Histamine and H_1-Antihistamines

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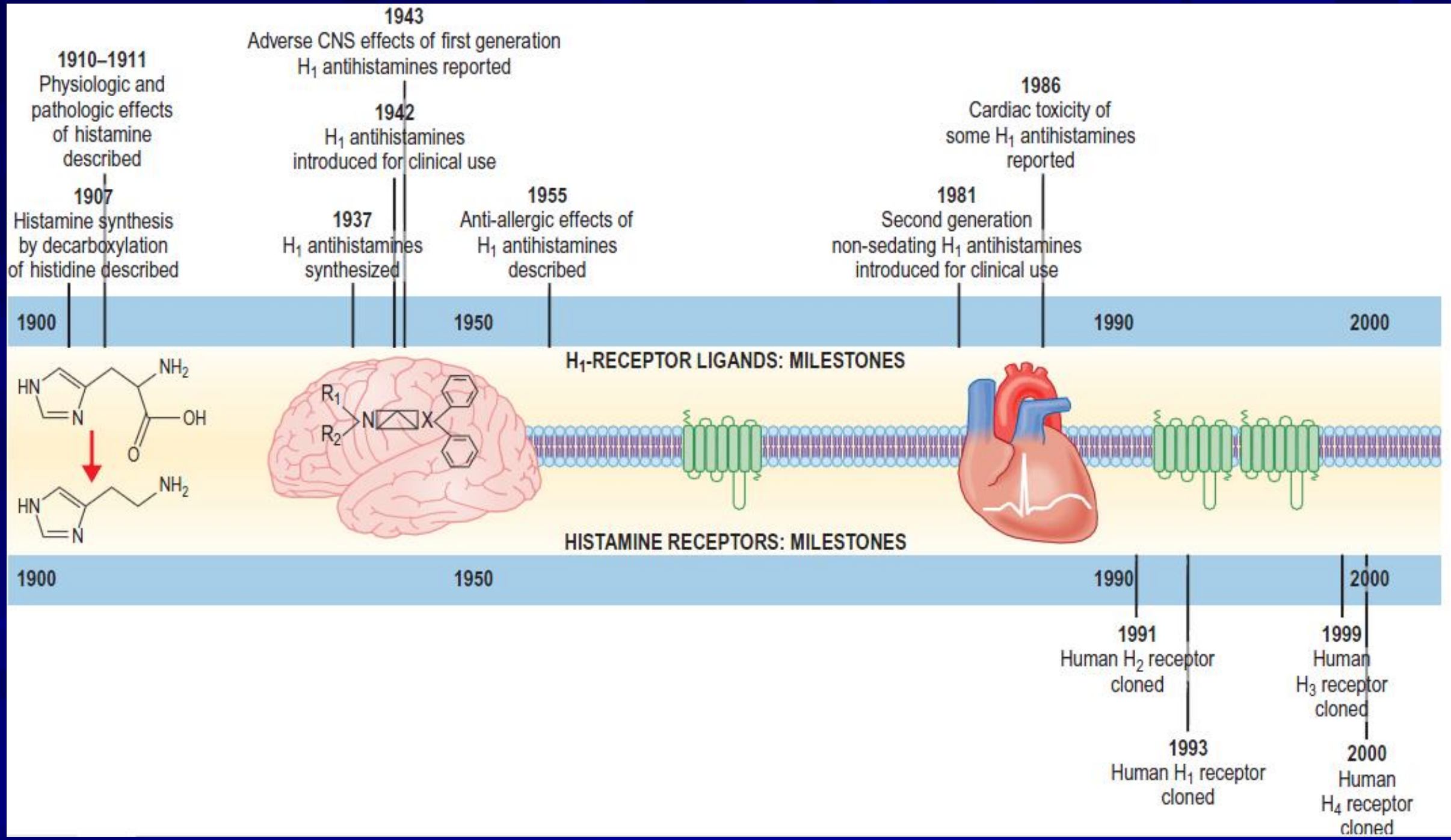
Objectives

- Learners will realize
  - What is histamine and how does it work?
  - What are H1-antihistamines?
  - What is the best time for their prescription and why?
  - What is the indication for H1-antihistamine use?
  - What are the H1-antihistamines side effects?

Introduction

- Histamine was isolated and characterized more than 100 years ago
- Medications targeting its receptors have been used for 70 years.
- Histamine has a major role in human health and disease
- Exerting diverse biologic effects through 1 of its 4 receptors, H1-, H2-, H3-, or H4-receptor.

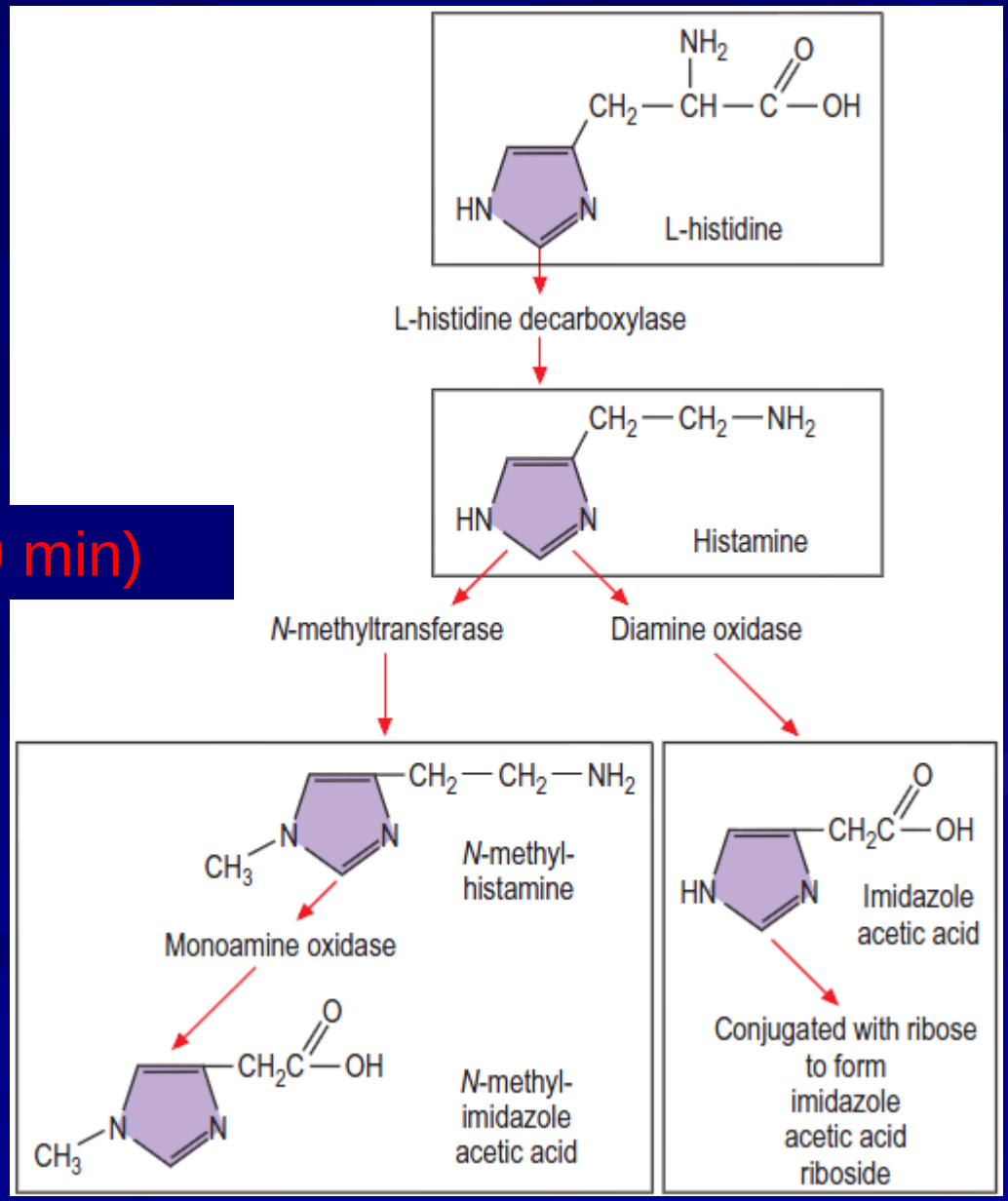

1910–1911
Physiologic and pathologic effects of histamine described
1907
Histamine synthesis by decarboxylation of histidine described
1943
Adverse CNS effects of first generation H_1 antihistamines reported
1942
H_1 antihistamines introduced for clinical use
1937
H_1 antihistamines synthesized
1955
Anti-allergic effects of H_1 antihistamines described
1986
Cardiac toxicity of some H_1 antihistamines reported
1981
Second generation non-sedating H_1 antihistamines introduced for clinical use
1900
1950
1990
2000
H_1-RECEPTOR LIGANDS: MILESTONES
HISTAMINE RECEPTORS: MILESTONES
1900
1950
1990
2000
1991
Human H_2 receptor cloned
1993
Human H_1 receptor cloned
1999
Human H_3 receptor cloned
2000
Human H_4 receptor cloned

Introduction

- In 1927, histamine was isolated from
  - **Lung**
  - **Skin**
  - **GI**
- The name “histamine” was given after the Greek word for tissue, *histos.*

Synthesis and catabolism of histamine in humans

a short-term action (1-10 min)



Metabolism & Synthesis

Sources:

Mast cell

Basophil

Gastric enterochromaffin-like cell

Histaminergic Neuron

Histamin Sources

Histidine decarboxylase

Mast cell

Basophil

Platelets

Monocytes

Macrophage

Dendritic cells

Neutrophils

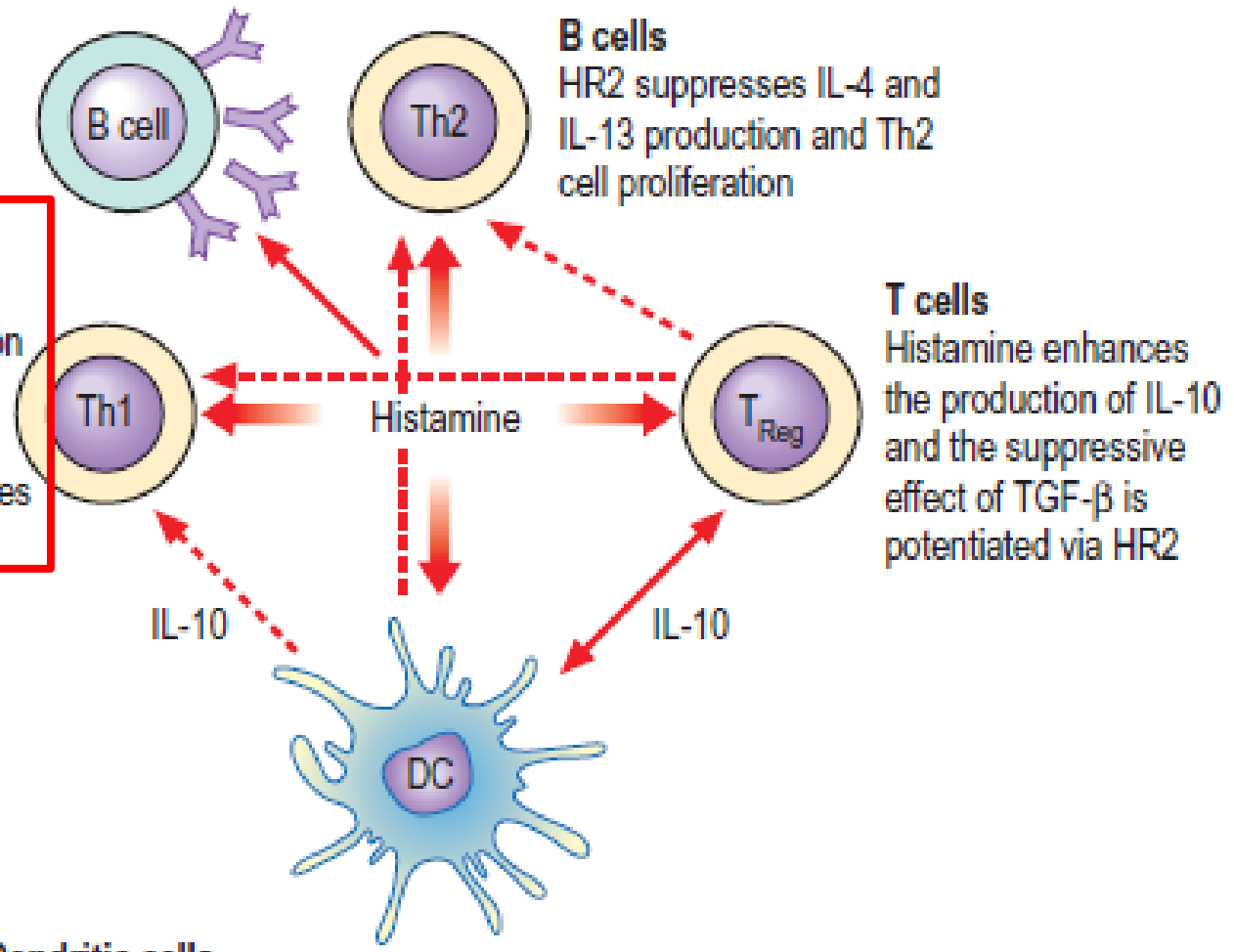
B cell & T cell

commensal and pathogenic bacteria express histamine decarboxylase enzyme and can actively produce histamine

Histamine specific receptors

- Mast cells
- endothelial cells of the vessels
- cells of sensitive nerve fibers
- bronchial smooth muscles

HR1 blocks humoral immunity, induces cellular immunity
HR2 blocks cellular immunity
HR1-deficient mice show increased specific IgE
HR2-deficient mice show suppressed specific IgE



B cells
HR2 suppresses IL-4 and IL-13 production and Th2 cell proliferation

Th1 cells
HR1 enhances IFN-γ production and Th1 cell proliferation, HR2 antagonizes this effect

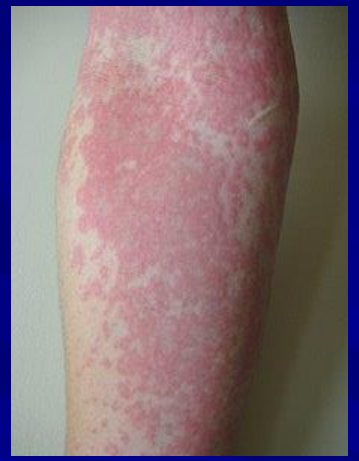
T cells
Histamine enhances the production of IL-10 and the suppressive effect of TGF-β is potentiated via HR2

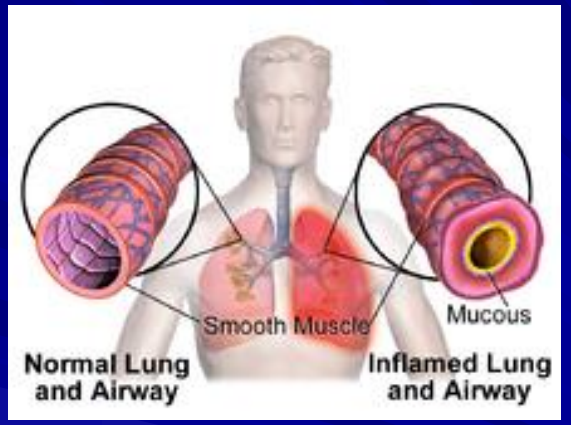
Dendritic cells
HR1 increases antigen-presenting capacity and Th1 priming.
HR2 induces IL-10 production, suppresses antigen presentation and aids development of IL-10-secreting Y cells

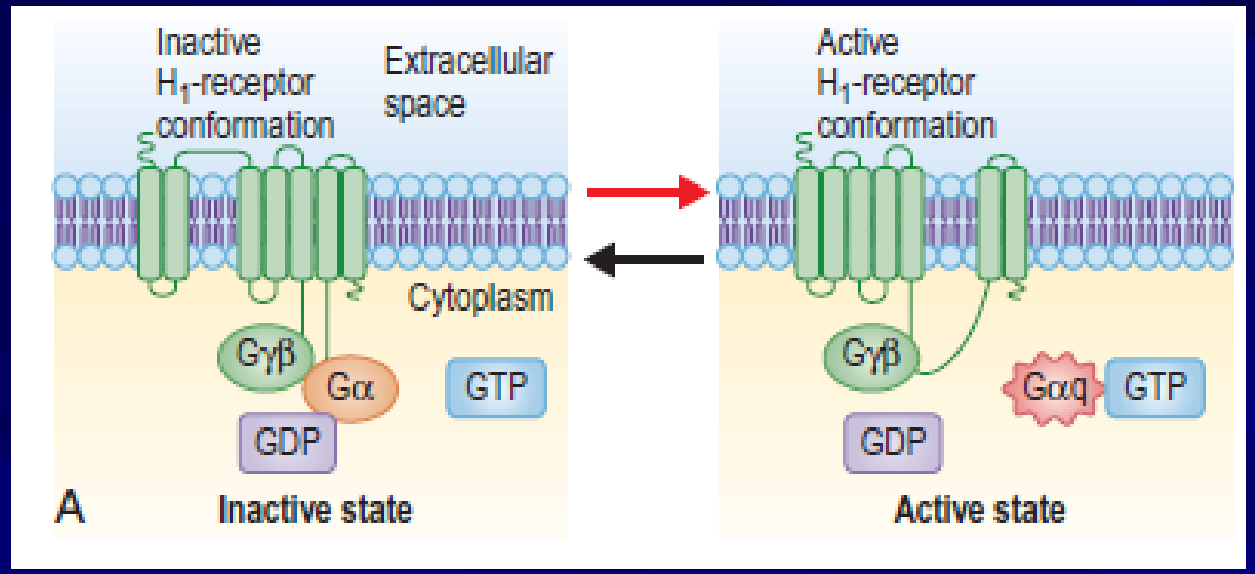
Histamine effect on mast cells and eosinophils

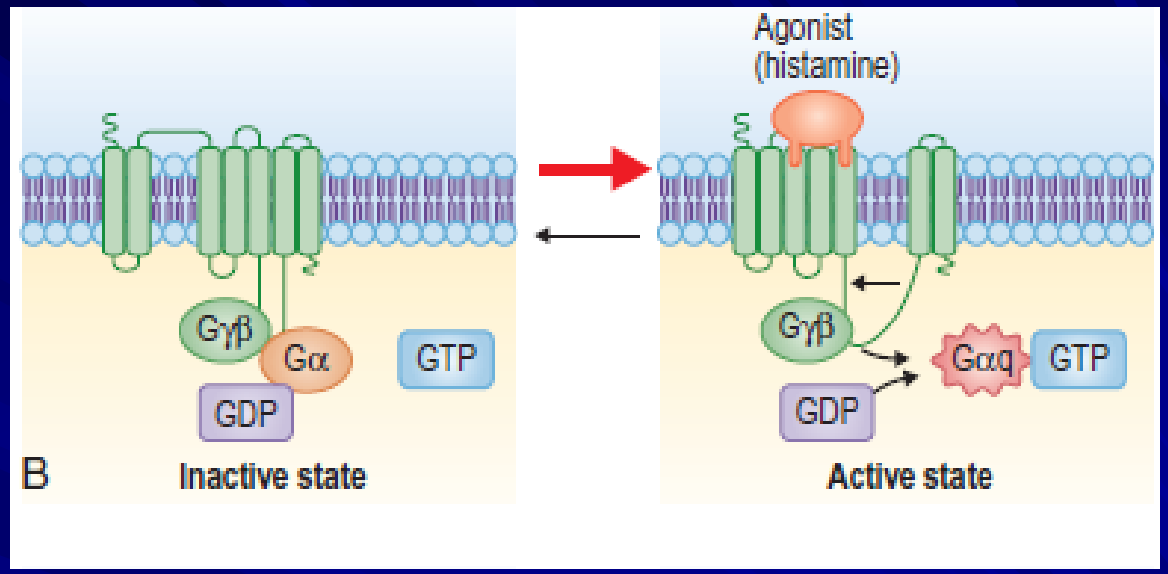
Histamine effects (H1-receptor)

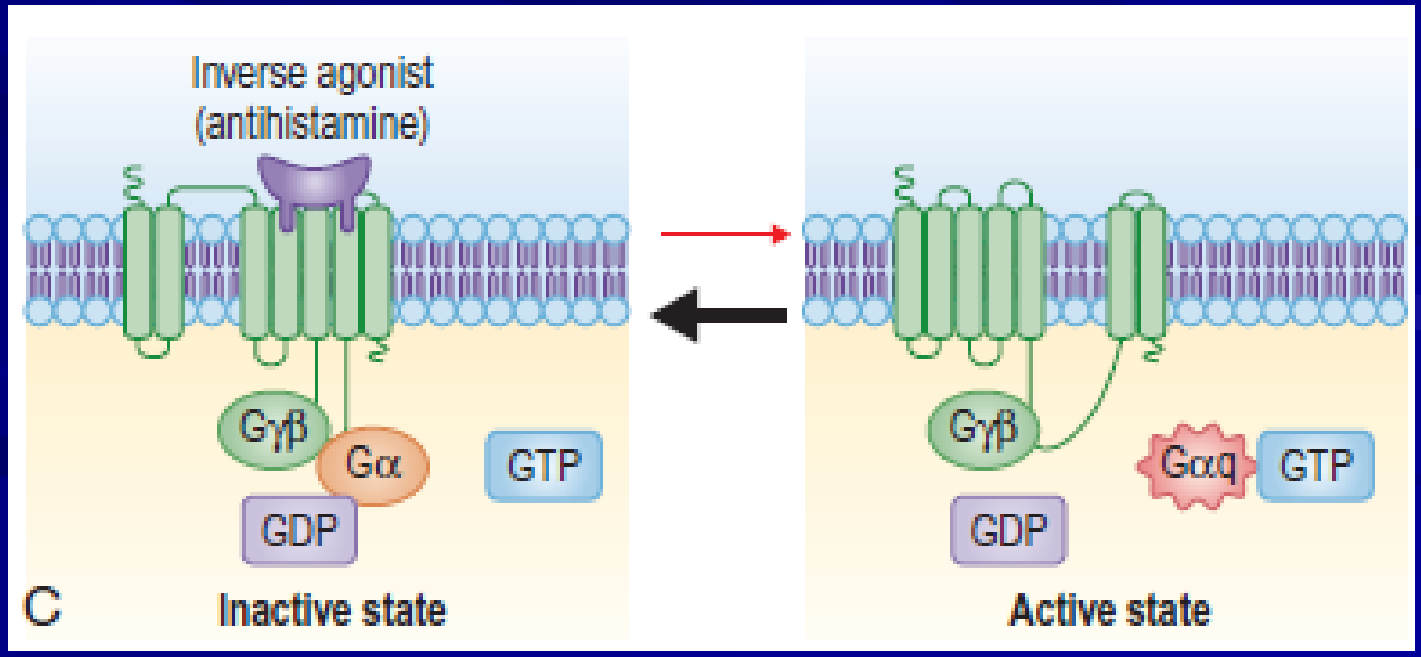
- Pruritus
- Include pain
- Vasodilation
- Mucus production
- Allergic inflammation
- Spasm of coronary arteries
- Smooth muscle contraction
- Increased vascular permeability
- Regulation of the sleep wake rhythm.
- Stimulation of parasympathetic nerve endings and reflexes.

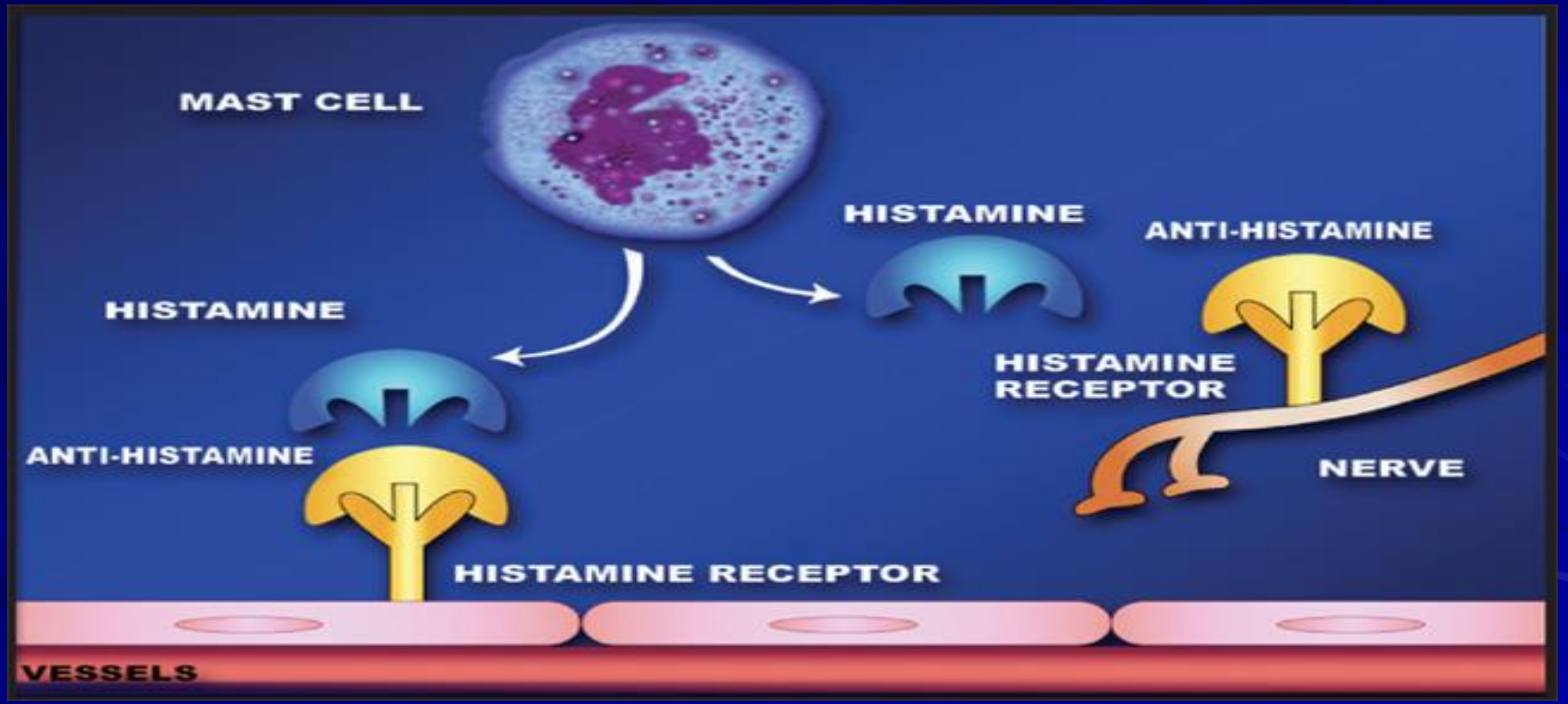





Inactive
H_1-receptor
conformation
Extracellular
space
Cytoplasm
Gγβ
Gα
GTP
GDP
A
Inactive state
Active
H_1-receptor
conformation
Gγβ
Gαq
GTP
GDP
Active state


Gγβ
Gα
GTP
GDP
B
Inactive state
Agonist
(histamine)
Gγβ
Gαq
GTP
GDP
Active state


Inverse agonist
(antihistamine)
Gγβ
Gα
GTP
GDP
C
Inactive state
Gγβ
Gαq
GTP
GDP
Active state


MAST CELL
HISTAMINE
ANTI-HISTAMINE
HISTAMINE
HISTAMINE
RECEPTOR
ANTI-HISTAMINE
NERVE
HISTAMINE RECEPTOR
VESSELS

Best time of dosing

- Antihistamines work best in preventing rather than reversing the actions of histamine

- Most effective when given at doses and dosing intervals resulting in the persistent saturation of target organ tissue histamine receptors.

H1-Antihistamines

- More than 45 H1 antihistamines are available worldwide, representing the largest class of medications used in the treatment of allergic diseases.

- Most recent additions of H1 antihistamines include bilastine and rupatadine for oral administration and bepotastine, alcaftadine, and olopatadine for ophthalmic application.

H_1-antihistamines: chemical and functional classification

Chemical class	Functional class	
	First-generation	Second-generation
Alkylamines	Brompheniramine, chlorpheniramine,	Acrivastine
Piperazines	hydroxyzine	Cetirizine, levocetirizine
Piperidines	Azatadine, cyproheptadine, ketotifen	Astemizole, desloratadine, ebastine, fexofenadine, levocabastine, loratadine, olopatadine, terfenadine
Ethanolamines	clemastine, dimenhydrinate, diphenhydramine,	–
Ethylenediamines	Antazoline, pyrilamine, tripelennamine	–
Phenothiazines	promethazine	–
Other	Doxepin	Azelastine, emedastine, epinastine

Cross the blood–brain barrier

- Lipophilicity
- Low molecular weight
- Positive electrostatic charge
- Lack of recognition by the P-glycoprotein efflux pump

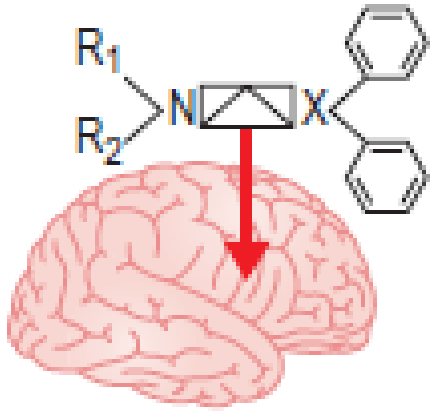
Cross the blood–brain barrier

- a study about cerebral histamine H1 receptor occupancy (H1RO) using positron emission tomography (PET) has shown that the most penetrating antihistamines in the brain are chlorphenamine, ketotifen and hydroxyzine

Antihistamine overdose

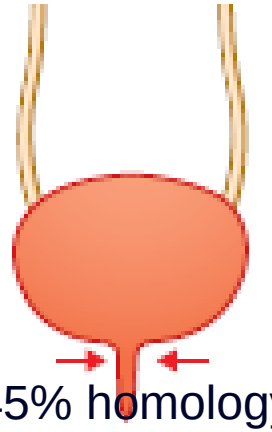
- Remains a risk, especially in children.
- Historically, diphenhydramine has been involved in episodes of overdose poisoning (some fatal), especially in children, partly because many preparations are sold OTC
- The most serious effects of overdose are attributable to neurological or cardiac alterations; for example, convulsions that are followed (at high dosages) by states of coma, which are sometimes irreversible

Potential Adverse Effects of First (Old)-Generation H_1 Antihistamines



CNS H_1 receptors

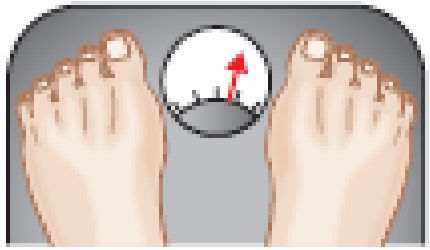
- ↓ Alertness, cognition, learning, memory, and psychomotor performance
- ↑ Impairment with or without sedation



45% homology

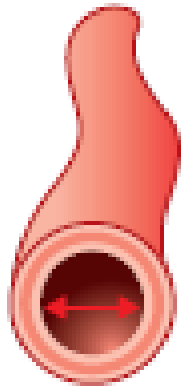
Muscarinic receptors

- ↑ Dry mouth
- ↑ Urinary retention
- ↑ Sinus tachycardia



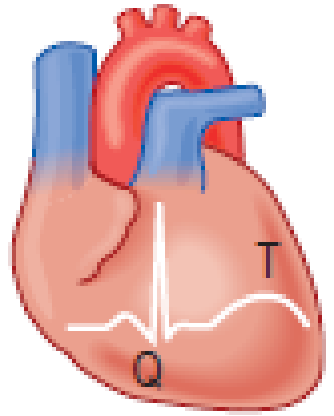
Serotonin receptors

- ↑ Appetite
- ↑ Weight gain



α-Adrenergic receptors

- ↑ Dizziness
- ↑ Postural hypotension



Cardiac ion channels (I_{Kr}, I_{Na}, and others)

- ↑ QT interval
- ↑ Ventricular arrhythmias

Pharmacokinetics

- Generally well absorbed
- bind to plasma proteins(70-97%)
- metabolized by the liver
- excreted in the urine within 24 h of intake.
- Therapeutic effect appears within 30-60 min,
- peaks within1-3 h,
- usually persists for 4-6 h (Chlorpheniramine, hydroxyzine a half-life of over 20 h in the adult).

Duration of the pharmacological effect

- Much longer than the plasma half-life,
- Volume of distribution of the drug
- Action of the metabolites (hydroxyzine and loratadine)
- Binding to plasma proteins is generally high (88-98%)

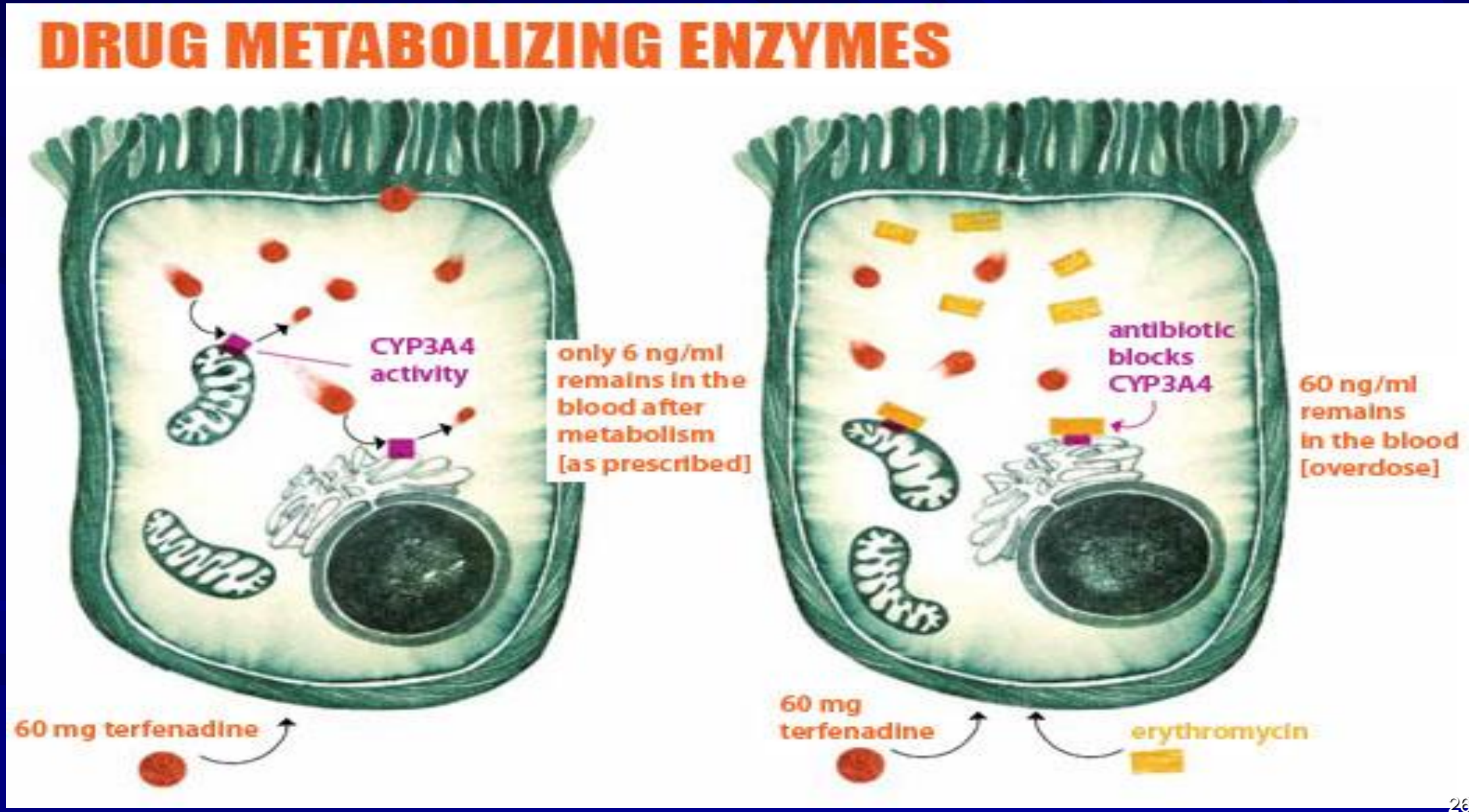
Pharmacodynamics

Onset of action and peak action

persistent effect

- Tissue/plasma concentration (cetirizine, fexofenadine)
- High receptor occupancy
- Hepatic (cetirizine) or renal dysfunction (fexofenadine & cetirizine)

DRUG METABOLIZING ENZYMES



Drug and food interaction

- CP450 inhibitors :reduced elimination
  - erythromycin and other macrolide antibiotics, ciprofloxacin, ketoconazole, itraconazole, and certain antidepressants

- Organic anion transporter inhibitors
  - Fruit juices (apple, orange, grapefruit) interfere with the absorption of fexofenadine: juices should be avoided 4 hr before or 1-2 hr after taking fexofenadine.

Drug	Impact of food
Loratadine	increased AUC 50%
Rupatidine	increased AUC 26%
bilastine	decreased AUC 30%
fexofenadine	Decrease absorption with CP450 inducers grapefruit juice, rifampin, and St. John's wort
	Decrease absorption with P-glycoprotein inhibitors such as erythromycin and ketoconazole
fexofenadine and bilastine	substrate of the P-glycoprotein efflux transporter in BBB
Fexofenadine	avoid administration within 15 minutes of ingestion of Al-Mg antacids

2nd generation

- Fexofenadine: least sedating (0%)
- Cetirizine: the most potential for sedation (26-30%)

Intranasal forms

- Azelastine and olopatadine (also as a mast cell stabilizer)
- A rapid onset of action, within 15 min vs 150 min for oral desloratadine
- Azelastine, systemically absorbed and cross the BBB
- Not currently approved for children <12 yr of age
- A bitter metallic taste is a common reason for non-adherence.

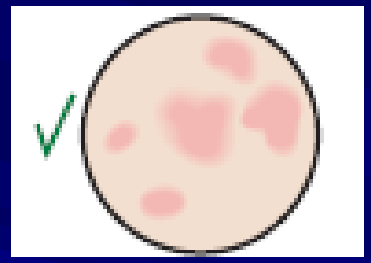
Ophthalmic formulations

- a rapid onset of action of 3 to 15 minutes.
- Some are reported to treat nasal symptoms in addition to conjunctival symptoms.
- In allergic conjunctivitis, a more favorable benefit/risk ratio than all other classes of medications, including NSAIDs, decongestants, and glucocorticoids

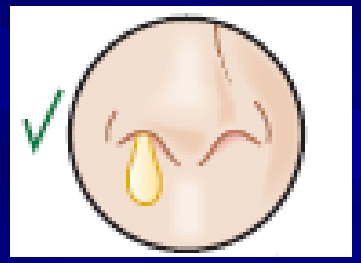
Conditions Currently Treated with H1 Antihistamines

Strong evidence base for 2nd-generation H1 antihistamine use

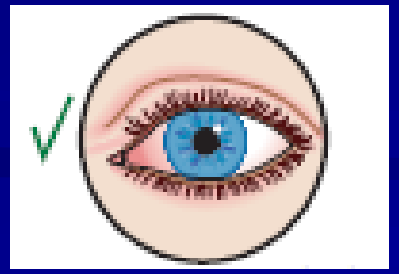
- Urticaria



- Allergic rhinitis



- Allergic conjunctivitis



Urticaria

- H1 antihistamines provide symptomatic relief of itching and reduce the number, size, and duration of flares (erythema).
- Relief may be incomplete, because additional vasoactive mediators contribute to the vasodilation, vascular permeability, and extravasation.
- Because of the unfavorable risk/benefit ratio due to relevant side-effects, first-generation antihistamines, if possible, should no longer be used in the treatment of rhinitis and urticaria.

Weak evidence base for H1 antihistamine use

- Atopic dermatitis
- Asthma
- Anaphylaxis
- Non-allergic angioedema
- Upper respiratory tract infections (colds)
- Otitis media
- Sinusitis
- Nasal polyps
- Non-specific cough
- Non-allergic, non-specific itching

Weak evidence base for first (old)-generation H1 antihistamine use in

- Diphenhydramine, Doxepin, Doxylamine, Pyrilamine
  - Insomnia
- Dimenhydrinate, diphenhydramine, and promethazine
  - Nausea
- Diphenhydramine, Hydroxyzine, Promethazine
  - Conscious sedation
  - Perioperative sedation
  - Analgesia

Weak evidence base for first (old)-generation H1 antihistamine use in

- Hydroxyzine
  - Anxiety
- Cyproheptadine
  - Serotonin syndrome
- Diphenhydramine, Cyproheptadine
  - Akathisia
- Cinnarizine, Dimenhydrinate, Diphenhydramine, Meclizine, Promethazine
  - Motion sickness
  - Vertigo

Efficacy of H_1-antihistamines in Allergic rhinitis

Role of histamine:

- sensory nerve stimulation
  - sneezing and itching nose & palate, throat, and ears
- parasympathetic reflex
  - rhinorrhea
- vasodilation & increased permeability of postcapillary venules
  - both rhinorrhea and congestion
- late allergic response;
  - recruitment, adherence, activation of epithelial cells, eosinophils, basophils, mast cells, T cells, and Langerhans cells
  - upregulation of the expression and mobilization of cell adhesion molecules

Practical issues

- More effective than cromolyn sodium
- Significantly less effective than intranasal corticosteroids
- Reduce symptoms
- Improve quality of life
- Dose–response curve, relatively flat

Selection

- No H1 antihistamine emerges with an overall superior efficacy profile that is clinically relevant.
  - safety
  - convenience of dose regimen
  - patient preference.

Allergic conjunctivitis

- Oral H_1-antihistamine
- Preferably a second-generation
- Topical ophthalmic, rapid onset of action of 3 to 15 min
- More favorable H1 antihistamines benefit/risk ratio than NSAIDs, decongestants, and glucocorticoids

Allergic conjunctivitis

- H1 antihistamines administered orally or applied directly to the conjunctivae relieve the itching, erythema, tearing, and edema
- Most ophthalmic H1 antihistamine formulations also function as mast cell stabilizers, because H1 antihistamines in high concentrations are applied directly to the conjunctivae; these high concentrations are difficult to achieve after oral dosing

Other diseases

- Upper respiratory tract infections
- Otitis media
- Asthma
- Urticaria
- Anaphylaxis
- Atopic dermatitis
- Insomnia and other CNS symptoms, and for vertigo or motion sickness

Adverse effects

- Central nervous system
- Serious toxicity
- Fatality
- Drugs of abuse

Adverse effects

- Cyproheptadine and ketotifen can increase appetite and cause weight gain, which does not occur with other antihistamines
- As regards the safety of these drugs, warnings have been issued, by the European Medicines Agency (EMA) on the use of first-generation anti-H1 for children under two years of age, especially for hydroxyzine.

Adverse effects

- That drug is associated with a low but definite risk of QT tract prolongation and torsade de pointes, conditions that can lead to an abnormal rhythm until cardiac arrest.

- Regarding the pediatric age, the maximum daily dose of hydroxyzine should not exceed 2 mg/kg (maximum 50 mg/day) in children weighing less than 40 kg.


Thank you