamine has an active chemotactic attraction for inflammatory cells (neutrophils, eosinophils, basophils, monocytes, and lymphocytes).

2.Chemical and Mechanical Release

Drugs such as morphine and tubocurarine, can displace histamine from its bound form within cells.

Mechanism of Action

Histamine exerts its biologic actions by combining with specific cellular receptors located on the surface membrane. The four different histamine receptors thus far characterized are designated H_1–H_4 and are described in Table 1.

Table 1 Histamine Receptor Subtypes.

Receptor Subtype	Distribution	Post receptor Mechanism
H_1	Smooth muscle, endothelium, brain	G_q, ↑ IP_3, DAG Bronchospasm,spasmogenic effect on smooth M. Vasodilation, skin itching
H_2	Gastric mucosa, cardiac muscle, mast cells, brain	G_s, ↑cAMP increase gastric HCL secretion Cardiac stimulation
H_3	Presynaptic: brain, other neurons	G_i, ↓cAMP/ decrease neurotransmitter release
H_4	Eosinophils, neutrophils, CD4 T cells	G_i, ↓cAMP/ play a role in chemotaxis

In **the brain,** H_1 and H_2 receptors are located on postsynaptic membranes, whereas H_3 receptors are predominantly presynaptic. Activation of H_3 receptors decreases transmitter release from histaminergic and other neurons. H_4 receptors are found mainly on leukocytes in the bone marrow and circulating blood. H_4 receptors appear to have very important chemotactic effects on eosinophils and mast cells.

Tissue and Organ System Effects of Histamine

Histamine exerts powerful effects on smooth and cardiac muscle, on certain endothelial and nerve cells, on the secretory cells of the stomach, and on inflammatory cells.

Nervous System

Histamine is a powerful stimulant of sensory nerve endings, especially those mediating pain and itching. This H_1-mediated effect is an important component of the urticarial response and reactions to insects and nettle stings.

Cardiovascular System

Direct vasodilator action of histamine (H1) by release of nitric oxide from the endothelium; decrease in systolic and diastolic blood pressure, flushing ,sense of warmth and headache , increase capillary permeability cause edema formation.

The increase in heart rate involves both stimulatory actions of histamine on the heart (H2) and a reflex tachycardia (vasodilation).

Smooth Muscle

Bronchiolar smooth muscle: histamine causes bronchoconstriction mediated by(H_1) receptors. However, patients with asthma are very sensitive to histamine.

Gastrointestinal tract smooth muscle: histamine causes contraction of intestinal smooth muscle. may cause diarrhea. This action of histamine is mediated by (H_1) receptors.

Other smooth muscle organs histamine generally has insignificant effects on the smooth muscle of the eye and genitourinary tract. However, pregnant women suffering anaphylactic reactions may abort as a result of histamine-induced contractions.

Secretory Tissue

Histamine has long been recognized as a powerful stimulant of gastric acid secretion. The effect is caused by activation of H_2 receptors on gastric parietal cells . Histamine also stimulates secretion in the small and large intestine.

Very high concentrations of histamine can cause adrenal medullary discharge.

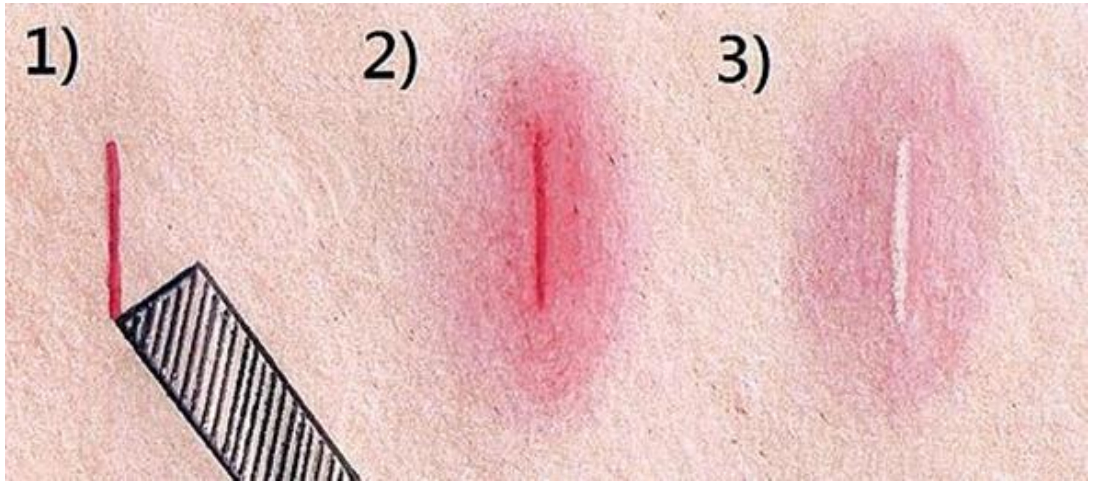
The "Triple Response"

If histamine is injected intradermally or when the skin is exposed to a physical trauma a triple response will be elicited is due to the release of histamine. That consists of:

1.Red spot: due to capillary dilatation

2.Flare: redness (extend about 1cm)caused by axon reflex

3.Edema(Wheal) : due to exudation of fluid from capillaries and venule(capillary permeability).



Nose :

1.runny nose and watery eyes(due to hypersecretion from glandular tissues)

2.sneezing(due to histamine -associated sensory neural stimulation).

3.Nasal congestion due to vascular congestion associated with vasodilation and increase capillary permeability) .

CNS:

Histamine neurons in the brain increase wakefulness and prevent sleep , block H1receptor in the brain cause sedation.

Hypothalamus H1 receptor in the brain are crucial for the regulation of the diurnal rhythm of food intake and the regulation of obesity.

Histamine Antagonists

The effects of histamine released in the body can be reduced in several ways.

1.Physiologic antagonists, especially epinephrine, have smooth muscle actions opposite to those of histamine, but they act at different receptors. adrenaline cause bronchodilation(β2)& vasoconstriction(α1). This is important clinically because injection of epinephrine can be lifesaving in systemic **anaphylaxis** and in other conditions in which massive release of histamine—and other mediators—occurs.

2. Release inhibitors (mast cell stabilizer)reduce histamine release from mast cell used as prophylactic in asthma. Cromolyn and nedocromil and ketotifen .

Beta$_2$-adrenoceptor agonists (e.g salbutamol)also appear capable of reducing histamine release.

3.Histamine receptor antagonists represent a third approach to the reduction of histamine-mediated responses.

H_1-Receptor blockers

Compounds that competitively block histamine at H_1 receptors have been used in the treatment of allergic conditions . Many are available without prescription, both alone and in combination formulations such as "cold pills" and sleep aids .

The H_1 receptor blockers are conveniently divided into :

First-generation (sedating antihistamine):

Diphenhydramine, doxylamine, hydroxyzine, chlorpheniramine, Cyproheptadine, cyclizine, meclizine, promethazine , Dimethindene .clemastine, triprolidine ,pheniramine.

The first-generation drugs enter the central nervous system readily. The older members of the first-generation agents, typified by **diphenhydramine, promethazine** are highly sedating. **Hydroxyzine** marked sedation .

Chlorpheniramine and **triprolidine** ,**cyclizine ,meclizine, dimethindene, clemastine, pheniramine** slight sedation.

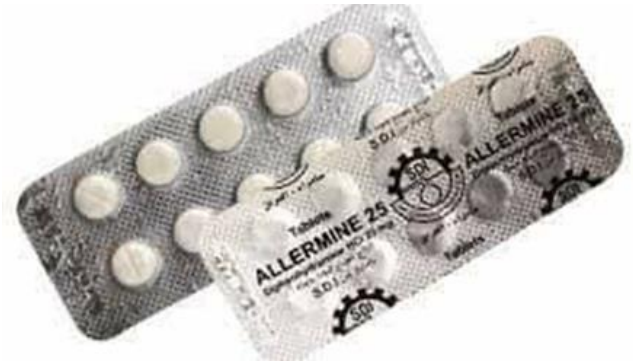
Doxylamine strong sedation used in treatment of Insomnia.

Some of these drugs have another action e.g anticholinergic, antiemetic , anti-serotonin and local anesthetic effects.

hydroxyzine

Diphenhydramine

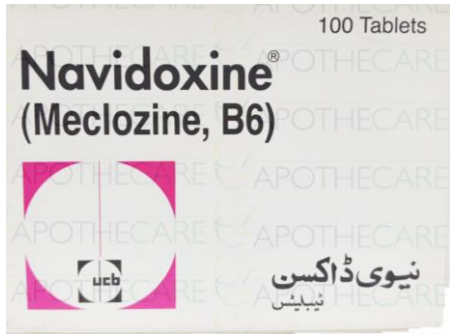
Allermine



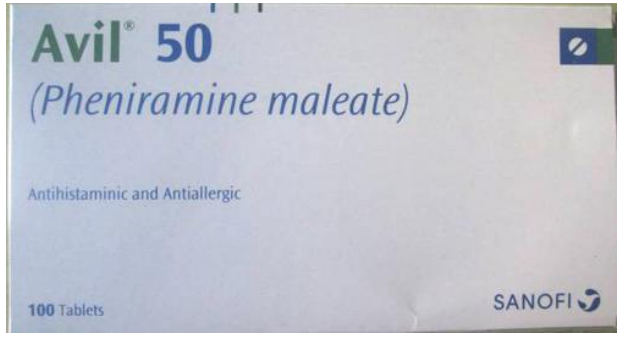
Doxylamine

chlorpheniramine

meclizine



pheniramine

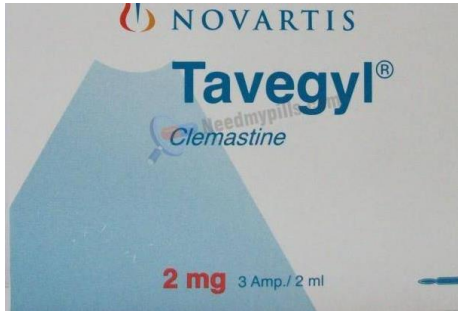


Cyproheptadine

Dimethindene

Tab.4mg ,Oral drop

clemastine



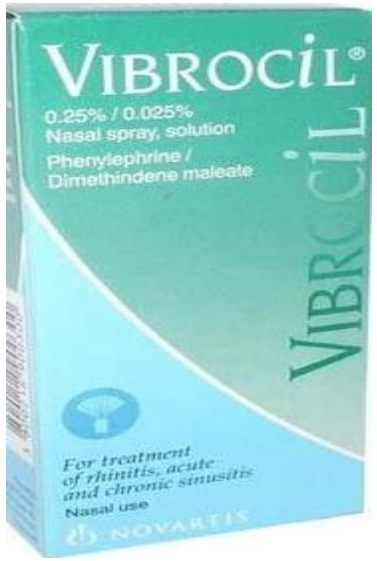
Combination antihistamine with other drugs(for cough, cold medication)

chlorpheniramine

Diphenhydramine

promethazine

chlorpheniramine



Dimethindene
Nasal spray

Triprolidine

Second-generation (non sedating antihistamine):, Cetirizine , levocetirizine , desloratadine, loratadine and fexofenadine are very similar to cetirizine

The second-generation H_1 blockers, typified by **cetirizine, fexofenadine,** and **loratadine,** are far less lipid soluble than the first-generation agents and have further reduced sedating and autonomic effects(no anticholinergic, no antiemetic ,no anti-serotonin activity)

Ketotifen ,**azelastine** mast cell stabilizer.in addition to H1 blocking effects

Olopatadine Opatanol® Eye drop

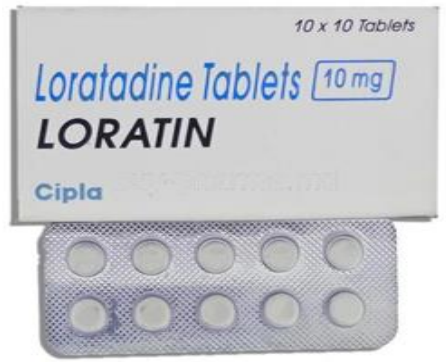
Ketotifen fumarate Zaditen ® Eye drop, oral

Azelastine HCl Rhinolast Nasal spray

Ketotifen

desloratadine

loratadine



fexofenadine

Azelastine

Olopatadine

levocetirizine

Pharmacokinetics:

Because they have been developed for use in chronic conditions, all H_1 blockers are active by the oral route. Several are promoted for topical use in the eye or nose. Most are metabolized extensively in the liver. Half-lives of the older(first gener.) H_1 blockers vary from 4–12 h. Most second-generation agents (e.g , fexofenadine, cetirizine, loratadine) have half-lives of 12–24 h.

Pharmacodynamics:

1.Sedation

A common effect of first-generation H_1 antagonists is sedation, but the intensity of this effect varies among chemical structure and lipophilicity. The effect is make them useful as "sleep aids" and unsuitable for daytime use. At very high toxic dose levels, marked stimulation, agitation, and even convulsions may produce coma.

Diphenhydramine, doxylamine are strong sedating

chlorpheniramine less sedative effects

Second-generation H_1 antagonists have little or no sedative or stimulant actions.

cetirizine and levocetirizine are partially sedating

2.Antinausea and Antiemetic Actions

Several first-generation H_1 antagonists have significant activity in preventing motion sickness. They are less effective against an episode of motion sickness already present. **promethazine**. They are usually not effective if symptoms are already present and, thus, should be taken prior to expected travel. The antiemetic action of these medications seems to be due to their blockade of central H1 and M1 muscarinic receptors.

cyclizine and **meclizine** also have significant activity in preventing motion sickness and are **less sedating** most patients.

Cinnarizine (stugeron)is an antihistamine (H1 receptors) and calcium channel blocker . It is prescribed for nausea and vomiting due to motion sickness or other sources such as chemotherapy, vertigo, or Ménière's disease.

3.Antimuscarinic Actions

Many first-generation agents, have significant atropine-like effects on peripheral muscarinic receptors. This action may be responsible for some of the (uncertain) benefits reported for nonallergic rhinorrhea but may also cause urinary retention and blurred vision.

4.Adrenoceptor-Blocking Actions

Alpha1-receptor blocking effects can be demonstrated for many first gener. H_1 antagonists, especially **promethazine**. This action may cause orthostatic hypotension in susceptible individuals.

Beta-receptor blockade is not observed.

5.Serotonin-Blocking Action

Strong blocking effects at serotonin receptors have been demonstrated for some first-generation H_1 antagonists, notably **cyproheptadine.** This drug is promoted as an anti-serotonin agent , Cyproheptadine also competes with serotonin at receptor sites in smooth muscle in the intestines and other locations. Antagonism of serotonin on the appetite center of the hypothalamus may account for Cyproheptadine's ability to stimulate appetite.

6.Local Anesthesia

Several first-generation H_1 antagonists are potent local anesthetics. They block sodium channels in excitable membranes in the same fashion as procaine and lidocaine. **Diphenhydramine and promethazine** are actually more potent than procaine as local anesthetics.

Clinical Uses of H_1-Receptor Antagonists

1.Allergic and inflammatory conditions.

H1-receptor blockers are useful in treating and preventing allergic reactions caused by antigens acting on immunoglobulin E (IgE) antibody for example:

a. Oral antihistamines are the drugs of choice in controlling the symptoms of allergic rhinitis and urticaria .second gener. More preferred in chronic urticaria.

b. Ophthalmic antihistamines, such as **azelastine and ketotifen** (H1-antihistamine and mast cell stabilizer) are useful for the treatment of allergic conjunctivitis., the H_1 antagonists are the drugs of choice and are often quite effective if given before exposure.

c. A nasal spray to treat allergic rhinitis : **Azelastine**

d. For atopic dermatitis, antihistaminic drugs such as **diphenhydramine** are used mostly for their sedative side effect, which reduces awareness of itching.

* in bronchial asthma, which involves several mediators, the H_1 antagonists are largely ineffective

2.Motion Sickness and nausea

First generation **diphenhydramine ,promethazine** .

Cyclizine ,meclizine also prevent motion sickness ,less sedation than diphenhydramine.

3.Somnifacient(hypnotic)

many first generation drugs such as **diphenhydramine** and **doxylamine**, have strong sedative properties and are used in the treatment of insomnia

Toxicity

First gener. systemic use include excitation and convulsions in children, postural hypotension, and allergic responses. First-generation antihistamines exert anticholinergic effects, leading not only to dryness in the nasal passage but also to a tendency to dry out the oral cavity. They also may cause blurred vision and retention of urine.

Betahistine is an analogue of histamine and is licensed for vertigo tinnitus, . and hearing loss associated with Ménière's disease (Ménière's disease is a disorder of the inner ear that can affect hearing and balance to a varying degree. It is characterized by episodes of vertigo, low-pitched tinnitus, and hearing loss).

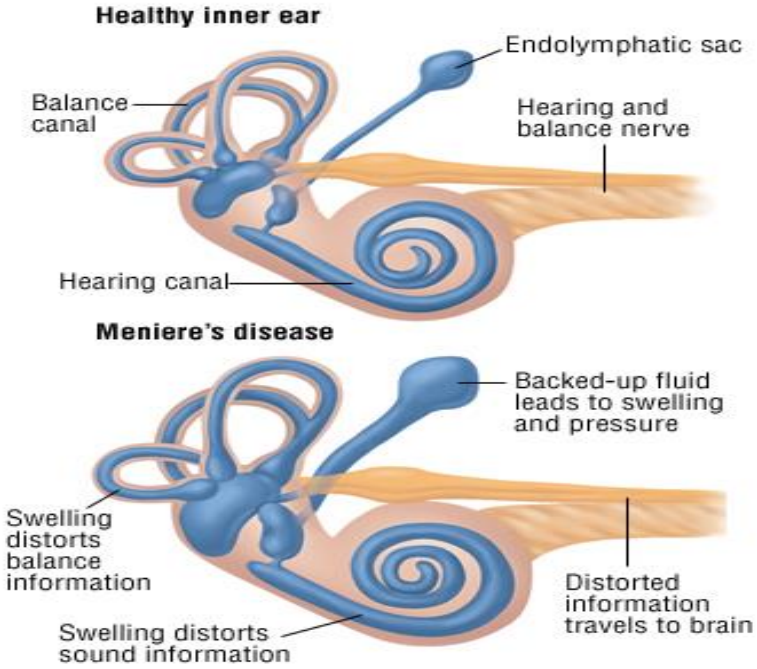
Betahistine is a strong antagonist of the histamine H_3 receptor and a weak agonist of the histamine H_1 receptor.

Betahistine has two mechanisms of action. Primarily, it is a weak agonist on the H_1 receptors located on blood vessels in the inner ear..

More importantly, betahistine has a powerful antagonistic effects at H_3 receptors, thereby increasing the levels of neurotransmitters histamine, . The increased amounts of histamine released from histaminergic nerve endings can stimulate receptors. This stimulation explains the potent vasodilatory effects of betahistine in the inner ear.

Betahistine seems to dilate the blood vessels within the inner ear which can relieve pressure from excess fluid and act on the smooth muscle.

Betahistine(Betaserc) Tab. 8, 16



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