PHARMACOLOGY (Antihistamines)

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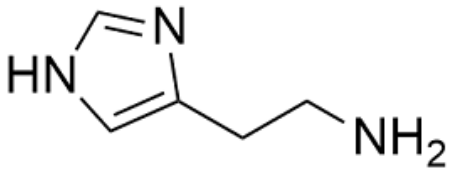
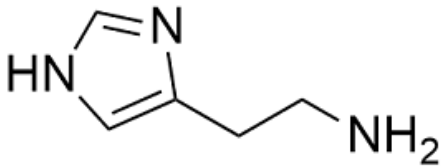
Histamine



Histamine

- Histamine is a chemical messenger mostly generated in mast cells.
- Histamine, mediates a wide range of cellular responses, including *allergic and inflammatory reactions, gastric acid secretion, and neurotransmission in parts of the brain*.
- Histamine has no clinical applications, but agents that inhibit the action of histamine (**antihistamines or histamine receptor blockers**) *have important therapeutic applications*.

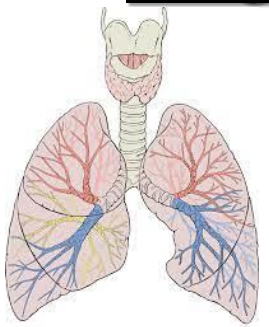


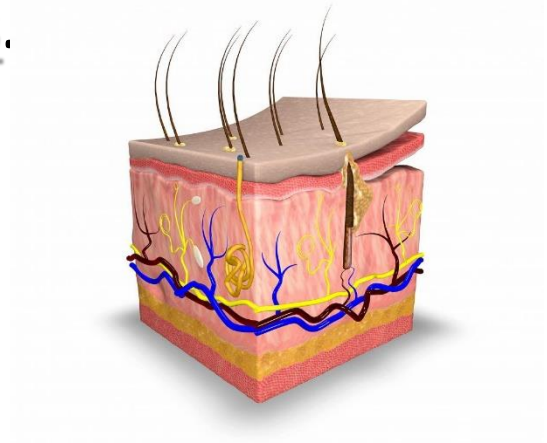
Histamine

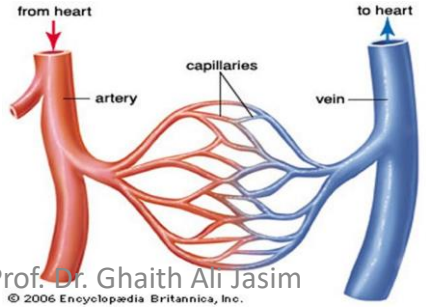
Location, synthesis, and release of histamine

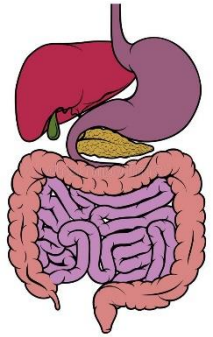
Location:

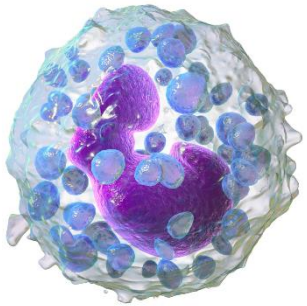
- Histamine is present in practically all tissues, with significant amounts in the **lungs, skin, blood vessels, and GI tract**.
- It is found at high concentration in **mast cells and basophils**.
- Histamine functions as a neurotransmitter in the brain.
- It also occurs as a component of venoms and in secretions from insect stings.



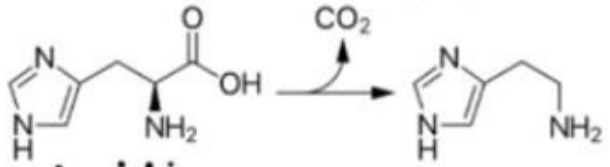




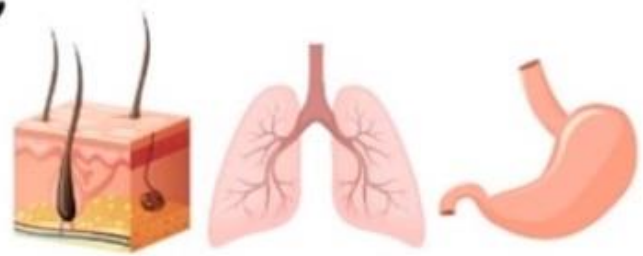




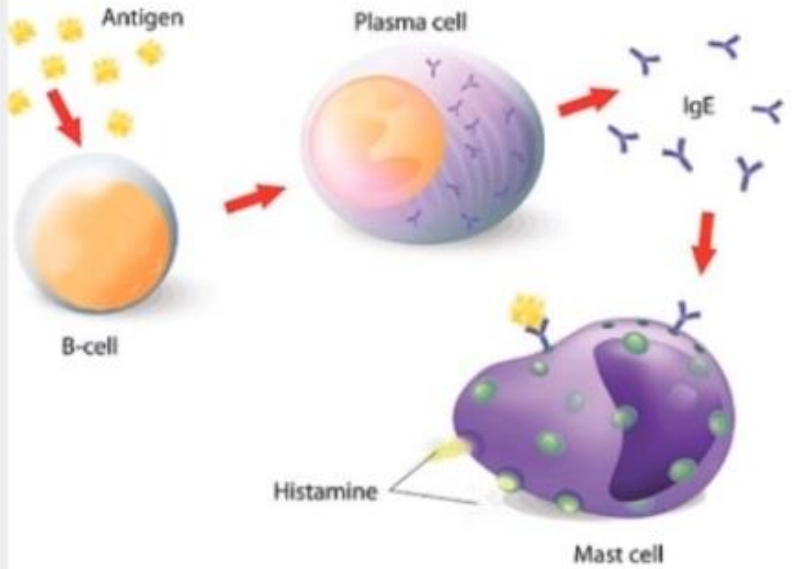
Histamine



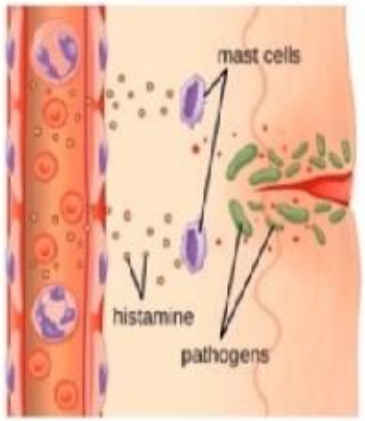
Histidine



Allergic reaction



Tissue injury



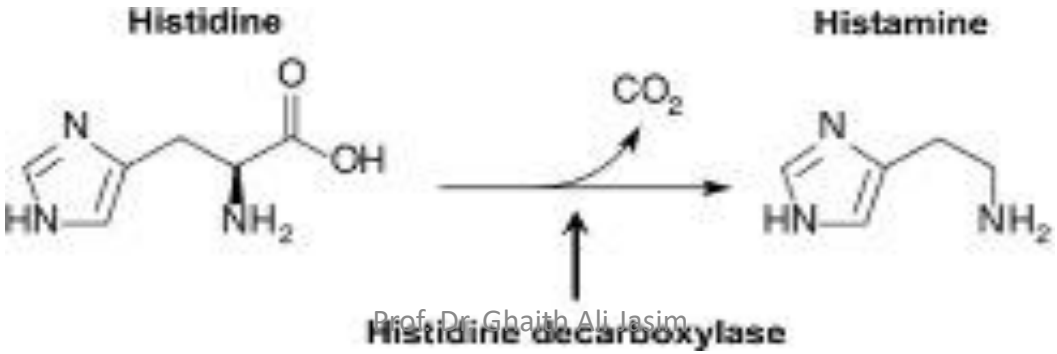
Drugs & Foreign chemicals

venoms
antibiotic bases
dyes
alkaloids
(morphine)

Location, synthesis, and release of histamine

Synthesis:

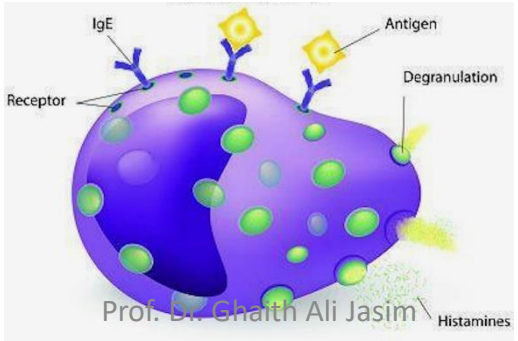
- **Histamine** is an amine "**biogenic amine**" formed by the decarboxylation of the amino acid histidine by the enzyme *histidine decarboxylase*, which is expressed in cells throughout the body, including neurons, gastric parietal cells, mast cells, and basophils.
- In **mast cells**, histamine is stored in granules. If histamine is not stored, it is rapidly inactivated by the enzyme amine oxidase.



Location, synthesis, and release of histamine

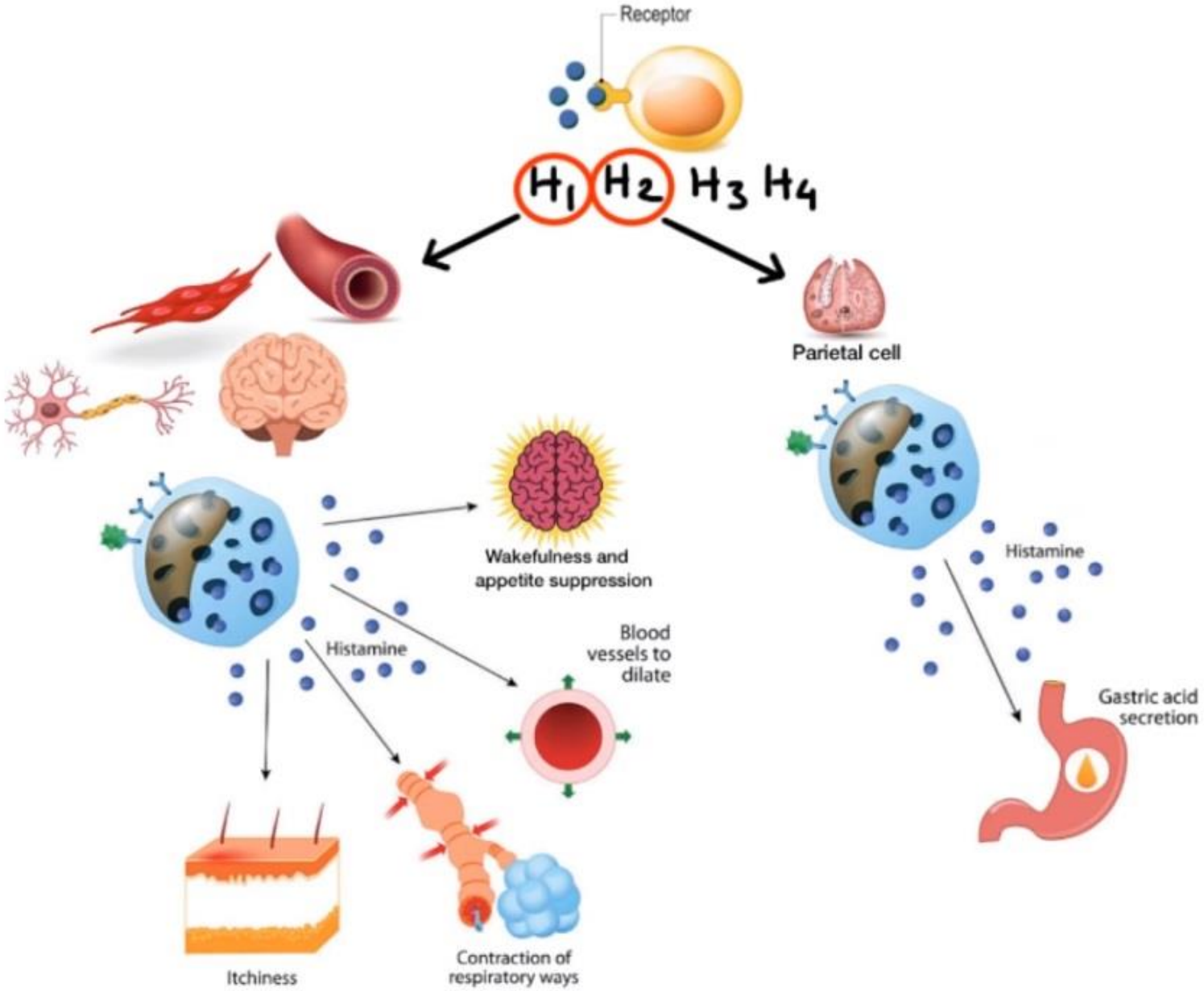
Release of histamine:

- histamine is one of several *chemical mediators* released in response to stimuli.
- The stimuli for release of histamine from tissues may include destruction of cells as a result of cold, toxins from organisms, venoms from insects and spiders, and trauma.
- Allergies and anaphylaxis can also trigger significant release of histamine

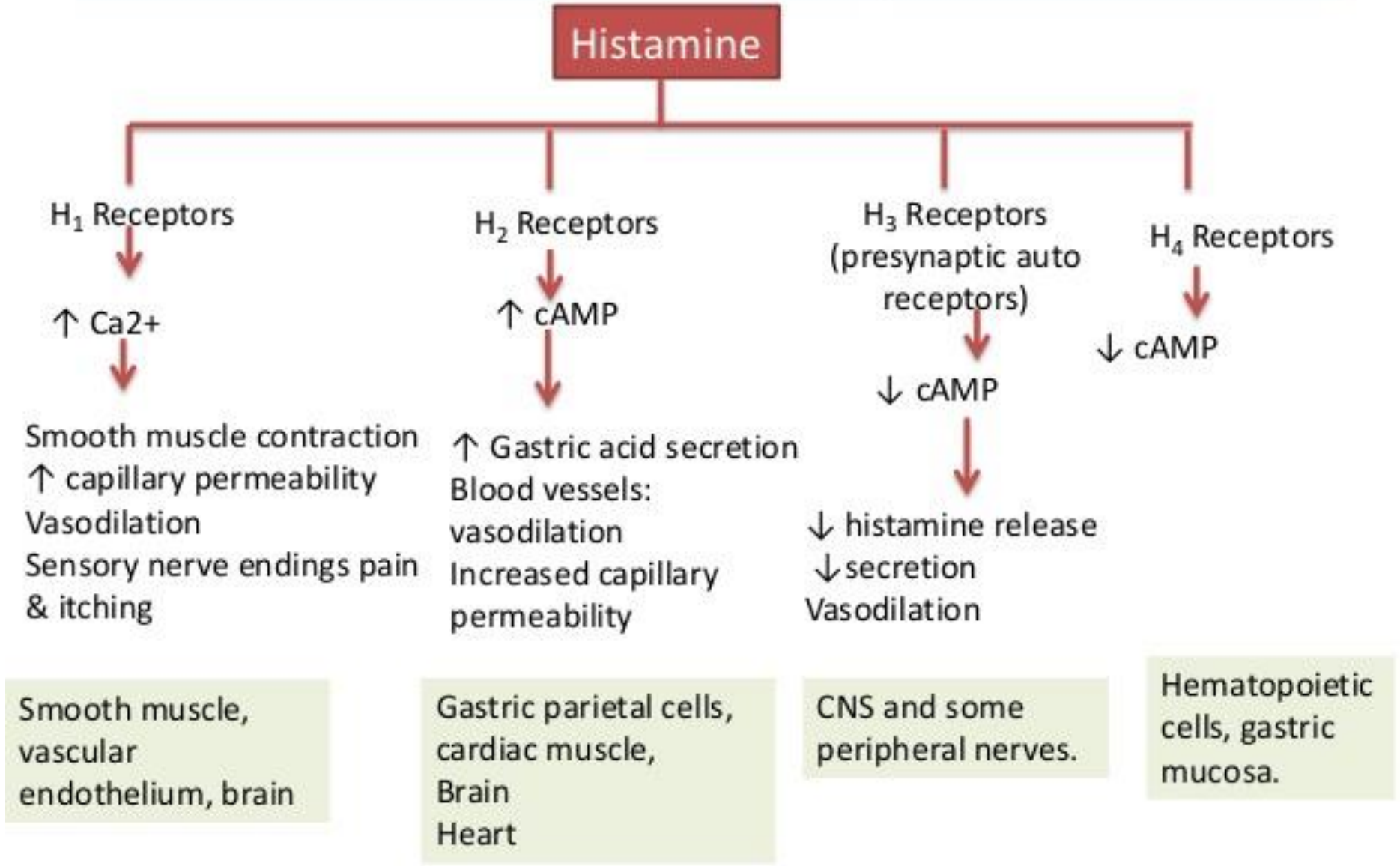


Histamine MOA

- Histamine exerts its effects by binding to various types of histamine receptors (H1, H2, H3, H4) .
- H1 and H2 receptors are widely expressed and are the targets of clinically useful drugs.
- Histamine has a wide range of pharmacologic effects that are mediated by both H1 and H2 receptors.
- H1 receptors are important in producing smooth muscle contraction and increasing capillary permeability.


Receptor
H1 H2 H3 H4
Parietal cell
Wakefulness and
appetite suppression
Histamine
Blood
vessels to
dilate
Histamine
Gastric acid
secretion
Itchiness
Contraction of
respiratory ways

Histamine Receptors



- **Histamine** promotes vasodilation of small blood vessels by causing the vascular endothelium to release nitric oxide.

- **Histamine** can enhance the secretion of pro-inflammatory cytokines in several cell types and in local tissues.

- **Histamine** H1 receptors mediate many pathological processes, including **allergic rhinitis, atopic dermatitis, conjunctivitis, urticaria, bronchoconstriction, asthma, and anaphylaxis**.

- **Histamine** stimulates the *parietal cells in the stomach, causing an increase in acid secretion via the activation of H2 receptors*

Histamin Role in allergy and anaphylaxis

Symptoms resulting from intravenous injection of histamine are similar to those associated with **anaphylactic shock** and allergic reactions.

These include:

1. contraction of airway smooth muscle,
2. stimulation of secretions,
3. dilation and increased permeability of the capillaries,
4. stimulation of sensory nerve endings.

***Symptoms associated with allergy and anaphylactic shock result from the release of certain mediators from their storage sites. Such mediators include: histamine, serotonin, leukotrienes, and the eosinophil chemotactic factor of anaphylaxis.

*These mediators cause a localized allergic reaction, producing, for example, actions on the skin or respiratory tract.

*These mediators may cause a full-blown anaphylactic response.

"the difference between these two situations results from differences in the ***sites from which mediators are released*** and ***in their rates of release***"

>>>> if the release of histamine *is slow enough to permit its inactivation before it enters the bloodstream* >>>> a local allergic reaction results.

>>>> if histamine release *is too fast for efficient inactivation* >>>> a full-blown anaphylactic reaction occurs.

((H1 Antihistamines))

- The term "antihistamine" refers primarily to the classic H1-receptor blockers. The H1 -receptor blockers can be divided into first- and second-generation drugs.

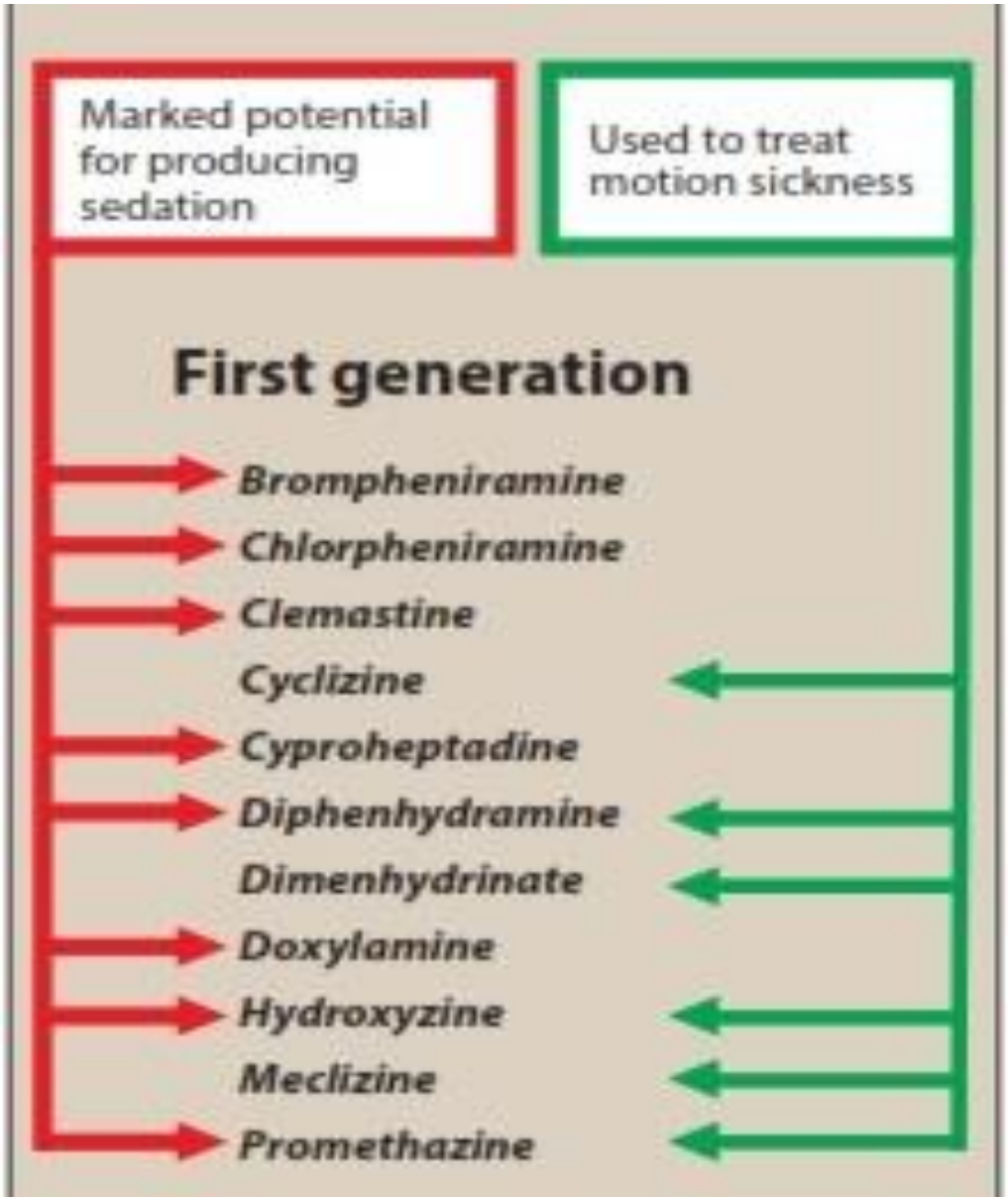
- **1st:** The older **first-generation** drugs are still widely used because they are effective and inexpensive.

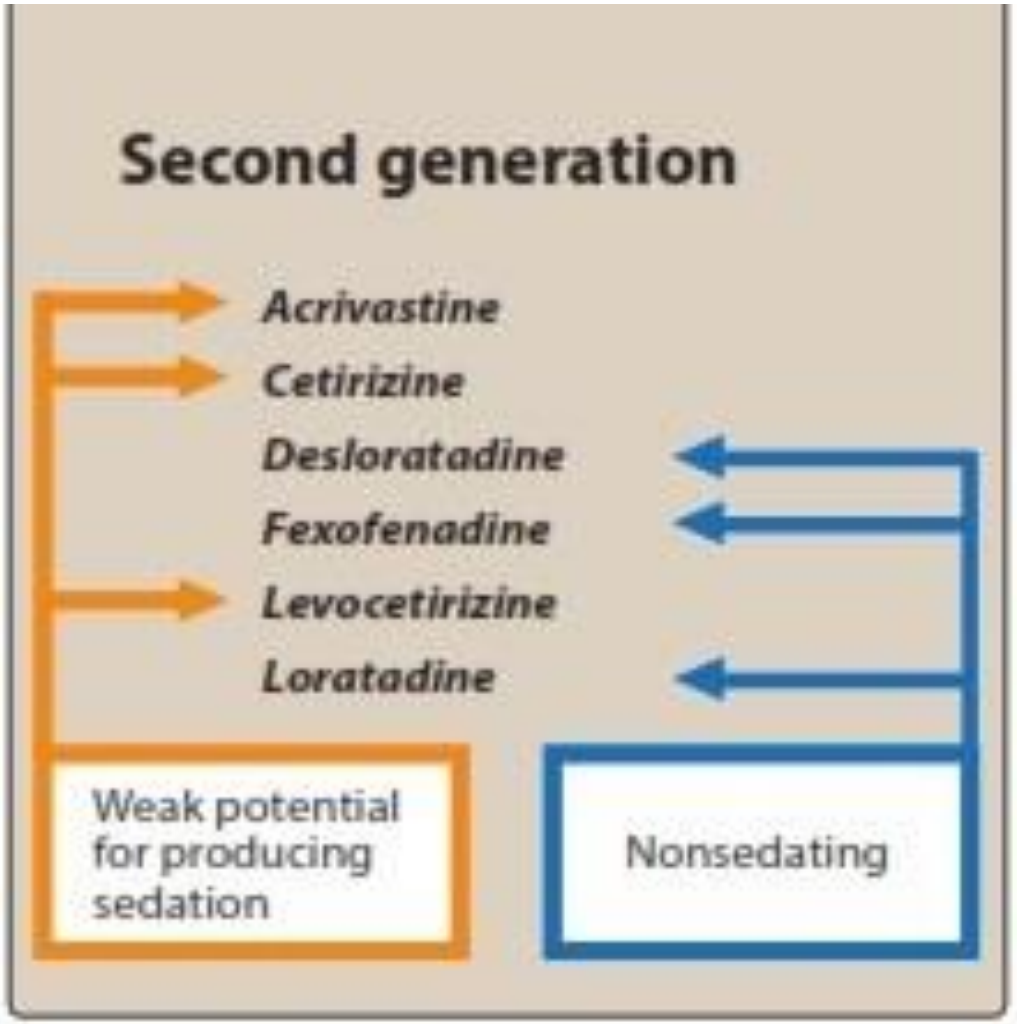
Most of these drugs penetrate the CNS and cause sedation.

These drugs tend to interact with other receptors, producing a variety of unwanted adverse effects.

- **2nd:** The **second-generation** agents are specific for peripheral H1 receptors.

Because they are made polar by adding carboxyl groups the second-generation agents **do not** penetrate the blood–brain barrier


Marked potential for producing sedation
Used to treat motion sickness
First generation
Brompheniramine
Chlorpheniramine
Clemastine
Cyclizine
Cyproheptadine
Diphenhydramine
Dimenhydrinate
Doxylamine
Hydroxyzine
Meclizine
Promethazine


Second generation
Acrivastine
Cetirizine
Desloratadine
Fexofenadine
Levocetirizine
Loratadine
Weak potential for producing sedation
Nonsedating

- The action of all the H1-receptor blockers is qualitatively similar… they ***block the receptor-mediated response of a target tissue***. ***"more effective in preventing symptoms than reversing them"***
- Most of these compounds do not influence the formation or release of histamine^.
- Additional effects unrelated to ability to block H1 receptors… block cholinergic, adrenergic, or serotonin receptors

- ***Cyproheptadine*** also acts as a serotonin antagonist on the appetite center and is sometimes used off-label as an appetite stimulant.
- ***Azelastine*** and ***Ketotifen*** also have mast cell stabilizing effects^ in addition to their histamine receptor–blocking effects.

Therapeutic use:

*** Allergic and inflammatory conditions:**

- H1-receptor blockers are useful in treating and preventing allergic reactions caused by antigens acting on immunoglobulin E antibody.
- "oral antihistamines are the drugs of choice in controlling the symptoms of allergic rhinitis and urticaria because histamine is the principal mediator released by mast cells".
- Ophthalmic antihistamines, such as ***azelastine***, ***olopatadine***, ***ketotifen*** are useful for the treatment of allergic conjunctivitis.
- H1-receptor blockers are not indicated in treating bronchial asthma, *"because histamine is only one of several mediators that are responsible for causing bronchial reactions"*

**Epinephrine* acts on smooth muscle that are opposite to those of histamine….via β2 receptors on smooth muscle, causing cAMP-mediated relaxation.

"epinephrine is the drug of choice in treating systemic anaphylaxis and other conditions that involve massive release of histamine.

* Motion sickness and nausea:

Along with the antimuscarinic agent ***scopolamine,*** certain H1-receptor blockers, such as:

- ***Diphenhydramine***
- ***Dimenhydrinate*** (a chemical combination of *diphenhydramine* and a chlorinated theophylline derivative),
- ***Cyclizine***
- ***Meclizine*** **(**useful for treatment of vertigo associated with vestibular disorders**)**
- ***Promethazine***

*are the most effective agents for prevention of the symptoms of motion sick- ness.

"They are usually not effective if symptoms are already present and, thus, should be taken prior to expected travel."

The antihistamines prevent or diminish nausea and vomiting mediated by both the chemoreceptor and vestibular pathways. The antiemetic action of these medications seems to be due to their blockade of central H1 and M1 muscarinic receptors.

* Somnifacients:

- First-generation antihistamines, such as:
- ***Diphenhydramine***
- ***Doxylamine***

*have **strong sedative properties** and are used in the treatment of insomnia

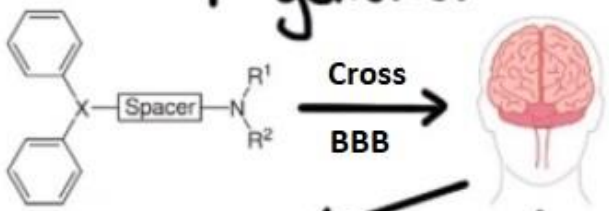
"These agents are available over-the-counter (OTC), or without a prescription"

The use of **1st-generation H1 antihistamines is contraindicated in the treatment of individuals working in jobs in which wakefulness is critical.

***The **2nd-generation** antihistamines have no value as somnifacients

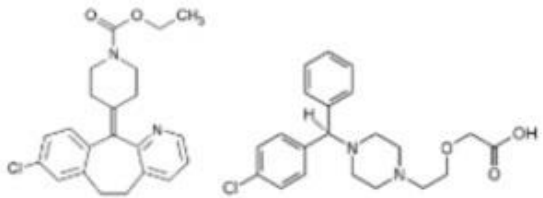
H1 Receptor Blockers
ANTIHISTAMINES

1st generation



relief of allergy related symptoms:
*inflammation
*itching
*runny nose

2nd generation

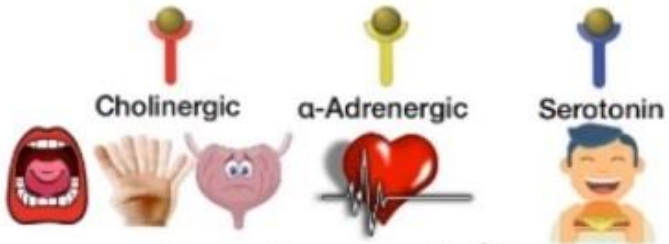


Cetirizine
Desloratadine
Fexoferadine

Levocetirizine
Loratadine

Azelastine
Olopatadine

Ketotifen



Brompheniramine
Chlorpheniramine
Clemastine

Cyproheptadine
Diphenhydramine
Doxylamine

Rx insomnia

Hydroxyzine
Meclizine
Promethazine

Rx motion sickness

Pharmacokinetics

- H1-receptor blockers are well absorbed after oral administration, with maximum serum levels occurring at 1 to 2 hours.
- The average plasma half-life is 4 to 6 hours, except for that of ***meclizine*** and the 2nd- generation agents… (12 to 24 hours)

$$(t½ = 0.693 \times Vd / CL)$$

- After a single oral dose, onset of action occurs within 1 to 3 hours. The duration of action for many oral antihistamines is 24 hours, allowing once-daily dosing.
- First-generation H1- receptor blockers are distributed in all tissues, including the CNS.

- All 1st-generation H1 antihistamines and some 2nd-generation H1 antihistamines, such as ***desloratadine*** and ***loratadine***, are metabolized by the hepatic cytochrome P450 system.

- ***Cetirizine*** and ***levocetirizine*** are excreted largely unchanged in urine,

- ***fexofenadine*** is excreted largely unchanged in feces.

- *Azelastine, olopatadine, ketotifen, alcaftadine, bepotastine,* and *emedastine* are available in **ophthalmic** formulations that allow for more targeted tissue delivery.
- *Azelastine* and *olopatadine* have **intranasal** formulations.

Adverse effects

- First-generation H1-receptor blockers have a low specificity, interacting with:

histamine receptors

muscarinic cholinergic receptors,

α-adrenergic receptors,

serotonin receptors

*as a result, the nature of the side effects varies with the structure of the drug.

"Some side effects may be undesirable, and others may be of therapeutic value"

Adverse effects…

Sedation:

First-generation H1 antihistamines, such as:

Chlorpheniramine

Diphenhydramine

Hydroxyzine

Promethazine

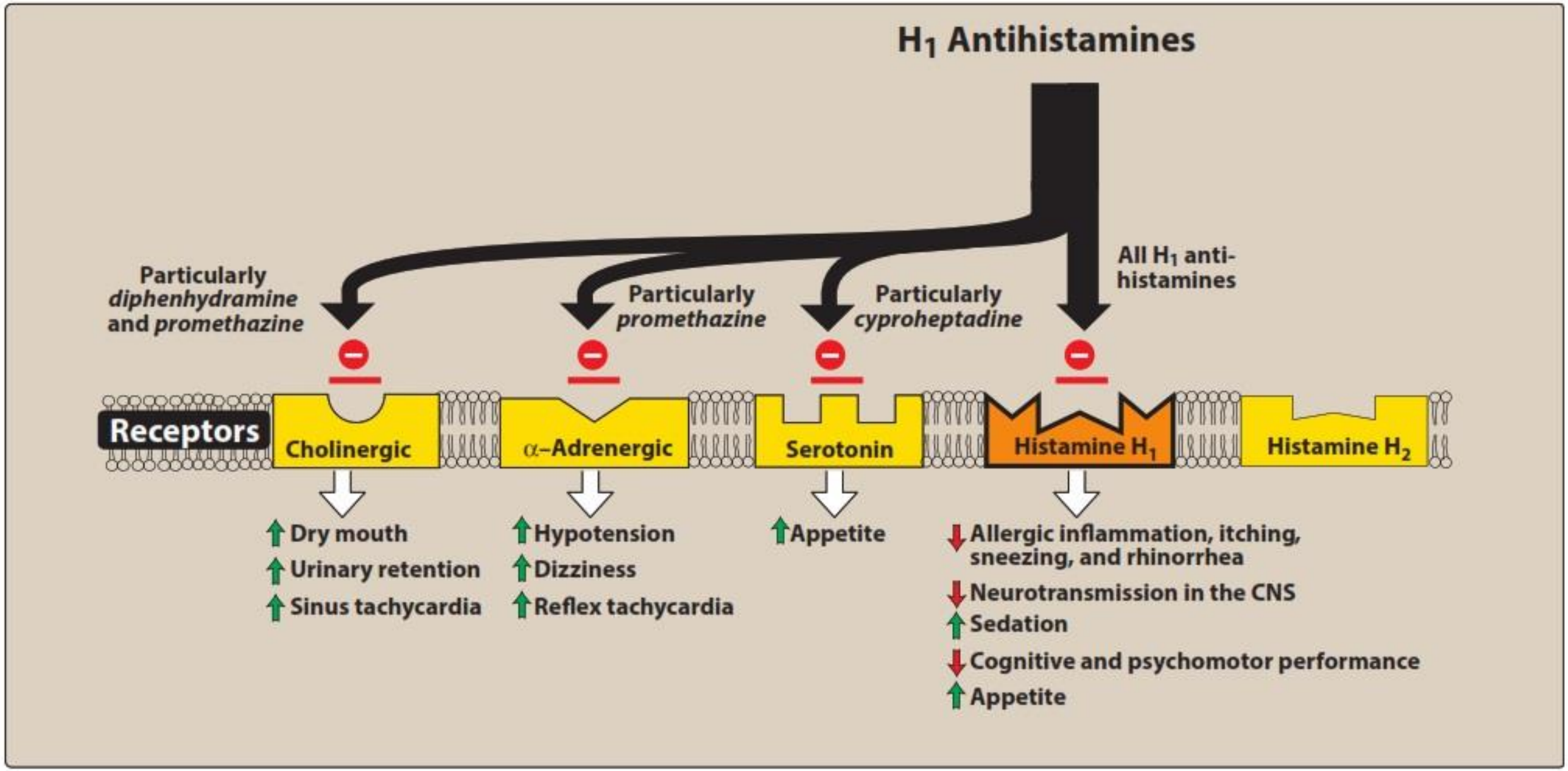
*bind to H1 receptors and block the neurotransmitter effect of histamine in the CNS…The most frequently observed adverse reaction is **sedation**.

Adverse effects…

- **Diphenhydramine** may cause paradoxical hyperactivity in young children "These may include hallucination, disorientation, uncontrollable crying or verbalization, agitation, restlessness, involuntary movement, self-injury, and aggressive or violent behavior".
- Other central actions include fatigue, dizziness, lack of coordination, and tremors.
- Sedation is less common with the second-generation drugs, since they do not readily enter the CNS

Adverse effects…

- 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.
- The most common adverse reaction associated with second-generation antihistamines is headache.
- Topical formulations of ***diphenhydramine*** can cause hypersensitivity reactions such as contact dermatitis when applied to the skin


H1 Antihistamines
Particularly diphenhydramine and promethazine
Particularly promethazine
Particularly cyproheptadine
All H1 anti-histamines
Receptors
Cholinergic
α–Adrenergic
Serotonin
Histamine H1
Histamine H2
Dry mouth
Urinary retention
Sinus tachycardia
Hypotension
Dizziness
Reflex tachycardia
Appetite
Allergic inflammation, itching, sneezing, and rhinorrhea
Neurotransmission in the CNS
Sedation
Cognitive and psychomotor performance
Appetite

Drug interactions H1-receptor blockers :

- Potentiation of effects of other CNS depressants, including alcohol.
- *MAOIs (monoamine oxidase inhibitors) can exacerbate the anticholinergic effects of the antihistamines.*
- Decrease the effectiveness of cholinesterase inhibitors, The first-generation antihistamines (*diphenhydramine* and others) with anticholinergic (antimuscarinic) (*donepezil, rivastigmine,* and *galantamine*) in the treatment of Alzheimer's disease.

((Histamine H2-receptor blockers))

- Histamine H2-receptor blockers (H2-receptor antagonists) have little, if any, affinity for H1 receptors.
- Antagonists of the histamine H2-receptor block the actions of histamine at all H2 rectors, their chief clinical use is as inhibitors of gastric acid secretion in the treatment of ulcers and heartburn.

*The four H2-receptor blockers

cimetidine,

ranitidine,

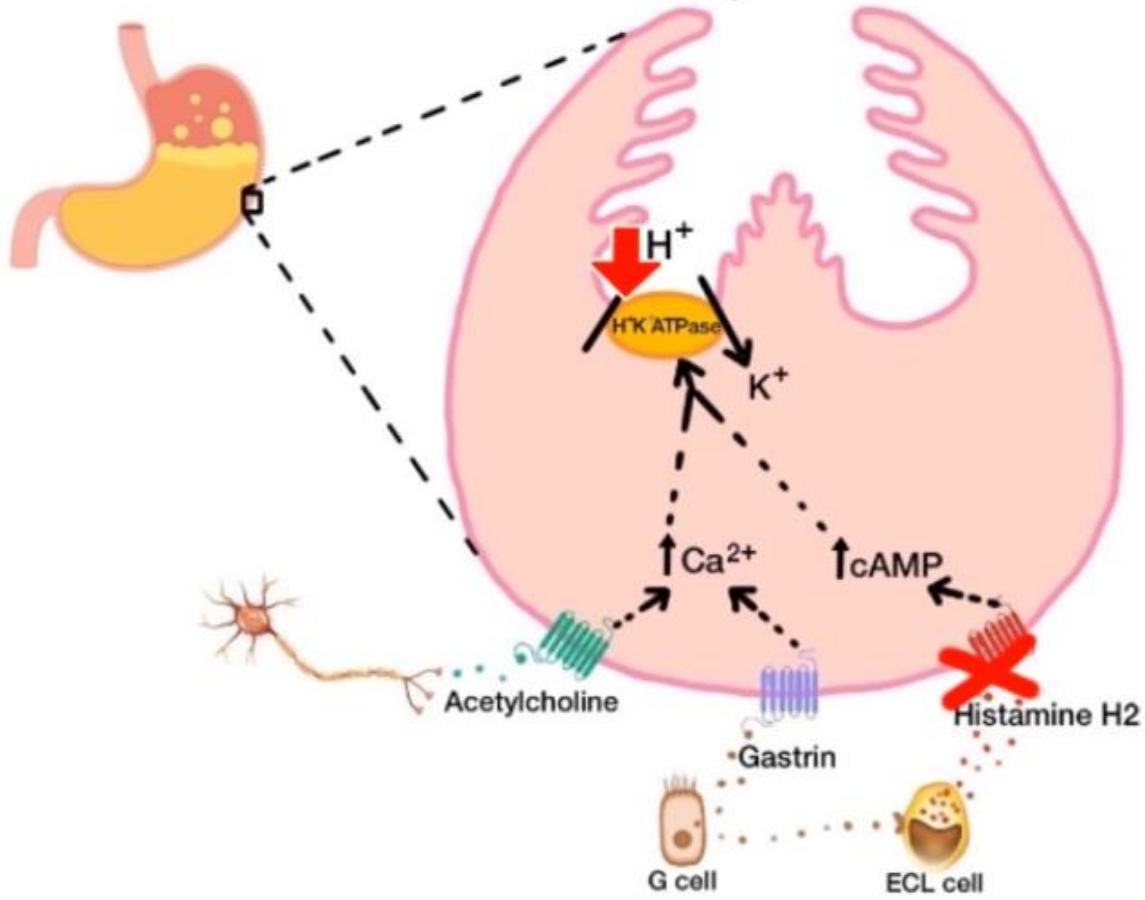
famotidine,

nizatidine

- Gastric acid secretion is stimulated by acetylcholine, histamine, and gastrin , The receptor-mediated binding of acetylcholine, histamine, or gastrin results in the activation of protein kinases, which in turn stimulates the H+/K+-adenosine triphosphatase (ATPase) proton pump to secrete hydrogen ions in exchange for K+ into the lumen of the stomach. By competitively blocking the binding of histamine to H2 receptors, these agents reduce the secretion of gastric acid.

- The four drugs used: ***cimetidine, ranitidine, famotidine,*** **and** ***nizatidine …*** potently inhibit (greater than 90%) basal, food-stimulated, and nocturnal secretion of gastric acid.
- *Cimetidine* was the first histamine H2-receptor antagonist. However, its utility is limited by its adverse effect profile and drug-drug interactions.

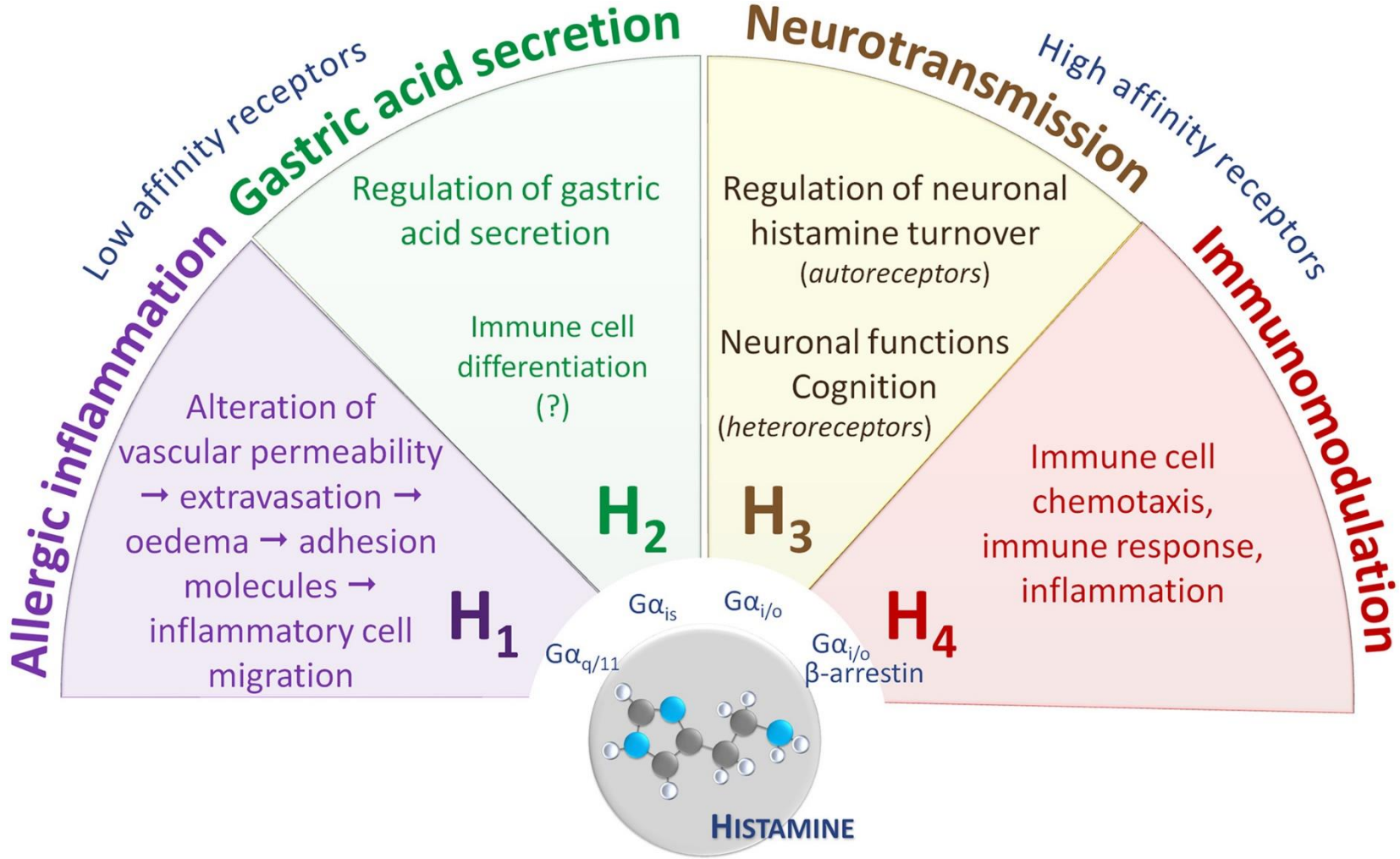
H2 Receptor Blockers



Cimetidine
Famotidine
Nizatidine
Ranitidine

AE: Headache

End of the lecture… good luck!



Mast cells – Basophils – Enterochromaffin-like cells – Neurons
Leukocytes – Platelets – Epithelial cells – Chondrocytes
Tumour cells – Other cells