Pharmacology 659

Histamine and Antihistaminics

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Histamine
Distribution

Mast cells (in tissues)
Basophils (in blood)
Skin
Gastric mucosa
Neurons in CNS
Regenerating or rapidly growing tissues
Mast cells and a basophil
Mast cells can be sensitized to release histamine by environmental allergens such as pollens and animal dander. These allergens are antigens which cause the body to generate antibodies, known as immunoglobulin E or IgE, which attach to the mast cells.
Pollen and mast cell sensitization
Synthesis and Metabolism of Histamine
Decarboxylation of histidine
The diagram illustrates the metabolism of histamine. Histamine undergoes N-methylation by N-Methyltransferase to form N-Methylhistamine. N-Methylhistamine is then metabolized by MAO-B to form N-Methylimidazoleacetic acid. Alternatively, histamine can be oxidized by Diamine Oxidase to Imidazoleacetic acid, which is subsequently ribosylated to form Imidazoleacetic acid riboside. Ribose is used in the ribosylation process.
Histamine Receptors
H₁ Histamine Receptors

Metabotropic G-protein-coupled receptors
Actions of Histamine in the Central Nervous System

Histaminergic neurons that have their cell bodies in the tuberomammillary nucleus of the hypothalamus. These histaminergic neurons of the tuberomammillary nucleus project to the cerebral cortex where they activate H₁ receptors.
Effects of $H_1$ Histamine Receptor Stimulation

Cardiovascular

- vasodilation
- increased vascular permeability
- hypotension
- tachycardia
- flushing
- headache
Effects of $H_1$ Histamine Receptor Stimulation

Pulmonary
bronchoconstriction

Cutaneous
urticaria
pruritus
pain

Other
allergic rhinitis
motion sickness
H₂ Histamine Receptors

Located on parietal cells

Primarily stimulate gastric acid secretion
Location of H$_2$ Receptors

Gastric parietal cells (oxyntic cells)
Vascular smooth muscle
Neutrophils
Central nervous system
Heart
Uterus
Activation of the H₂ receptor results in the following physiological responses:

Stimulation of gastric acid secretion

Smooth muscle relaxation

Vasodilation – phosphokinase A (PKA) activity causes phosphorylation of myosin light-chain kinase, decreasing its activity. The subsequent smooth muscle relaxation leads to vasodilation

Inhibition of antibody synthesis, T-cell proliferation and cytokine production
Diagram - Component regions and cells of body glands

- Mucous columnar cells
- Mucous neck cells
- Parietal cells
- Endocrine cells
- Chief (zymogenic) cells
- Pit
- Lobe
- Neck
- Base
H₃ Histamine Receptors

Found on central nervous system and to a lesser extent peripheral nervous system tissue

Decreased neurotransmitter release: histamine, acetylcholine, norepinephrine, serotonin
Tissue distribution of H₃ receptors

Central nervous system
Peripheral nervous system
Heart
Lungs
Gastrointestinal tract
Endothelial cells
H₄ Histamine Receptors

Found primarily in the basophils and in the bone marrow. They are also found in the thymus, small intestine, spleen, and colon

Play a role in chemotaxis
Histamine Receptor Antagonists
H₁- and H₂ receptor antagonists compete with histamine for histamine receptor sites.

However, these are not typical competitive antagonists.

These receptor sites possess constitutive activity and the antagonists actually act as inverse agonists.
Inverse agonist

An inverse agonist is an agent which binds to the same receptor binding-site as an agonist for that receptor and reverses constitutive activity of receptors. Inverse agonists exert an effect that is opposite to that of a receptor agonist. Inverse agonists are effective against certain types of receptors (e.g. certain histamine receptors and GABA receptors which have intrinsic activity without the action of a ligand upon them (also referred to as 'constitutive activity').)
Constitutive activity

A receptor, which is capable of producing its biological response in the absence of a bound ligand, is said to display constitutive activity. The constitutive activity of receptors may be reversed by inverse agonist binding. Mutations in receptors that result in increased constitutive activity appear to underlie some inherited diseases, such as precocious puberty (due to mutations in luteinizing hormone receptors) and hyperthyroidism (due to mutations in thyroid-stimulating hormone receptors).
H₁-antihistamines are clinically used in the treatment of histamine-mediated allergic conditions. Specifically, these indications might include:

- Allergic rhinitis
- Allergic conjunctivitis
- Allergic dermatological conditions (contact dermatitis)
- Urticaria
- Angioedema
- Diarrhea
- Pruritus (atopic dermatitis, insect bites)
- Anaphylactic or anaphylactoid reactions—adjunct only
- Nausea and vomiting (first-generation H₁-antihistamines)
- Sedation (first-generation H₁-antihistamines)
First Generation H₁-Histamine Receptor Antagonists
(non-selective, classical)

These are the oldest H₁-antihistaminergic drugs and are relatively inexpensive and widely available. They are effective in the relief of allergic symptoms, but are moderately to highly-potent muscarinic receptor-antagonists as well. These agents also commonly have actions at α-adrenergic receptors and/or 5-HT receptors. This lack of receptor-selectivity is the basis of the poor tolerability-profile of some of these agents, especially compared with the second-generation H₁-antihistamines. Patient response and occurrence of adverse drug reactions vary greatly between classes and between agents within classes.
Some First Generation H₁-Histamine Receptor Antagonists

Diphenhydramine (Benadryl Allergy®, Nytol®, Sominex®)
Brompheniramine (Dimetapp Cold & Allergy Elixir®, Robitussin Allergy & Cough Liquid®)
Chlorpheniramine (Singlet®)
Dimenhydrinate (Dramamine Original®)
Doxylamine (Vicks NyQuil®, Alka-Seltzer Plus Night-Time Cold Medicine®)
Adverse drug reactions are most commonly associated with the first-generation H₁-antihistamines are due to their relative lack of selectivity for the H₁-receptor.

The most common adverse effect is sedation; this "side-effect" is utilized in many OTC sleeping-aid preparations.

Other common adverse effects in first-generation H₁-antihistamines include dizziness, tinnitus, blurred vision, euphoria, incoordination, anxiety, insomnia, tremor, nausea and vomiting, constipation, diarrhea, dry mouth, and dry cough.

Infrequent adverse effects include urinary retention, palpitations, hypotension, headache, hallucination, and psychosis.
Second Generation H₁-Histamine Receptor Antagonists

Second generation H₁-antihistamines are newer drugs that are much more selective for peripheral H₁ receptors in preference to the central nervous system histaminergic and cholinergic receptors. This selectivity significantly reduces the occurrence of adverse drug reactions compared with first-generation agents, while still providing effective relief of allergic conditions.

The most common adverse effects noted for second-generation agents include drowsiness, fatigue, headache, nausea and dry mouth.
Some Second Generation H₁-Histamine Receptor Antagonists

- Acrivastine (Semprex-D® with pseudoepherine)
- Cetirizine (Zyrtec®)
- Loratadine (Claritin®)
- Mizolastine (Mizollen®, Mistamine®)

Topical:

- Azelastine (Astelin®, nasal spray)
- Levocabastine (Livostin®, eye drop)
- Olopatadine (Patanol®, eye drop)
Third Generation H$_1$-Histamine Receptor Antagonists

Third-generation H$_1$--antihistamines are the active enantiomer (levocetirizine) or metabolite (desloratadine and fexofenadine) derivatives of second-generation drugs intended to have increased efficacy with fewer adverse drug reactions. Indeed, fexofenadine is associated with a decreased risk of cardiac arrhythmia compared to terfenadine. However, there is little evidence for any advantage of levocetirizine or desloratadine, compared to cetirizine or loratadine, respectively.
Some Third Generation H$_1$-Histamine Receptor Antagonists

- Levocetirizine (XYXAL®)
- Desloratadine (Clarinex®)
- Fexofenadine (Allegra®)
H₂-Receptor Antagonists

The H₂-receptor antagonists are competitive antagonists of histamine at the parietal cell H₂ receptor. They suppress the normal secretion of acid by parietal cells and the meal-stimulated secretion of acid. They accomplish this by two mechanisms: Histamine released by enterochromaffin-like cells (ECL) in the stomach is blocked from binding on parietal cell H₂ receptors, which stimulate acid secretion; therefore, other substances that promote acid secretion (such as gastrin and acetylcholine) have a reduced effect on parietal cells when the H₂ receptors are blocked.

Like the H₁-antihistamines, the H₂ antagonists are inverse agonists rather than true receptor antagonists.
H₂-antagonists are clinically used in the treatment of acid-related gastrointestinal conditions. Specifically, these indications may include:

- Peptic ulcer disease (PUD)
- Gastroesophageal reflux disease (GERD/GORD)
- Dyspepsia

Some studies suggest that H₂-antagonists might be effective in treating herpes viruses, such as shingles and herpes simplex.
**H₂ Histamine Receptor Antagonists**

H₂ antagonists are used to reduce the secretion of gastric acid, treating gastrointestinal conditions including peptic ulcers and gastroesophageal reflux disease.

- Cimetidine (Tagamet®)
- Famotidine (Pepcid®)
- Ranitidine (Zantac®)
- Nizatidine (Axid®)
- Roxatidine (Roxit®)
- Lafutidine
H₂ Histamine Receptor Antagonists

H₂ antagonists are generally well-tolerated, except for cimetidine which produces the following adverse drug reactions: hypotension, headache, tiredness, dizziness, confusion, diarrhea, constipation, and rash. In males cimetidine can cause gynecomastia, loss of libido, and impotence, which are reversible upon discontinuation.

In one study of elderly African Americans, long-term use of H₂ blockers appeared to increase the risk of cognitive decline.
Metabolism of H₂ Histamine Receptor Antagonists
H₃ Histamine Receptor Antagonists

H₃ antagonists are experimental drugs that have a stimulant and nootropic effect. They are being investigated for the treatment of conditions such as ADHD, Alzheimer's Disease, and schizophrenia.

A-349,821
ABT-239
Ciproxifan
Clobenpropit
Thioperamide
H₃ receptors are primarily found in the brain and are inhibitory autoreceptors located on histaminergic nerve terminals, which modulate the release of histamine.

Histamine release in the brain triggers secondary release of excitatory neurotransmitters such as glutamate and acetylcholine via stimulation of H₁ receptors in the cerebral cortex. Consequently unlike the H₁ antagonist antihistamines which are sedating, H₃ antagonists have stimulant and nootropic effects, and are being researched as potential drugs for the treatment of neurodegenerative conditions such as Alzheimer's disease.
H₄ Histamine Receptor Antagonists

H₄ antagonists appear to have an immunomodulatory role and are being investigated as antiinflammatory and analgesic drugs.

Thioperamide
JNJ 7777120
VUF-6002
Inhibitors of histamine release

These agents (mast cell stabilizers) appear to stabilize the mast cells to prevent degranulation and mediator release. Although this is an unlikely method of action.

Examples:

Cromoglicate (cromolyn)
Nedocromil
Many drugs, used for other indications, possess unwanted antihistaminergic activity.

Large doses of vitamin C are known to alleviate shock by inhibiting deaminizing proteins that release histamine.