Histamine and Antihistamines
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Learning Objectives
1. Histamines
   a) Pharmacological effects
   b) Sites of action
   c) Conditions which cause release
   c) Diagnostic uses of histamine
2. Know the pharmacological effects, mechanisms of action, therapeutic uses, side-effects & drug interactions:
   a) H1 blockers
      - First generation: diphenhydramine (Benadryl), dimenhydrinate (Dramamine), chlorpheniramine (Chlor-Trimeton), promethazine (Phenergan)
      - Second generation: fexofenadine (Allegra), loratadine (Claritin), cetirizine (Zyrtec)
   b) H2 blockers: cimetidine (Tagamet), ranitidine (Zantac), Famotidine (Pepcid), Nizatidine (Axid)
   c) cromolyn sodium

Histamine Pharmacology
First autacoid to be discovered. (Greek: autos=self; akos=cure)
Synthesized in 1907
Demonstrated to be a natural constituent of mammalian tissues (1927)
Involved in inflammatory and anaphylactic reactions.
Local application causes swelling redness, and edema, mimicking a mild inflammatory reaction.
Large systemic doses leads to profound vascular changes similar to those seen after shock or anaphylactic origin

Histamine Formation
Synthesized in mammalian tissues by decarboxylation of the amino acid l-histidine

Histamine Stored in complex with:
- Heparin
- Chondroitin Sulfate
- Eosinophilic Chemotactic Factor
- Neutrophilic Chemotactic Factor
- Proteases

Histamine Metabolism
- Ring methylation by histamine n-methyltransferase
- MAO activity
- Oxidative deamination
- Urinary excretion of metabolites
Conditions That Release Histamine

1. **Tissue injury**: Any physical or chemical agent that injures tissue, skin or mucosa are particularly sensitive to injury and will cause the immediate release of histamine from mast cells.

2. **Allergic reactions**: Exposure of an antigen to a previously sensitized (exposed) subject can immediately trigger allergic reactions. If sensitized by IgE antibodies attached to their surface membranes will degranulate when exposed to the appropriate antigen and release histamine, ATP and other mediators.

3. **Drugs and other foreign compounds**: morphine, dextran, antimalarial drugs, dyes, antibiotic bases, alkaloids, amides, quaternary ammonium compounds, enzymes (phospholipase C). Penicillins, Tetracyclines, Basic drugs- amides, amidines, diaminides, Toxins, venoms, Proteolytic enzymes, Bradykinin, Kallidin, & Substance P

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3 Types of Histamine Receptors

1. **H₁ receptors**: mediate effects on smooth muscle leading to vasodilation, increased vascular permeability, and contraction of nonvascular smooth muscle.

2. **H₂ receptors**: mediate histamine stimulation of gastric acid secretion and may be involved in cardiac stimulation.

3. **H₃ receptors**: feedback inhibitors in CNS, gastrointestinal tract, lung, heart (currently no therapeutic agents).

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Pharmacological Effects of Histamine

1. **Cardiovascular system.**
   a) triple effect on terminal vasculature (itching & pain):
      i. redening at injection site due to vasodilation
      ii. wheal or disk of edema within 1 to 2 min
      iii. a large, bright crimson flare or halo surrounding the wheal
   b) i.v. histamine: fall in blood pressure, cutaneous flushing, over the face and upper trunk, rise in skin temperature, intense headache.

2. **Smooth muscle of bronchioles**: causes contraction of nonvascular smooth muscle. Asthmatics may experience marked bronchial constriction compared with normal subjects.

3. **Exocrine glands**: potent stimulator of gastric secretion (HCl & pepsin), enhances salivary and lacrimal gland secretion (minimal unless large doses are given), stimulates chromaaffin cells in adrenal medulla to secrete catecholamines.

4. **Peripheral Nervous system**: itching and pain

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Pharmacological Effects:

**Exocrine Glands**

- Gastric glands
- Salivary glands
- Sweat glands
- Pancreas
- Bronchial glands
- Lacrimal glands

↑ Secretion
Pharmacological Effects: Arterioles, Capillaries & Venules

Vasodilation
Increased permeability (edema)
Systemic hypotension

Pharmacological Effects: Vascular Smooth Muscles

Bronchial tree
Gastrointestinal tract
Uterus

Diagnostic Uses of Histamine

Gastric secretion: 1 mg Histamine subcutaneously to stimulate gastric secretion (no major effects on blood vessels), gastric fluid can then be sampled and acid content determined.

Pulmonary function: Dry powder inhaler for asthma

Toxic reactions and side effects

Cutaneous flushing
Hypotension
Headache
Visual disturbances
Dyspnea
GI disturbances

Antihistamines Background

Daniel Bovet, Nobel Prize 1944
Synthesized first antihistamines
Compounds appeared to block the pharmacological effects of histamine through their structural similarities

General Mechanism of Action of Antihistamines

Blocks action of histamine at receptor
Competes with histamine for binding
Displaces histamine from receptor
Most beneficial when given early
First Generation H1 Blockers

<table>
<thead>
<tr>
<th>Ethanolamines</th>
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<tbody>
<tr>
<td>diphenhydramine (Benadryl) marked sedation, antiemetic</td>
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<tr>
<td>dimenhydramine (Dramamine) marked sedation, antiemetic</td>
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<tr>
<td>carboxinamine (Clisin) slight to moderate sedation</td>
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<td>doxylamine (Decapryn) OTC “sleep aid”</td>
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<th>Ethylenediamines</th>
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<tr>
<td>tripelennamine (Pyribenzamine) moderate sedation</td>
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<td>pyrilamine (Neo-Antergan) moderate sedation</td>
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<th>Piperazines:</th>
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<tr>
<td>meclizine (Bonine) marked sedation</td>
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<tr>
<td>cyclizine (Marezine) slight sedation, antiemetic</td>
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<td>hydroxyzine (Atarax) marked sedation</td>
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<th>Alkylamines</th>
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<tr>
<td>chlorpheniramine (Chlor-Trimeton) slight sedation</td>
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<tr>
<td>brompheniramine (Dimetane) slight sedation</td>
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<tr>
<th>Phenothiazines</th>
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<tbody>
<tr>
<td>promethazine (Phenergan) slight sedation, antiemetic</td>
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<tr>
<th>Miscellaneous</th>
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<tr>
<td>cyproheptadine (Periactin) moderate sedation, antiserotonin activity</td>
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Second Generation H1 Blockers

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<tr>
<th>Piperidines</th>
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<tr>
<td>fexofenadine (Allegra)</td>
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<td>loratadine (Claritin) long action</td>
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<td>Cetirizine (Zyrtec)</td>
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Histamine vs. Antihistamine

Cardiovascular Effects

**Histamine**
dilation of small blood vessels / increased permeability

**Antihistamine**
prevents dilation / prevents increased permeability

Histamine Decreases Blood Pressure

Histamine vs. Antihistamine:

Smooth Muscle Effects

**Histamine**
Stimulates exocrine glands (salivary, gastric, lacrimal, & bronchial secretions)

**Antihistamine**
prevents: salivary, gastric, lacrimal, & bronchial secretions

Histamine vs. Antihistamine:

Immune Effects

**Histamine**
mast cell release: histamine & other substances released

**Antihistamine**
bind to receptors and prevents histamine from eliciting a response
First Generation Antihistamines (Ethanolamines)

Diphenhydramine HCl (Benadryl®)
Parke Davis (1946)
Currently sold OTC by Pfizer, Inc., Warner -Lambert Consumer Healthcare

First Generation Antihistamines (Phenothiazines)

Promethazine HCl (Phenergan®)
Wyeth (1951)
Available only by prescription

First Generation Antihistamines (Alkylamines)

Chlorpheniramine maleate (Chlor Trimeton®)
Schering (1949)
Currently sold OTC by Schering-Plough Healthcare Products

First Generation Antihistamines

Side Effects
Sedating
Anticholinergic
Many available Over- the- Counter (OTC)
Inexpensive (Average $4.50/pack)
56% of allergy sufferers use OTC, but only $325 million in sales

Second Generation Antihistamines

Generally do not cause the sedation and drying seen in first generation antihistamines
Do not cross the blood-brain barrier as readily as First Generation compounds
Lipophobicity
Large molecular size
Electrostatic charge

Second Generation H1 Blockers

- Alkyl amines
  - Acrivastine (Seprex-D): trade name contains other medications
- Piperazines
  - Cetirizine HCl (Zyrtec)
- Phthalazines
  - Azelastine HCl (Asterlin): nose spray
- Piperidines
  - Fexofenadine (Allegra)
  - Levocabastine HCl (Claritan)
  - Desloratadine (Clarinex)
  - Ebastine (Ebastel)
  - Mizolastine (Mizollen)
Second Generation Antihistamines: (one step backwards)

Non-sedating Terfenadine (Seldane®)
Caused fatal heartbeat irregularities when taken with certain drugs and foods
Ketoconazole, erythromycin, grapefruit juice interfered with drug metabolism increasing the concentration of terfenadine in bloodstream
Removed from the market (1992)

Second Generation Antihistamines: Fexofenadine HCl (Allegra®)
Safe metabolite of Terfenadine
FDA approved on July 25, 1996
Non-sedating (FAA, Air force, Navy approved)
Clinical studies showed no cardiac side effects

Second Generation Antihistamines: Loratadine (Claritin®)
Schering-Plough, Inc. FDA approved 1993
Developed from Azatadine
Non-sedating (FAA, Air force, Navy approved)
No reported cardiac side effects up to 160 mg

Second Generation Antihistamines: Cetirizine (Zyrtec®)
Pfizer, Inc and UCB Pharma Inc.
FDA approved 1995
Metabolite of hydroxyzine
Effective against rash/hives
No reported cardiac side effects
Potential for sedation

Specificity of Selected H1 Blockers

Therapeutic Uses of H1 Blockers
1. Allergic rhinitis, relieves rhinorrhea, sneezing, and itching of eyes and nasal mucosa.
2. Common cold: palliative, dries out the nasal mucosa. Often combined with nasal decongestant and analgesics.
3. Allergic dermatoses: can control itching associated with insect bites.
4. Outpatient procedures for preanesthetic sedation and prevention of nausea and vomiting (Promethazine (Phenergan)). Phenergan also inhibits salivary and bronchial secretions and can be used as a local anesthetic.
5. Antiemetic: prevention or treatment of nausea and vomiting (Bendectin, doxylamine with pyridoxine).
6. Hypnotics: limited value.
7. Other uses:
   a. Reduction of tremors and muscle rigidity in Parkinson's disease
   b. Treatment of migraine headaches
### Non-selective Effects of H<sub>1</sub> Blockers

1. antinausea and antiemetic effects (antimuscarinic effects)
2. antiparkinsonism effects (antimuscarinic effects)
3. local anesthesia, blockade of sodium channels (diphenhydramine and promethazine)

### Mechanism of Action: H<sub>1</sub> Antagonists

Displaces histamine from the H<sub>1</sub> receptor, which is a G-protein coupled receptor.

Histamine leads to formation of IP3 and a release of stored Ca<sup>++</sup>, followed by a cascade of other events.

H<sub>1</sub> receptor blockade prevents this activity and leads to a decrease in Ca<sup>++</sup> inside of the cell.

### Toxic Reactions & Side Effects of H<sub>1</sub> Blockers

1. CNS depression (mainly in first generation agents).
2. Allergic reactions (topical application).
3. Appetite loss, nausea and vomiting, constipation or diarrhea.
4. Insomnia, tremors, nervousness, irritability, tachycardia, dry mouth, blurred vision, urinary retention, constipation or diarrhea.
5. CNS stimulation with hallucinations, motor disturbances (tremors and convulsions), and death.
6. Secreted in breast milk and can cross the placenta.

### Drug Interactions of H<sub>1</sub> Blockers

1. Antihistamines that produce sedation can potentiate CNS depressants (e.g., barbiturates, opiates, general anesthetics, and alcohol).
2. Antihistamines that possess anticholinergic actions can produce manifestations of excessive blockade if given with anticholinergic drugs (e.g., dry mouth, constipation, or blurred vision).
3. Terfenadine (Seldane) taken with grapefruit juice or erythromycin or other drugs that inhibit the enzyme, CYP3A4 can lead to cardiac toxicity. Taken off the market.

### H<sub>2</sub> Receptors in the Stomach

- Histamine is released by enterochromaffin cell (ECL) in the gastric mucosa in response to gastrin.
- Histamine binds to H<sub>2</sub> receptors on the parietal cells and causes HCl secretion.
- H<sub>2</sub> blockers decreases HCl secretion.

### OTC Available H<sub>2</sub> Antagonists

1. cimetidine (Tagamet) associated with most side effects
2. ranitidine (Zantac)
3. famotidine (Pepcid)
4. nizatidine (Axid)
**H₂ Antagonist Pharmacological Effects**

1. Competitive antagonists at the H₂ receptors
2. Inhibits secretory function of gastric mucosa.
3. Few other effects than those on gastric secretion.
4. Reduces gastric acid volume & concentration of pepsin

**Most Common Adverse Effects**

1. Diarrhea
2. Dizziness
3. Somnolence
4. Headache
5. Rash
6. Constipation
7. Vomiting
8. Arthralgia

**H₂ Antagonist Therapeutic Uses**

1. Duodenal ulcer
2. Gastric ulcer
3. Zollinger-Ellison syndrome (a rare disorder that causes ulcers in the stomach and duodenum from excessive gastric pepsin & HCl)
4. Gastroesophageal reflux disease
5. Used prior to surgery in patients with GI obstruction to elevate gastric pH
6. Reflux esophagitis
7. Antacid

**H₂ Antagonists: Mechanisms of Action**

Displaces histamine from the H₂ receptor, a G-protein coupled receptor

Because histamine activates cAMP, H₂ blockers lead to a decrease in cAMP and a concomitant decrease in Ca²⁺

**Toxic Reactions (Mostly Associated With Cimetidine (Tagamet))**

1. Most common (seen in only 1-2% of patients): diarrhea, dizziness, somnolence, headache, and rash. Also constipation, vomiting and arthralgia
2. CNS effects: slurred speech, delirium, confusion. Most commonly seen in older patients or those with liver or kidney impairment
3. Endocrine function (minor and reversible): antiandrogen effects, e.g., loss of libido, impotence, reduced sperm count
4. Blood dyscrasias
5. Liver: reversible cholestasis (impairment of bile flow)

**H₂ Antagonist Drug Interaction**

Cimetidine: increased activity of drugs that are metabolized through cytochrome P450 pathway and also reduces blood flow through the liver including. e.g., warfarin, phenytoin, propanolol, metoprolol, quinidine, caffeine, lidocaine, theophylline, benzodiazepines, ethanol, tricyclic antidepressants, and calcium channel blockers.

All H₂ blockers except famotidine (Pepcid) increase the bioavailability of ethanol. Agents that inhibit gastric secretion alter the bioavailability and rate of absorption of many other drugs.
**Is there a link between H2 blockers and dementia?**


**OBJECTIVES:** To evaluate the association between histamine-2 receptor antagonist (H2A) exposure and incident cognitive impairment in a community-based sample of African Americans.

**DESIGN:** Five-year longitudinal observational study.

**PARTICIPANTS:** A sample of 1,558 community-dwelling African Americans aged 65 and older with no baseline cognitive impairment living in Indianapolis, Indiana.

**RESULTS:** Incident cognitive impairment occurred in 275 (17.7%) participants. After controlling for age, education, baseline cognitive score, the use of anticholinergics, and history of diabetes mellitus and depression, continuous use of H2As was associated with greater risk of incident cognitive impairment than for nonusers (odds ratio 2.42; 95% confidence interval 1.17–5.04).

**CONCLUSION:** H2As might be a risk factor for the development of cognitive impairment in African Americans. This finding requires confirmation from future studies.

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**H3 and H4 Receptor Drugs**

H3 receptors are known to function as feedback inhibitors in a wide variety of organ systems

CNS: agonists cause sedation
antagonists/inverse agonists induce arousal and have beneficial effects on learning and memory
feeding effects mixed (agonists reduced feeding but H3 KO mice exhibited obesity)
GI: agonists down regulate histamine and thus the production of gastrin & HCl

**Preclinical data**
H3 receptor antagonists enhance attention and learning, stimulate arousal, and may have antiepileptic effects

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**H4 receptor antagonists possess anti-inflammatory properties and may be useful to treat allergic rhinitis, asthma and rheumatoid arthritis**

**Clinical Uses:** Presently, H3 and H4 agonists and antagonists are available only for research purposes

**Mechanisms of Action**
G-protein coupled receptor, decreases of intracellular Ca++

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**Inhibitors of Histamine Release**

Cromolyn sodium (Intal, Nasalcrom)
Nedocromil Sodium

**in vitro studies**: Reduces the release of histamine, other granular contents & leukotriene production.
Devoid of bronchodilating capability
Inhibits pulmonary mast cell degranulation in response to a variety of stimuli including the interaction between cell-bound IgE and specific antigen.
Does not relax bronchial or other smooth muscle in vitro or, in the short term, *in vivo*. However, long term administration diminishes bronchial hyperactivity.

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**Histamine Release Inhibitors: Therapeutic Uses**
mild to moderate bronchial asthma to prevent asthma attacks.
effective in children
reduces need of steroid or bronchodilators
ineffective for an acute attack
becomes effective over time (e.g. 2-3 weeks)
alergic rhinitis
atopic diseases of the eye
giant papillary conjunctivitis

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**Histamine Release Inhibitors**

**Dosage form**
aerosol powder (Intal) and solution - asthma
nasal spray (Nasalcrom) - allergic rhinitis
optic solution 4% - (Opticrom) - allergic conjunctivitis

**Toxicity**
well tolerated, few adverse reactions
irritation due to powder inhalation
Stinging, Burning, Bad Taste
Coughing, sneezing, allergic reactions
Learning Objectives

I. Histamines
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II. Know the pharmacological effects, mechanisms of action, therapeutic uses, side-effects & drug interactions:
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      - First generation: diphenhydramine (Benadryl), dimenhydrinate (Dramamine), chlorpheniramine (Chlor-Trimeton), promethazine (Phenergan)
   b) H2 blockers: cimetidine (Tagamet), ranitidine (Zantac), Famotidine (Pepcid), Nizatidine (Axid)
   c) Cromolyn sodium

Practice Questions

1) Which of the following antihistamines is most likely to potentiate the CNS depressant effects of alcohol?
   A. Promethazine (Phenergan)
   B. Loratadine (Claritin)
   C. Rantidine (Zantac)
   D. Chlorpheniramine (Chlor-Trimeton)
   E. none of the above

2) Rantidine (Zantac), an H2 receptor antagonist, is most likely to produce which of the following effects?
   A. inhibition of the "triple effect" of histamine
   B. inhibition of gastric secretions
   C. inhibition of nausea and vomiting
   D. sedation
   E. inhibition of salivary and bronchial secretions

3) Which of the following statements about antihistamines is correct?
   A. antihistamines prevent histamine release
   B. antihistamines produce their effects through competition at the receptor
   C. antihistamines promote histamine degradation
   D. antihistamines prevent histamine synthesis
   E. all of the above statements are correct

4) Which of the following effects is NOT associated with histamine?
   A. triple effect
   B. progressive fall in blood pressure
   C. headache
   D. secretion of catecholamines from chromaffin cells in adrenal medulla
   E. sedation

5) Which of the following drugs would be the best treatment for allergic rhinitis if you operated heavy machinery?
   A. diphenhydramine (Benadryl)
   B. nizatidine (Axid)
   C. promethazine (Phenergan)
   D. fexofenadine (Allegra)
   E. rantidine (Zantac)

6) Nizatidine (Axid) an H2 antagonist, can be effectively used for the control of ______.
   A. itching associated with insect bites
   B. asthma
   C. indigestion
   D. the triple effect
   E. insomnia

7) Antihistamines acting at the ______ receptor are most likely to ________.
   A. H1 receptor; inhibit the "triple effect" of histamine
   B. H2 receptor; inhibit the "triple effect" of histamine
   C. H1 receptor; reverse anaphylaxis
   D. H2 receptor; reverse anaphylaxis
   E. H1 receptor; block gastric secretions

8) Which of the following effects is most commonly associated with histamine?
   A. progressive increase in blood pressure
   B. progressive decrease in blood pressure
   C. decrease in gastric secretions
   D. triple effect
   E. sedation