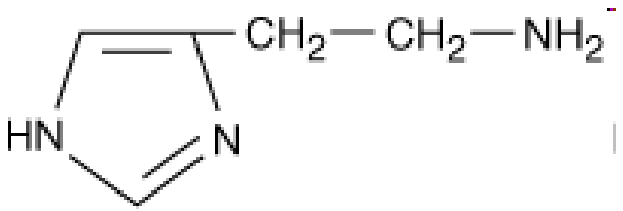
Module: Autacoids
Subject: Pharmacology
Lecture:



Histamine

Autacoids-Histamine & Antihistamines-1 & 2

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Autacoids-Overview

- Histamine, serotonin, prostaglandins, & some vasoactive peptides belong to a group of compounds called autacoids
- They all have the common feature of being formed by the tissues on which they act; thus, they function as local hormones
- The word autacoid comes from the Greek:
  - autos (self) &
  - akos(medicinal agent, or remedy)
- The autacoids also differ from circulating hormones in that they are produced by many tissues rather than in specific endocrine glands

Histamine-Pharmacology

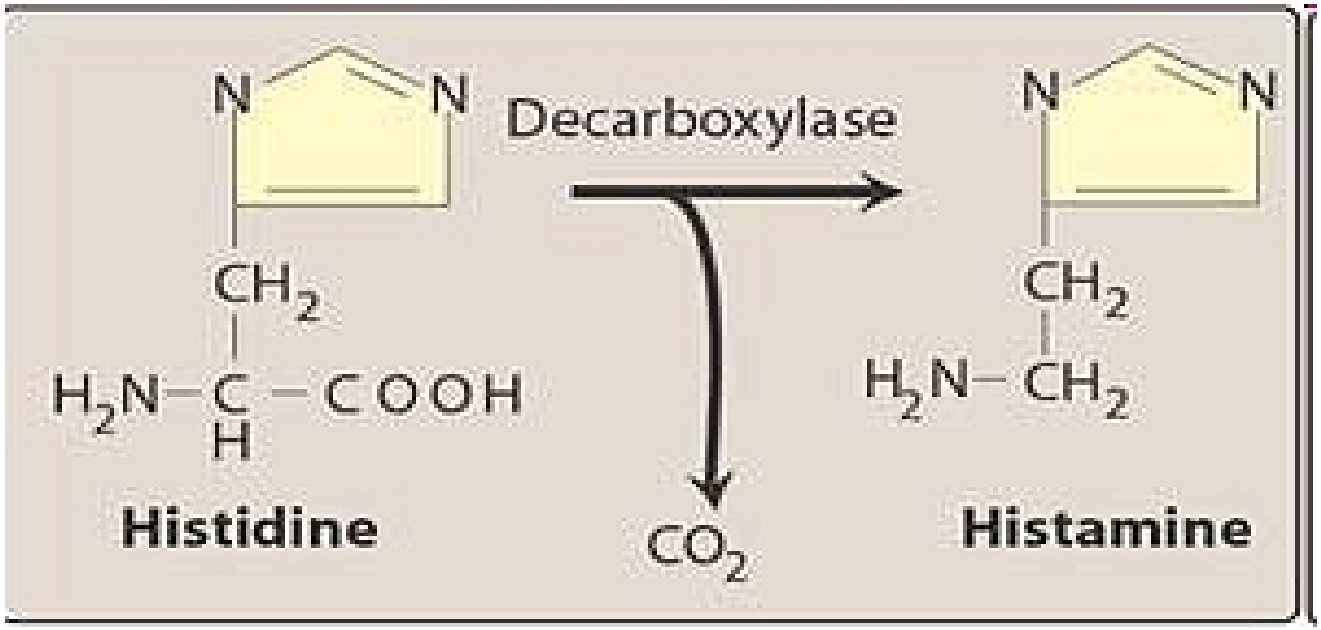
- First autacoid to be discovered
- Synthesized in 1907
- Demonstrated to be a natural constituent of mammalian tissues(1927)
- Involved in inflammatory & anaphylactic reactions
- Local application causes redness, swelling, & edema mimicking a mild inflammatory reaction
- Large systemic doses leads to profound vascular changes similar to those seen after shock or anaphylaxis

Histamine-Pharmacology(contd.)

- Histamine is a chemical messenger that mediates a wide range of cellular responses, including:
  - Allergic and inflammatory reactions
  - Gastric acid secretion, &
  - 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

Histamine-Biosynthesis

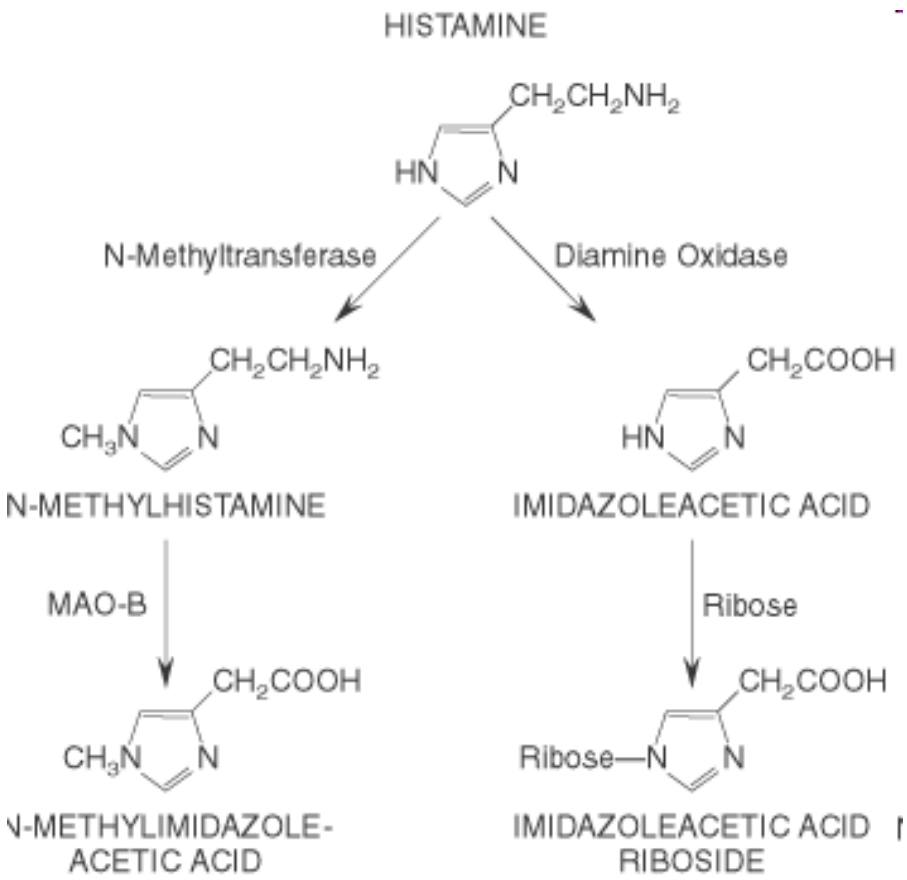
- Histamine occurs in plants as well as in animal tissues & is a component of some venoms & stinging secretions
- Biosynthesized in mammalian tissues
- Decarboxylation of the amino acid L-Histidine yields Histamine



Histamine-Storage

- In mast cells, histamine(positively charged) is held by an acidic protein and heparin(negatively charged) within intracellular granules
- Stored in complex with:
  - Heparin
  - Chondroitin sulphate
  - Eosinophilic Chemotactic Factor
  - Neutrophilic Chemotactic Factor
  - Proteases

Histamine-Degradation



- Degraded rapidly by oxidation to imidazole acetic acid
- Degraded rapidly by methylation to N-methyl histamine
- Very little histamine is excreted unchanged

Histamine-Conditions causing Release

- Tissue Injury
- Allergic Reactions
- Drugs & other foreign compounds

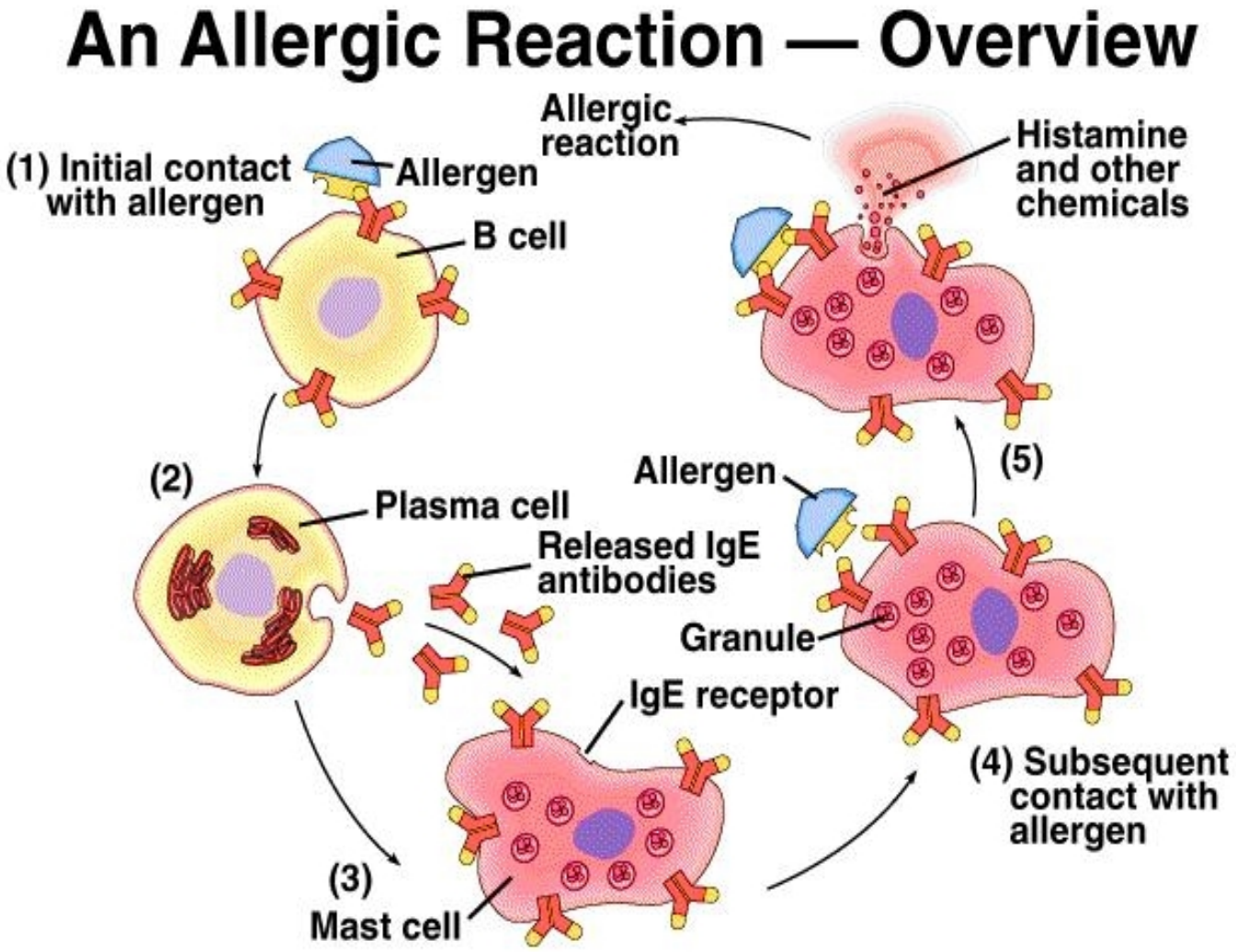
Histamine-Conditions causing Release

- Tissue Injury
  - Any physical(mechanical) 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
  - Chemical and mechanical mast cell injury causes degranulation & histamine release
  - **Compound 48/80,** an experimental drug, selectively releases histamine from tissue mast cells by an exocytotic degranulation process requiring energy & calcium

Histamine-Conditions causing Release

- 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, mast cells will degranulate when exposed to the appropriate antigen & release histamine, ATP and other mediators

Histamine & Allergic Reaction



Histamine-Conditions causing Release(contd.)

- Drugs & other foreign compounds:
  - Morphine/Dextran/Antimalarial drugs/Dyes/Antibiotic bases/Alkaloids/Amides/Quaternary ammonium compounds/Enzymes(PL-C)/Penicillins/Tetracyclines/ Basic drugs(Amides/Amidines/Diamidines)/Toxins/ Venoms/Proteolytic enzymes/Bradykin/Kallidin & Substance P
  - Displace histamine from its bound form within cells
  - This type of release does not require energy and is not associated with mast cell injury or degranulation

Histamine-Receptors

- 4 Types of Histamine Receptors(all GPCR's):
  - H1 receptors:
    - Mediate effects on smooth muscle leading to vasodilation (relaxation of vascular smooth muscle), increased permeability & contraction of non-vascular smooth muscle
  - H2 receptors:
    - Mediate histamine stimulation of gastric acid secretion & may be involved in cardiac stimulation
  - H3 receptors:
    - Feedback inhibition in CNS, GIT, Lungs & Heart
  - H4 receptors:
    - Eosinophils, Neutrophils & CD4 T-cells

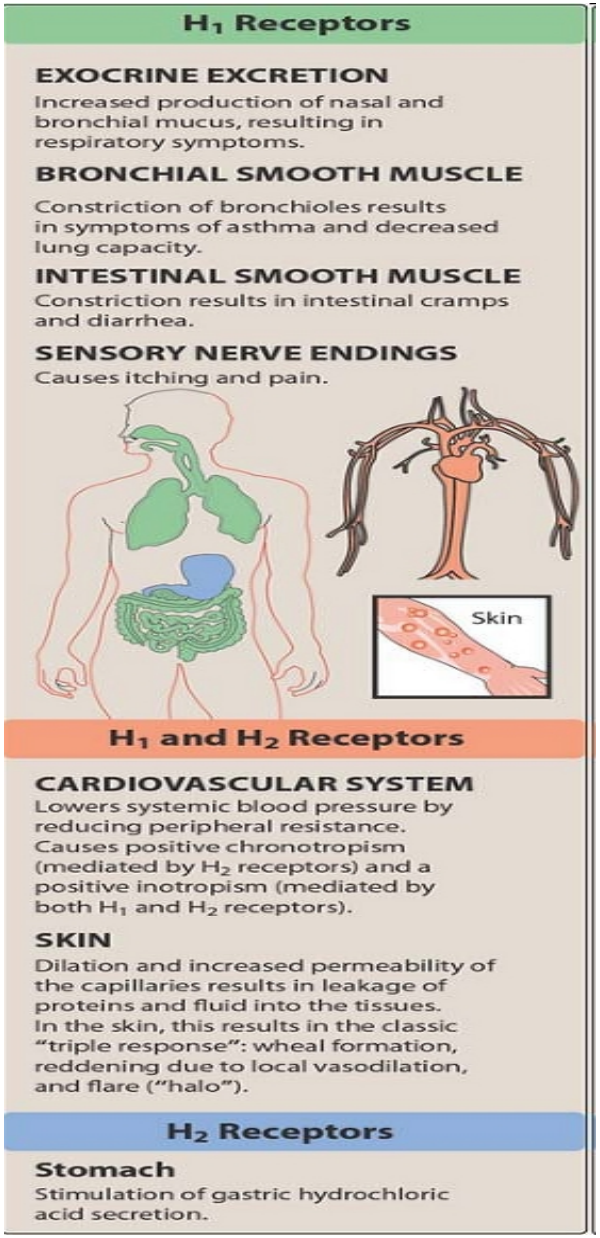
Histamine-Receptor Subtypes

Receptor	Mechanism	Function	Antagonists
H1	Gq, ↑ IP3 & DAG	■Ileum contraction ■Modulate circadian cycle ■Itching ■Systemic vasodilatation ■Bronchoconstriction	Diphenhydramine/Loratadine/Cetirizine/ Fexofenadine
H2	Gs, ↑cAMP, ↑Ca2+	■Speed up sinus rhythm ■Stimulation of gastric secretion ■Smooth muscle relaxation ■Inhibit antibody synthesis, T-cell proliferation & cytokine production	Cimetidine/ Ranitidine/ Famotidine/ Nizatidine

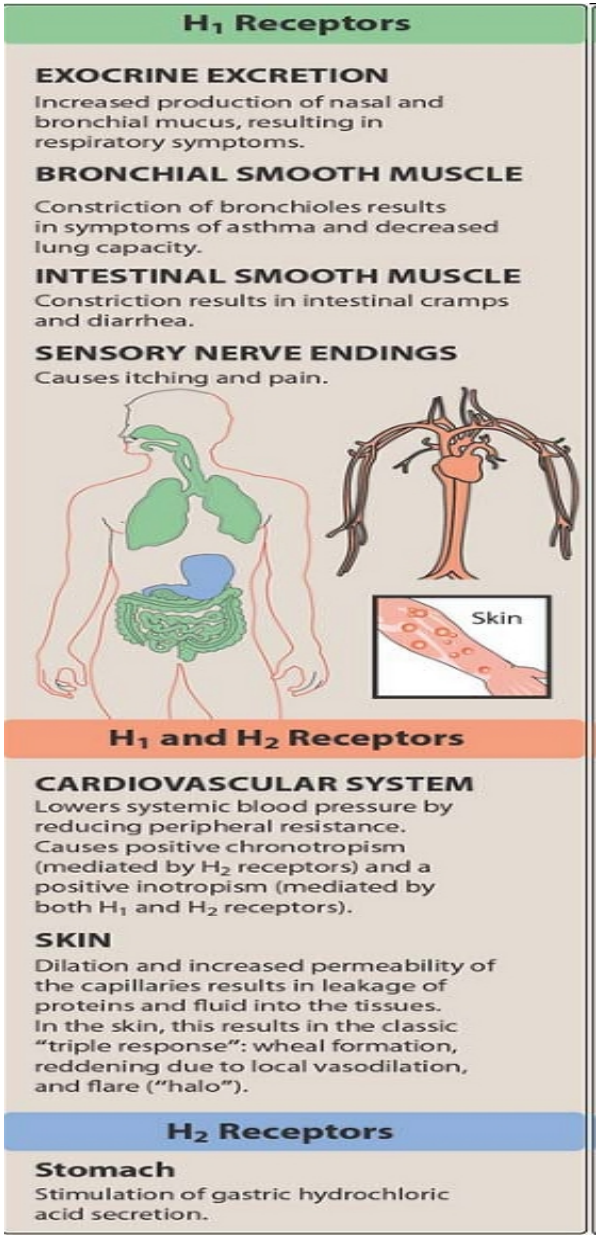
Histamine-Receptor Subtypes

Receptor	Mechanism	Function	Antagonists
H3	Gi, ↓cAMP	■Decrease Acetylcholine, Serotonin and Norepinephrine neurotransmitter release in the CNS ■Presynaptic autoreceptors	ABT-239/ Ciproxifan/ Clobenpropit/T hioperamide
H4	Gi, ↓cAMP	■Mediate mast cell chemotaxis	Thioperamide/ JNJ 7777120

Histamine-Pharmacological Actions(H1)



- Exocrine Excretion(H1)
  - ↑ Production of nasal + bronchial mucus
- Bronchial Smooth Muscle(H1)
  - Bronchiolar constriction
  - Asthmatic symptoms
  - ↓ Lung capacity
- Intestinal Smooth Muscle(H1)
  - Contraction ⟶ Intestinal cramps & diarrhea
- Sensory Nerve Endings(H1)
  - Itching & pain

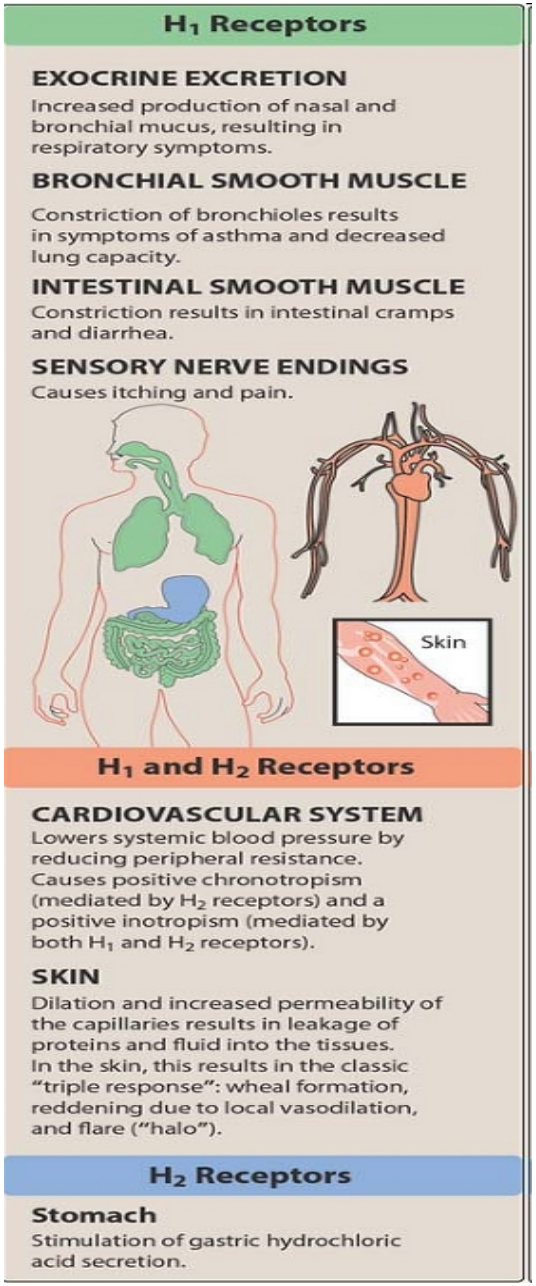


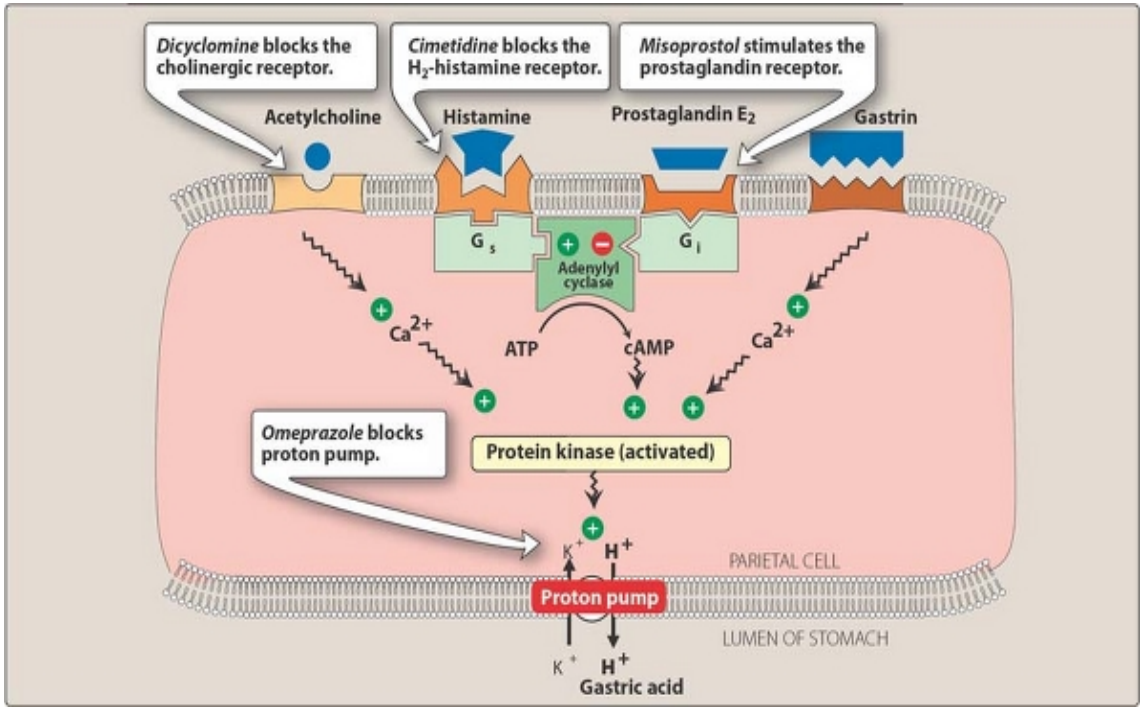
Histamine-Pharmacological Actions(H1&2)

- Cardiovascular System(H1&2)
  - ↓ Peripheral resistance →↓Systemic BP
  - +ve chronotropism(H2)
  - +ve inotropism
- Skin(H1&2)
  - Dilatation & ↑ permeability of the venules
  - Leakage of fluid + proteins into the tissues
  - Classic "triple-response"(wheal formation+ reddening due to local VD(<1-2 min)+ flare(halo)

Histamine-Pharmacological Actions(H2)

- Stomach(H2)
  - ↑ Gastric HCl secretion

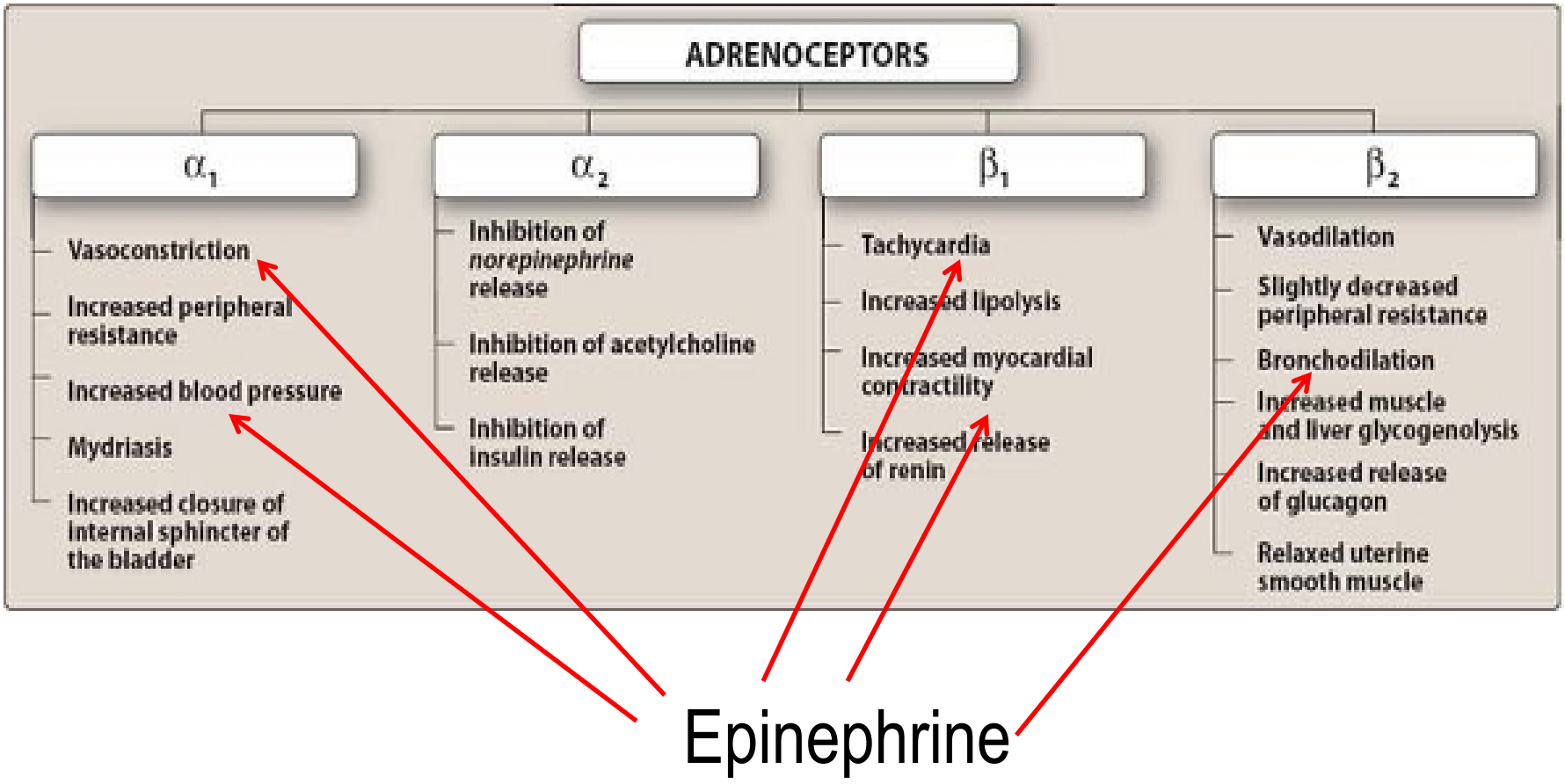




Histamine Antagonists

- The effects of histamine released in the body can be reduced in several ways
- **Physiologic antagonists,** especially epinephrine, have smooth muscle actions opposite to those of histamine, by acting at different receptors
- This is important clinically because injection of epinephrine can be lifesaving in systemic **anaphylaxis**/other conditions in which massive release of histamine(and other more important mediators)occurs

Adrenoceptor Agonists(Sympathomimetics)- Major Effects Mediated By Alpha & Beta Adrenoceptors for Epinephrine in the Management of Anaphylaxis



Adrenoceptor Agonists(Sympathomimetics)- Use of Epinephrine in Anaphylaxis

- Anaphylaxis
  - Epinephrine is the drug of choice for the immediate treatment of anaphylactic shock
  - It is an effective physiologic antagonist of many of the mediators of anaphylaxis
  - Epinephrine is sometimes supplemented with antihistamines and corticosteroids, but these agents are neither as efficacious as epinephrine nor as rapid acting

Histamine Antagonists-Release Inhibitors

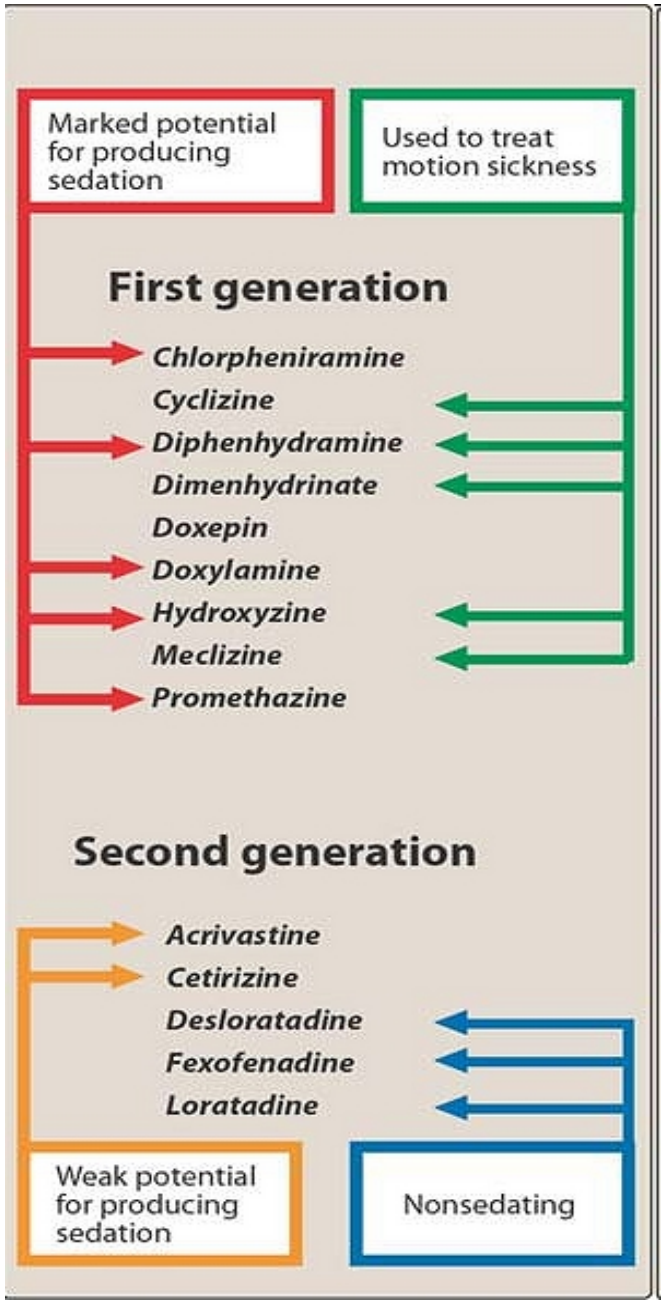
- **Release inhibitors** reduce the degranulation of mast cells that results from immunologic triggering by antigen -IgE interaction
- **Cromolyn** and **nedocromil** appear to have this effect and have been used in the treatment of asthma, although the molecular mechanism underlying their action is not fully understood
- Beta2-adrenoceptor agonists also appear capable of reducing histamine release

Histamine Release Inhibitors- Therapeutic Uses

- Mild to moderate bronchial asthma
  - To prevent acute attacks
  - Effective in children
  - Reduces need of steroids or bronchodilators
  - Ineffective for an acute attack
  - Becomes effective over time(e.g., 2-3 weeks)
- Allergic rhinitis
- Atopic diseases of the eye
- Giant papillary conjunctivitis

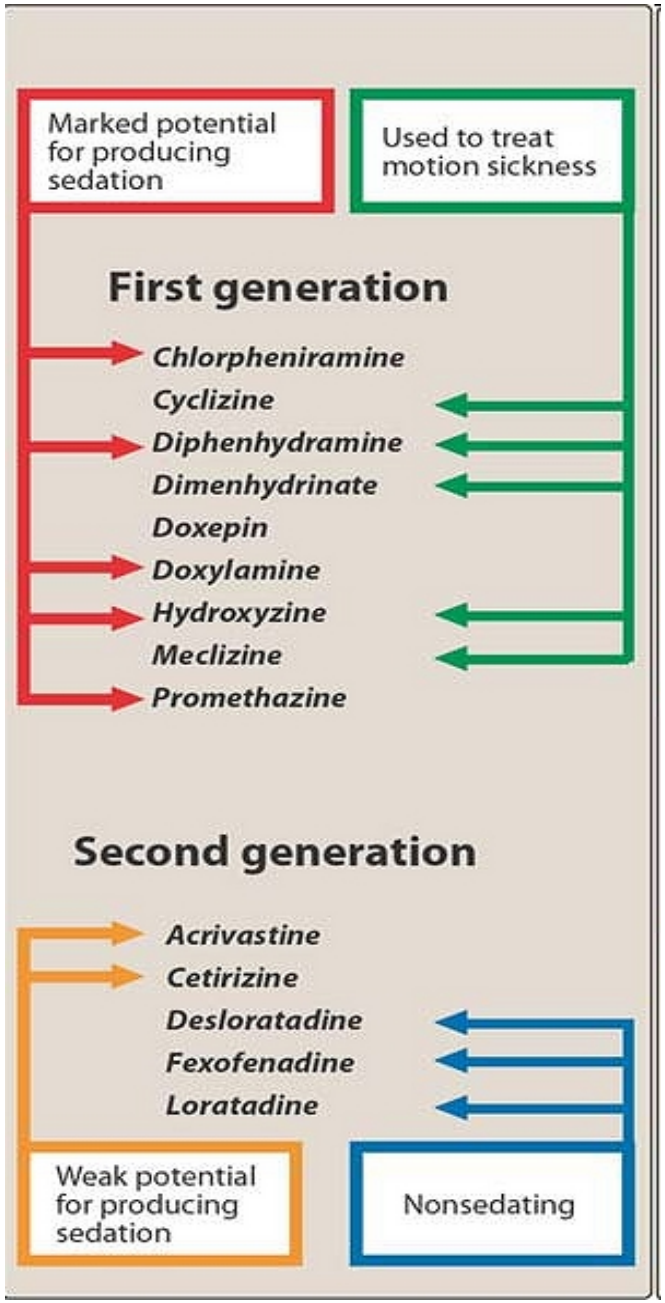
H1 Antihistamines-Overview

- The term antihistamine, refers to the classic H1-receptor blockers
- These compounds do not influence the formation or release of histamine; rather, they block the receptor-mediated response of a target tissue
- This contrasts with the action of cromolyn & nedocromil, which inhibit the release of histamine from mast cells and are useful in the treatment of asthma



H1 Antihistamines-2 Generations

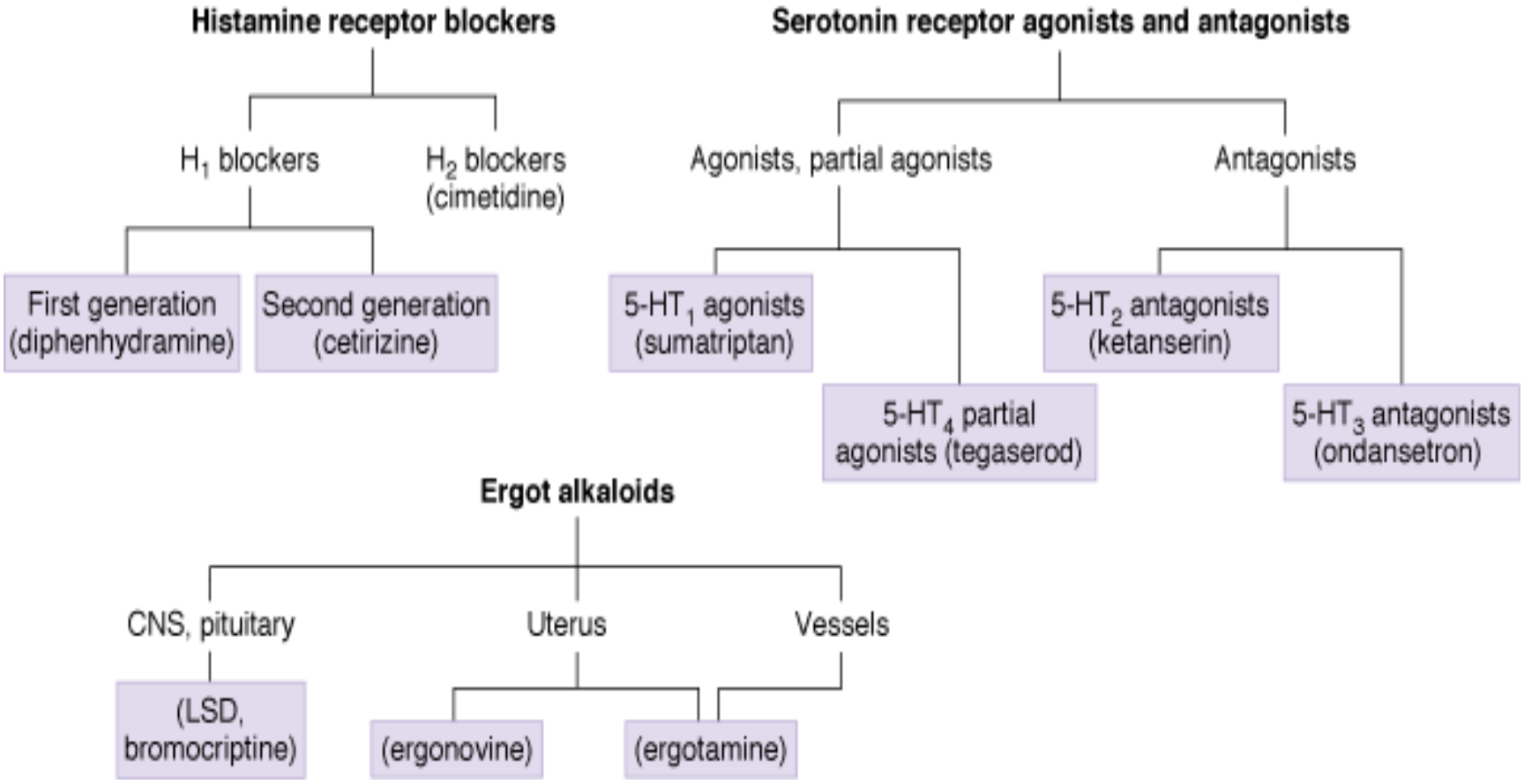
- The H1-receptor blockers can be divided into first- & second-generation drugs
- The older first-generation drugs are still widely used because they are effective and inexpensive
- However, most of these drugs penetrate the CNS and cause sedation



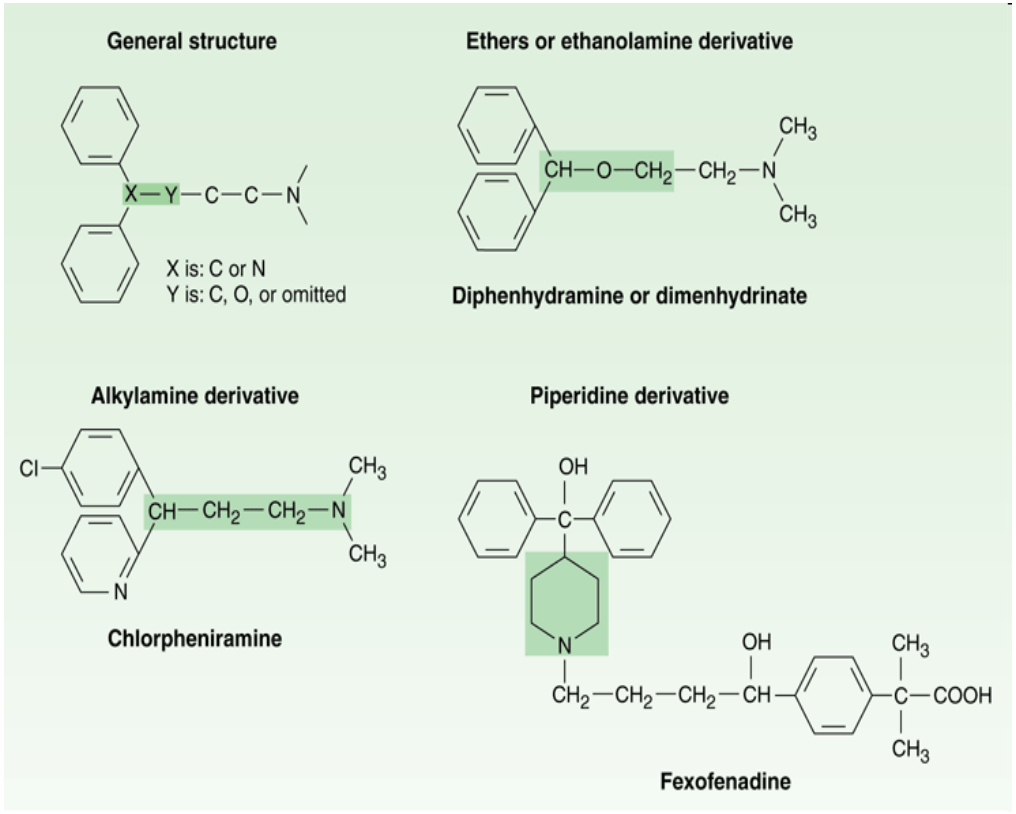
H1 Antihistamines-2 Generations

- By contrast, the second-generation agents are specific for H1 receptors
- Because they do not penetrate the blood-brain barrier, they show less CNS toxicity than the first-generation drugs
- Among these agents loratadine/ desloratadine/fexofenadine produce the least sedation

Histamine Receptor Blockers- Classification

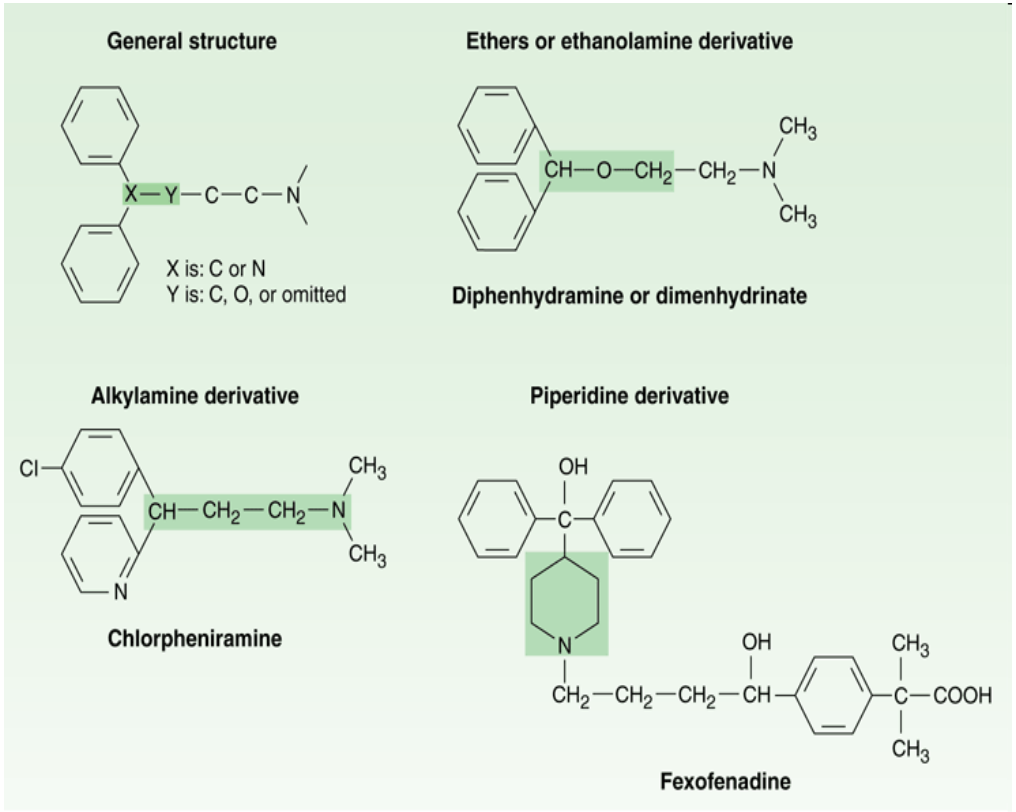


General Structure of H1 Antagonist Drugs & examples of the Major Subgroups



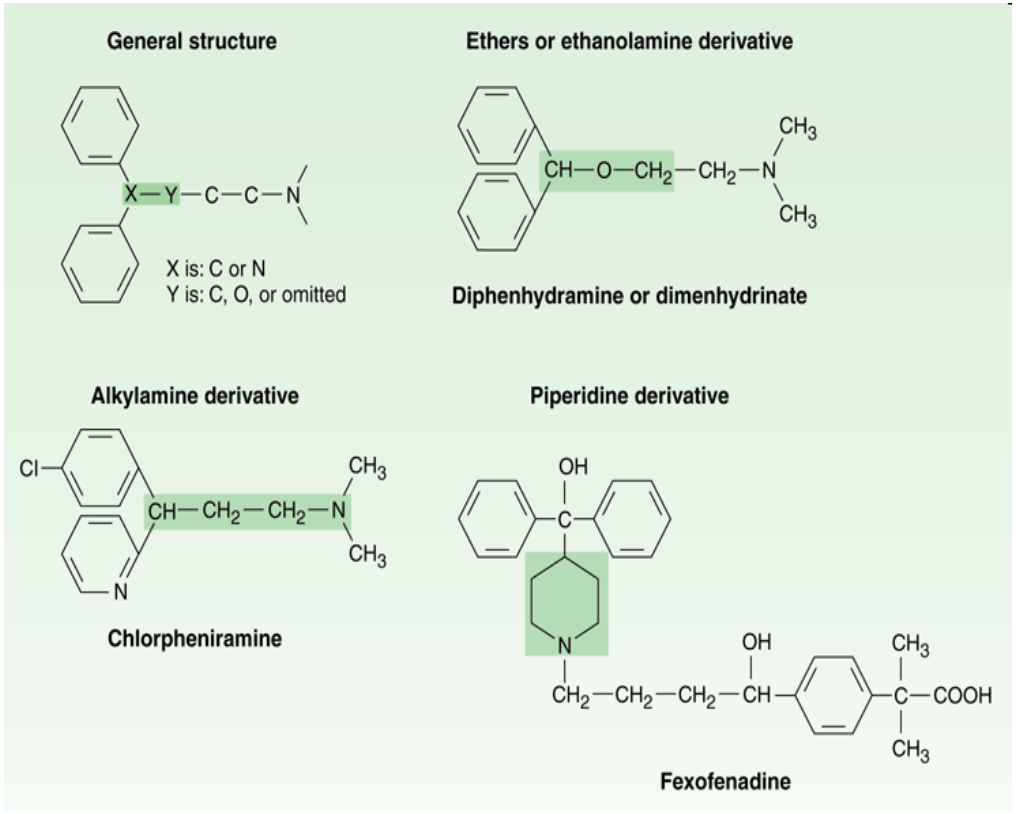
- First Generation
  - Alkylamines
    - Pheniramine/Chlorpheniramine/Dexchlorpheniramine/Brompheniramine/Triprolidine
  - Ethanolamines
    - Carbinoxamine/ Clemastine/ Diphenhydramine/ Dimenhydrinate/ Doxylamine

General Structure of H1 Antagonist Drugs & examples of the Major Subgroups



- First Generation(contd.)
  - Ethylenediamines
    - Antazoline/Mepyramine (Pyrilamine)
  - Piperazines
    - Cyclizine/Chlorcyclizine /Hydroxyzine/Meclizine
  - Tricyclics
    - Alimemazine(Trimepra zine)/Azatadine/ Cyproheptadine/ Ketotifen/Promethazine

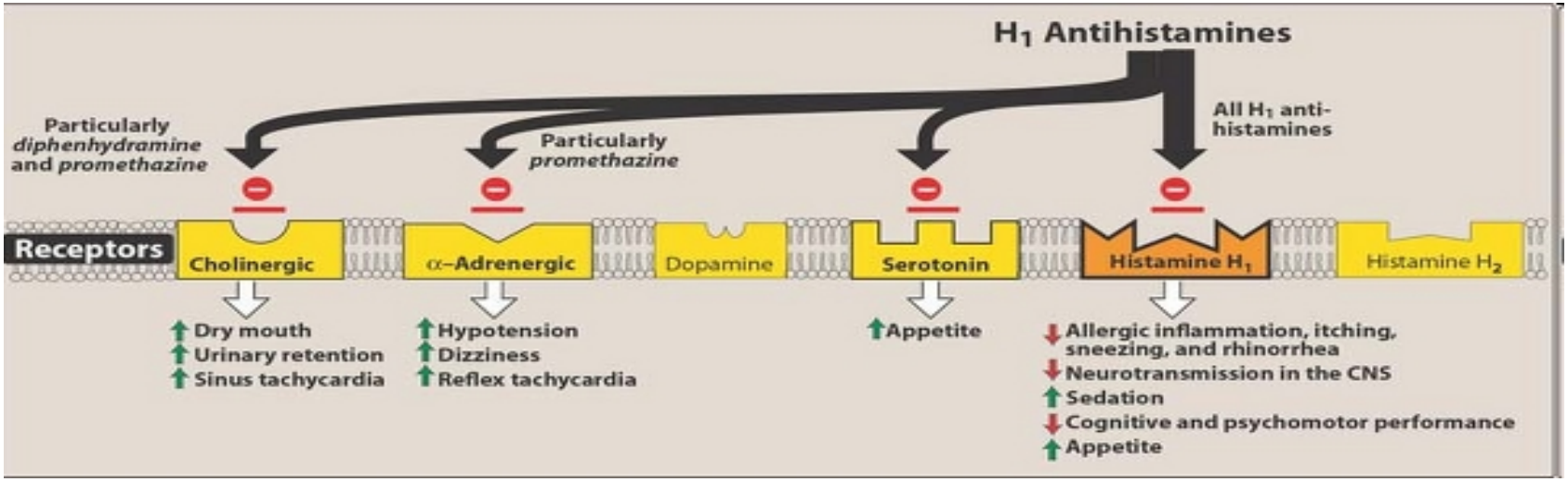
General Structure of H1 Antagonist Drugs & examples of the Major Subgroups



- Second Generation
  - Acrivastine(modification of Triprolidine)
  - Azelastine
  - Cetirizine(Piperazine)
  - Desloratadine(Piperidine)
  - Fexofenadine(Piperidine)
  - Loratadine(Piperidine)
  - Levocabastine

Antihistamines-Mechanism of Action(PD)

- **Actions**
  - The action of all the H1-receptor blockers is qualitatively similar(block action of histamine at H1 receptors)
  - However, most of these blockers have additional effects unrelated to their blocking of H1 receptors
  - These effects probably reflect binding of the H1 antagonists to cholinergic, adrenergic, or serotonin receptors



Antihistamines-Mechanism of Action(PD)

- **Sedation**
  - A common effect of first-generation H1 antagonists is sedation, but the intensity of this effect varies among chemical subgroups
  - Second-generation H1 antagonists have little or no sedative or stimulant actions
  - These drugs (or their active metabolites) also have far fewer autonomic effects than the first-generation antihistamines

Antihistamines-Mechanism of Action(PD)

- **Antinausea and Antiemetic Actions**
  - Several first- generation H1 antagonists have significant activity in preventing motion sickness
  - They are less effective against an episode of motion sickness already present

Antihistamines-Mechanism of Action(PD)

- **Antiparkinsonian Effects**
  - H1 antagonists, especially diphenhydramine, have significant acute suppressant effects on the EPS associated with certain antipsychotic drugs
  - Given parenterally for acute dystonic reactions to antipsychotics

Antihistamines-Mechanism of Action(PD)

- **Anticholinoceptor Actions**
  - First-generation agents, especially those of ethanolamine and ethylenediamine subgroups, have significant atropine-like effects on peripheral muscarinic receptors
  - Benefits reported for nonallergic rhinorrhea
  - May also cause urinary retention and blurred vision

Antihistamines-Mechanism of Action(PD)

- **Adrenoceptor-Blocking Actions**
  - Alpha-receptor blocking effects demonstrable for many H1 antagonists, especially phenothiazine subgroup, e.g., **promethazine**
  - This action may cause orthostatic hypotension in susceptible individuals

Antihistamines-Mechanism of Action(PD)

- **Serotonin-Blocking Action**
  - Strong blocking effects at serotonin receptors have been demonstrated for some first-generation H1 antagonists, notably **cyproheptadine**
  - Its structure resembles that of the phenothiazine antihistamines, and it is a potent H1-blocking agent

Antihistamines-Mechanism of Action(PD)

- **Local Anesthesia**
  - Several first-generation H1 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

Antihistamines-PK

- Absorption
  - These agents are rapidly absorbed after oral administration
  - Peak blood concentrations occur in 1–2 hours
- Distribution
  - Widely distributed throughout the body
  - First-generation drugs enter CNS readily
- Biotransformation(Metabolism)
  - Some of them are extensively metabolized, primarily by microsomal systems in the liver
  - Several of the second-generation agents are metabolized by the CYP3A4 system and thus are subject to important interactions when other drugs(such as ketoconazole) inhibit this subtype of P450 enzymes

Antihistamines-PK(contd.)

- The newer agents are considerably less lipid-soluble than the first-generation drugs and are substrates of the P-glycoprotein transporter in the blood-brain barrier
- As a result they enter the CNS with difficulty or not at all
- Many H1 antagonists have active metabolites

Antihistamines-PK(contd.)

Parent Drug	Active Metabolite	Available as Drug
Hydroxyzine	Cetirizine	Yes
Loratadine	Desloratadine	Yes
Terfenadine	Fexofenadine	Yes

- Elimination
  - Cetirizine is excreted largely unchanged in the urine, &
  - Fexofenadine is excreted largely unchanged in the feces

Antihistamines-Therapeutic Uses

- **Allergic and inflammatory conditions**
- H1-receptor blockers useful in treating allergies caused by antigens acting on immunoglobulin E antibody–sensitized mast cells
- Antihistamines are the drugs of choice in controlling the symptoms of allergic rhinitis and urticaria, because histamine is the principal mediator
- However, the H1-receptor blockers are ineffective in treating bronchial asthma, because histamine is only one of several mediators of that condition(LTs are the main mediators)

Antihistamines-Therapeutic Uses

- **Motion sickness/Nausea:**
- Along with the antimuscarinic agent scopolamine, certain H1-receptor blockers, such as diphenhydramine, dimenhydrinate, cyclizine, meclizine, and hydroxyzine, are the most effective agents for prevention of the symptoms of motion sickness
- Prevent or diminish vomiting and nausea mediated by both the chemoreceptor and vestibular pathways
- The antiemetic action of these medications seems to be due to their blockade of central H1 + muscarinic receptors

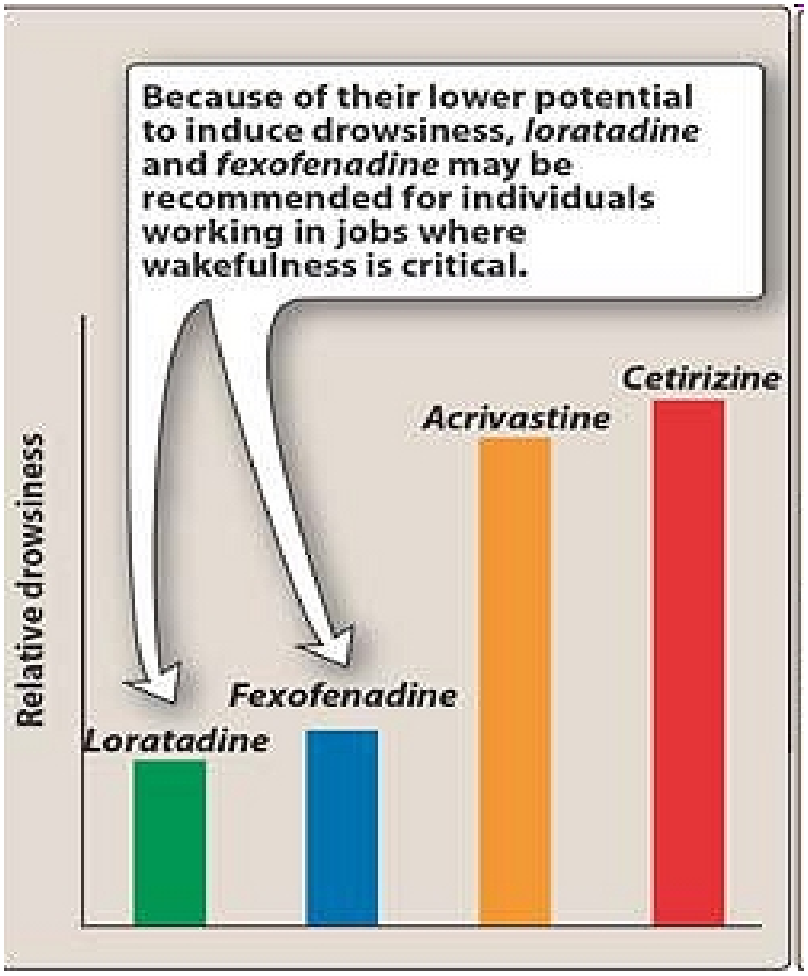
Antihistamines-Therapeutic Uses

- **Somnifacients:**
- Although they are not the medication of choice, many first-generation antihistamines, such as diphenhydramine and doxylamine, have strong sedative properties and are used in the treatment of insomnia
- The use of first-generation H1 antihistamines is contraindicated in the treatment of individuals working in jobs where wakefulness is critical

Antihistamines-Therapeutic Uses

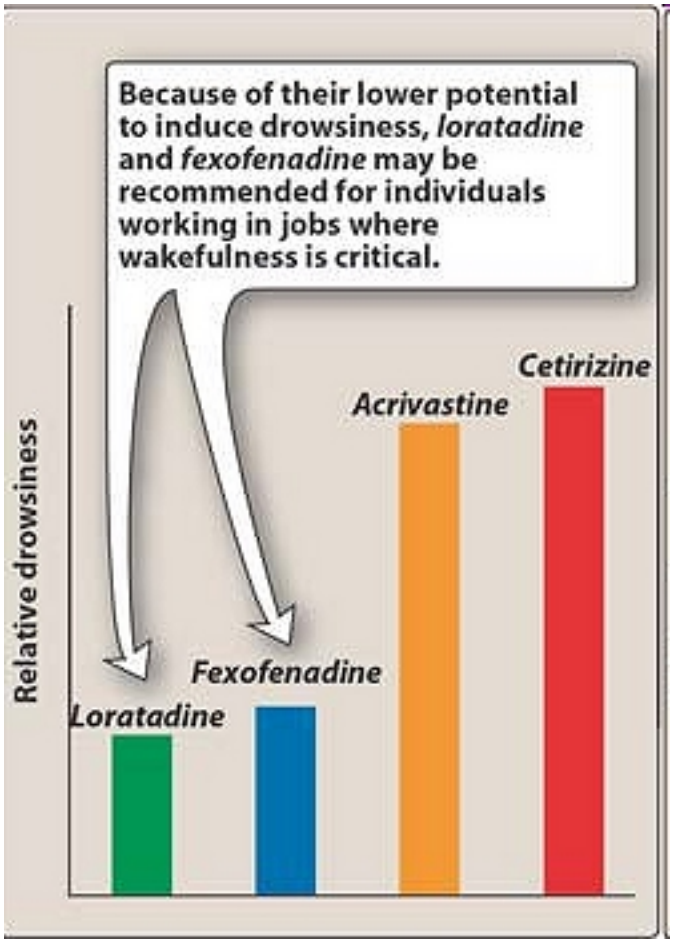
- **Nausea and Vomiting of Pregnancy:**
- Several H1-antagonist drugs have been studied for possible use in treating "morning sickness"
- The piperazine derivatives were withdrawn from such use when it was demonstrated that they have teratogenic effects in rodents

Antihistamines-Adverse Effects & Toxicity



- **Sedation:**
  - First-generation H1 antihistamines, such as chlorpheniramine, diphenhydramine, hydroxyzine, and promethazine, bind to H1 receptors and block the neurotransmitter effect of histamine in the CNS
  - The most frequently observed adverse reaction is sedation

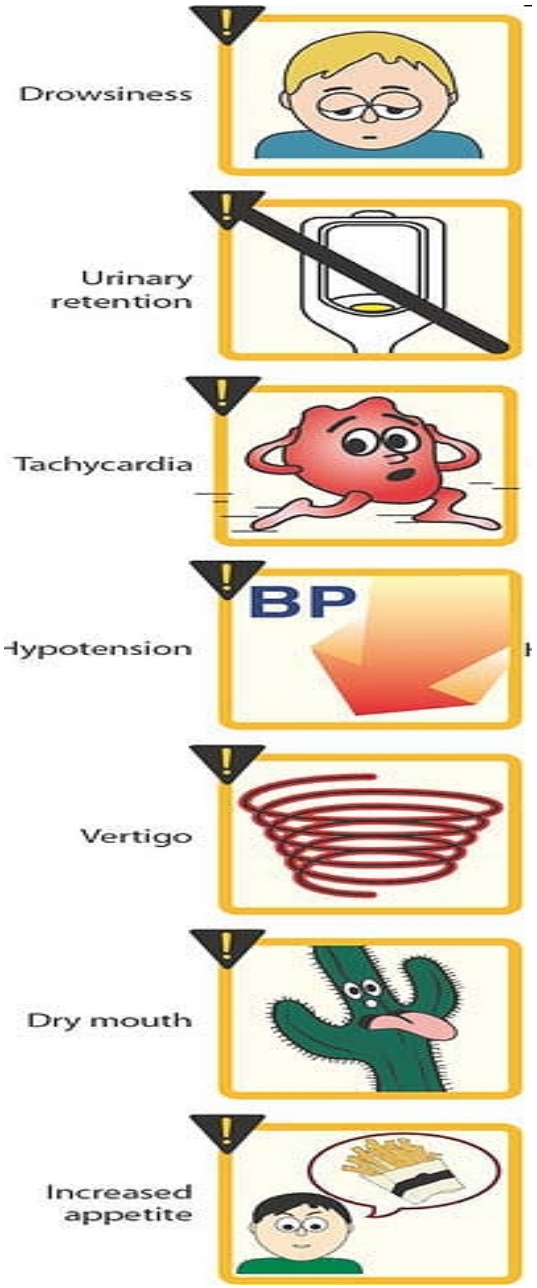
Antihistamines-Adverse Effects & Toxicity



- **Sedation:**
  - Sedation is less common with the second-generation drugs, which do not readily enter the CNS
  - Second-generation H1 antihistamines are specific for H1 receptors and penetrate the CNS poorly
  - They show less sedation and other CNS effects

Antihistamines-Adverse Effects & Toxicity

- **Other CNS actions:**
  - Other central actions include tinnitus, fatigue, dizziness, lassitude(a sense of weariness), incoordination, blurred vision, and tremors



Antihistamines-Adverse Effects & Toxicity

- **Dry mouth:**
  - Oral antihistamines also exert weak anticholinergic effects, leading not only to a drying of the nasal passage but also to a tendency to dry the oral cavity
  - Blurred vision can occur as well with some drugs