Histidine → Histamine

**Histamine Synthesis.**

Once synthesized it is either stored or rapidly inactivated.

Widely distributed and found in most tissues.

**Histamine Storage.**

The chief site of histamine storage in most tissues is the mast cell and in the blood it is the basophil (synthesized and stored in secretory granules).

Other sites include histaminergic neurons (in the brain), cells of the epidermis, and cells in regenerating or rapidly growing tissues.
HISTAMINE RELEASE

- Bound form is biologically inactive.

- Release triggered by antigen binding, neuropeptides, various drugs and toxins.

Mast cells release histamines when the allergen is encountered.

HISTAMINE RELEASE

- Mast cells and basophil - immunologic.

- These cells if sensitized by IgE antibodies attached to their surface membranes degranulate when exposed to the appropriate antigen.

Also requires energy and calcium.

Other mediators also released.

HISTAMINE RELEASE

- Turnover rate of histamine in these granules is slow and it may take weeks before concn’s of it return to normal.

Turnover at the nonmast cell sites is rapid as the histamine is continuously released rather than stored.

Non-mast cell sites contribute significantly to the daily excretion of histamine and its metabolites in the urine.
HISTAMINE RELEASE

- Turnover at the nonmast cell sites is rapid as the histamine is continuously released rather than stored.

- Enterochromaffin like cells—endocrine cells in the stomach lining—vagal impulse (ACH) or gastrin.

- Histaminergic neurons (CNS)—nerve impulse.

DRUGS, POLYPEPTIDES AND VENOMS CAUSING HISTAMINE RELEASE

- Tubocurarine, succinylcholine, morphine, radiocontrast media and certain carbohydrate plasma expanders.

- Vancomycin

- Basic polypeptides (e.g., polymyxin B)

- Snake venoms (contain polypeptides)
HISTAMINE METABOLISM

- Rapidly degraded after release.

Histamine Metabolism

MECHANISM OF ACTION

- Binds specific cellular receptors located on the membrane.
- \( H_1, H_2, H_3, \) and \( H_4 \)

H_1 RECEPTORS

- Widespread, found in bronchial and intestinal smooth muscle, cardiac muscle, endothelial layer of small vasculature, various regions of brain (post-synaptic) and peripheral sensory nerve endings.

H_2 RECEPTORS

- Widespread-vascular smooth muscle, cardiac muscle, gastric parietal cells, various regions of brain and mast cells.
### H3 Receptors

- High expression in histaminergic neurons (especially in the CNS).
- Function as feedback inhibitors not only of histamine but also of other neurotransmitters (ACH, dopamine, NE, and serotonin).
- Agonists promote sleep.
- Antagonists are being studied for neuropsychiatric diseases.

### H4 Receptors

- Similar signal transduction to H3.
- Found mainly in blood cells in the bone marrow and circulating blood.
- May function in the differentiation of myeloblasts and promyelocytes.

### Physiological Effects of Histamine

#### Cardiovascular Effects

- Dilation of small blood vessels resulting in flushing, lowered total peripheral resistance and a fall in systemic blood pressure.

#### Vasodilation

- In humans, this is the most important vasoconstrictor effect of histamine (H1 and H2 receptors).

### Histamine Induced Vasodilation

[Diagram showing vasodilation mechanisms involving smooth muscle cells, endothelial cells, and changes in calcium and cyclic AMP.]
INCREASED CAPILLARY PERMEABILITY

- Classical effect on small blood vessels resulting in loss of plasma protein and fluid into the extracellular spaces (formation of edema).

- Results from endothelial cell retraction (H₁ effect).

TRIPLE RESPONSE

- Used to quantify the extent of an allergic response of an individual.

DIRECT CARDIAC EFFECTS

- Increased contractility and pacemaker rate (H₂ mediated).

ANAPHYLACTIC SHOCK

- Large scale systemic release of histamine and other inflammatory mediators
EFFECTS ON EXTRAVASCULAR SMOOTH MUSCLE
- Contraction of smooth muscle in bronchi and gut (H₁ effect).

EFFECTS ON GASTRIC ACID SECRETION
- Histamine is a powerful stimulant of stomach acid secretion (pepsin also) (H₂ receptors).
- Acid secretion is also stimulated by vagal nerve activity and gastrin.

CNS
- Neurotransmitter in the CNS.
- Found in the hypothalamus and other brain regions.
- May play a role in many CNS functions (wakefulness, body temp).
- H₁ and H₂ receptors.

NERVE ENDINGS
- Powerful stimulant of sensory nerve endings especially those mediating pain and itching (H₁).

ALLERGIC INFLAMMATION AND IMMUNE MODULATION
- Increased release of histamine and other mediators from mast cells.
- Most effects occur through H₁ receptors.

Role in allergic inflammation and immune modulation
- Increased cytokines and cellular adhesion molecule expression.
- Role in autoimmunity and malignant disease.
**OTHER BIOLOGICAL EFFECTS OF HISTAMINE**

- Cell proliferation and differentiation.
- Hematopoiesis.
- Embryonic development.
- Regeneration and wound healing.

**HISTAMINE ANTAGONISTS**

- Epinephrine is a physiological antagonist.
- Histamine release inhibitors - cromolyn, nedocromil and some β2 adrenergic agonists.

**RECEPTOR BLOCKERS**

**H2 BLOCKERS**

- Inhibitors of inflammation (allergic rhinitis, asthma and rheumatoid arthritis)

**H3 BLOCKERS**

- Thioperamide, clobenpropit, ciproxifan and proxifan.
- Arousal from sleep, improve attention and learning effects, suppress food intake, increase locomotion and increase anxiety.

**H4 BLOCKERS**

- Cimetidine, famotidine, nizatidine, ranitidine.
H₁-RECEPTOR BLOCKERS

- Inverse agonists. Shift equilibrium towards inactive state.
- Traditionally classified into 6 chemical groups (see syllabus).
- Like histamine many of these are substituted ethylamines. Most have a tertiary amino group linked by a 2 or 3 atom chain to two aromatic substituents.

\[
\begin{array}{c}
X & -Y & C & C & N \\
& & & & \text{CH₃} \text{CH₃}
\end{array}
\]

H₁ Receptor Blockers

H₁-RECEPTOR ANTIHISTAMINES

- Often classified into first and second generation compounds.

PHARMACOKINETICS

- Rapidly absorbed following oral administration with an onset of action of 1-3 hrs and peak blood concentrations occurring in 2-3 hrs.
- Widely distributed throughout the body (1st. genr’n drugs enter the CNS readily).

PHARMACOKINETICS

- Extensively metabolized by microsomal systems in the liver (CYP 3A4) (some may induce microsomal enzymes).

PHARMACOKINETICS

- Duration of action is usually 4-6 hrs., but several are longer-acting with a duration of 12-24 hrs.
PHARMACOLOGICAL PROPERTIES

- Inhibit most responses of smooth muscle to histamine.
- Strongly block the action of histamine that results in increased permeability and formation of edema and wheal.

PHARMACOLOGICAL PROPERTIES

- Antiallergic and anti-inflammatory activities
  - Decreased allergic inflammation, itching, sneezing, rhinorrhea and wheal formation.
  - Decreased antigen presentation, expression of cell-adhesion molecules, chemotaxis and proinflammatory cytokines.
  - Inhibition of mediator release.
  - Block some parts of anaphylaxis.

PHARMACOLOGICAL PROPERTIES

- Effects on the CNS
  - Anticholinergic effects
  - Local anesthetic effects

DRUG INTERACTIONS

COMMON THERAPEUTIC USES

- Second generation compounds have been well studied in RCT's.
- Best to take H₁ antihistamines on a regular basis rather than prn.
- Tolerance does not develop.

COMMON THERAPEUTIC USES

- Dose response curve for efficacy is flat in contrast to curve for adverse effects (especially 1st gen).
- Relief from symptoms may be incomplete.
Seasonal allergic rhinitis and conjunctivitis

- Relieve nasal itching, sneezing, rhinorrhea and congestion etc.
- Various H1 cpds have similar efficacy.
- Topical intranasal or ophthalmic agents have a more rapid onset.

Seasonal allergic rhinitis and conjunctivitis

- Choice of drug depends on safety, patient’s preference, formulation and route of administration.
- Many are available in fixed dose combos with pseudoephedrine (or phenylephrine).

OTHER AIRWAY DISORDERS

- Widely used for symptoms of upper RTIs, otitis media and sinusitis (but evidence doesn’t support use).
- Same for persistent asthma.
- Effective in patients with allergic inflammation throughout upper and lower airways.

Urticaria

Spider  Mosquito  Honeybee
OTHER ALLERGIC AND IMMUNOLOGIC DISORDERS

- Ancillary treatment of anaphylaxis.
- Relief of itching and glucocorticoid-sparing effect in atopic dermatitis.

CNS AND VESTIBULAR DISORDERS

- Insomnia
- Perioperative sedation
- For analgesia, akathisia, serotonin syndrome, anxiety and other CNS conditions.
- Antiemetic effects.
- Prevention and treatment of motion sickness, vertigo and related disorders.

ADVERSE EFFECTS

CNS

- Interference with neurotransmitter effects of histamine.
- Daytime drowsiness and slowed reaction time; impair psychomotor performance and interfere with learning and decrease work productivity, dizziness, headache.
- CNS stimulation—nervousness, tremors, hallucinations.
- None or less with 2nd gener’n drugs.

APPETITE AND GI DISORDERS

- Blockade of muscarinic, α-adrenergic and serotonin receptors
- Constipation, diarrhea
- Appetite stimulation and weight gain
- Nausea and vomiting
- None or less with 2nd generation cpds.
DRY MOUTH AND SINUSES

GLAUCOMA, PALPITATIONS, HEADACHE, DYSURIA

- Urinary retention and hesitancy
- Erectile dysfunction

CARDIAC EFFECTS

- Dose-related sinus tachycardia
- Reflex tachycardia

Polymorphic Ventricular Tachycardia

- Rarely terfenadine and astemizole cause prolongation of the QT interval with resultant polymorphic ventricular tachycardia (torsades de pointes).

- The parent drug (but not the carboxy metabolite) blocks delayed rectifier potassium channels.

POLYMORPHIC VENTRICULAR TACHYCARDIA

- It occurs with high doses or with blockage of hepatic metabolism (CYP3A4).

Polymorphic Ventricular Tachycardia

- Most commonly associated with combined use of macrolide antibiotics and certain antifungal agents.
ALLERGIC REACTIONS

- Dermatitis
- Drug fever
- Photosensitization

TERATOGENICITY

- Doxylamine in bendectin was reported to show teratogenic effects.

CARCINOGENICITY AND MUTAGENICITY

- Most studies with animals and clinical experience do not suggest carcinogenicity.

ABUSE OF ANTIHISTAMINES

- Euphoria
- Hallucinations

FIRST GENERATION H1 ANTAGONISTS

- Diphenhydramine
- Chlorpheniramine
- Promethazine, azelastine, dimenhydrinate, doxylamine, pyrilamine, hydroxyzine, cyclizine, brompheniramine, cyproheptadine

DIPHENHYDRAMINE (Benadryl)

- Oral and topical preparations
- Allergic rhinitis
- OTC sleep aids
- Motion sickness (pronounced anticholinergic properties)
- Sedation is fairly prominent
- Topical—allergic responses
| **CHLORPHENIRAMINE**  
(Chlortrimeton) | **AZELASTINE**  
| ✓ Common in OTC cold remedies. | ✓ May cause sedation due to systemic absorption.  
| ✓ Typically less sedation than with diphenhydramine, but varies with the patient. |  

| **PROMETHAZINE**  
| ✓ Oral  
| ✓ Most commonly used as an antiemetic.  
| ✓ Pronounced sedative effect. | **SECOND GENERATION ANTAGONISTS**  
|  

| **LORATIDINE (Claritin)**  
| ✓ Prodrug, but no evidence for binding to cardiac K⁺ channels.  
| ✓ Effective for treating seasonal allergies  
| ✓ otc | ✓ Loratidine  
| ✓ Fexofenadine  
| ✓ Terfenadine  
| ✓ Astemizole  
| ✓ Ebastine  
| ✓ Cetirizine  
| ✓ Desloratidine |  

| **FEXOFENADINE (Allegra)**  
| ✓ Effective for treating seasonal allergies and urticaria.  
| ✓ It is the active metabolite of terfenadine so it avoids problems with cardiac arrhythmias.  
| ✓ Seems to offer the best combination of effectiveness and safety. |  

EBASTINE

- Well tolerated and effective treatment for allergic rhinitis and urticaria.
- Prodrug with no evidence of binding cardiac K⁺ channels.

CETIRIZINE (Zyrtec)

- Most potent antihistamine.
- Associated with more sedation than other second generation compounds.
- Minimal anticholinergic effects.
- Active metabolite. Free of cardiac effects.

LEVOCETIRIZINE

- Rapid onset, long duration
- Lacks adverse effects

DESLORATIDINE

- Active metabolite of loratidine.
- No advantage over other 2nd generation cpds. including loratidine

ACRIVASTINE (Semprex)

- Effective in treating seasonal and perennial allergic rhinitis and histamine-mediated dermatoses
- Relatively non-sedating.