

# Histamine and H<sub>1</sub>-Antihistamines

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# Objectives

**Learners will realize •**

**What is histamine and how does it work? •**

**What are H1-antihistamines? •**

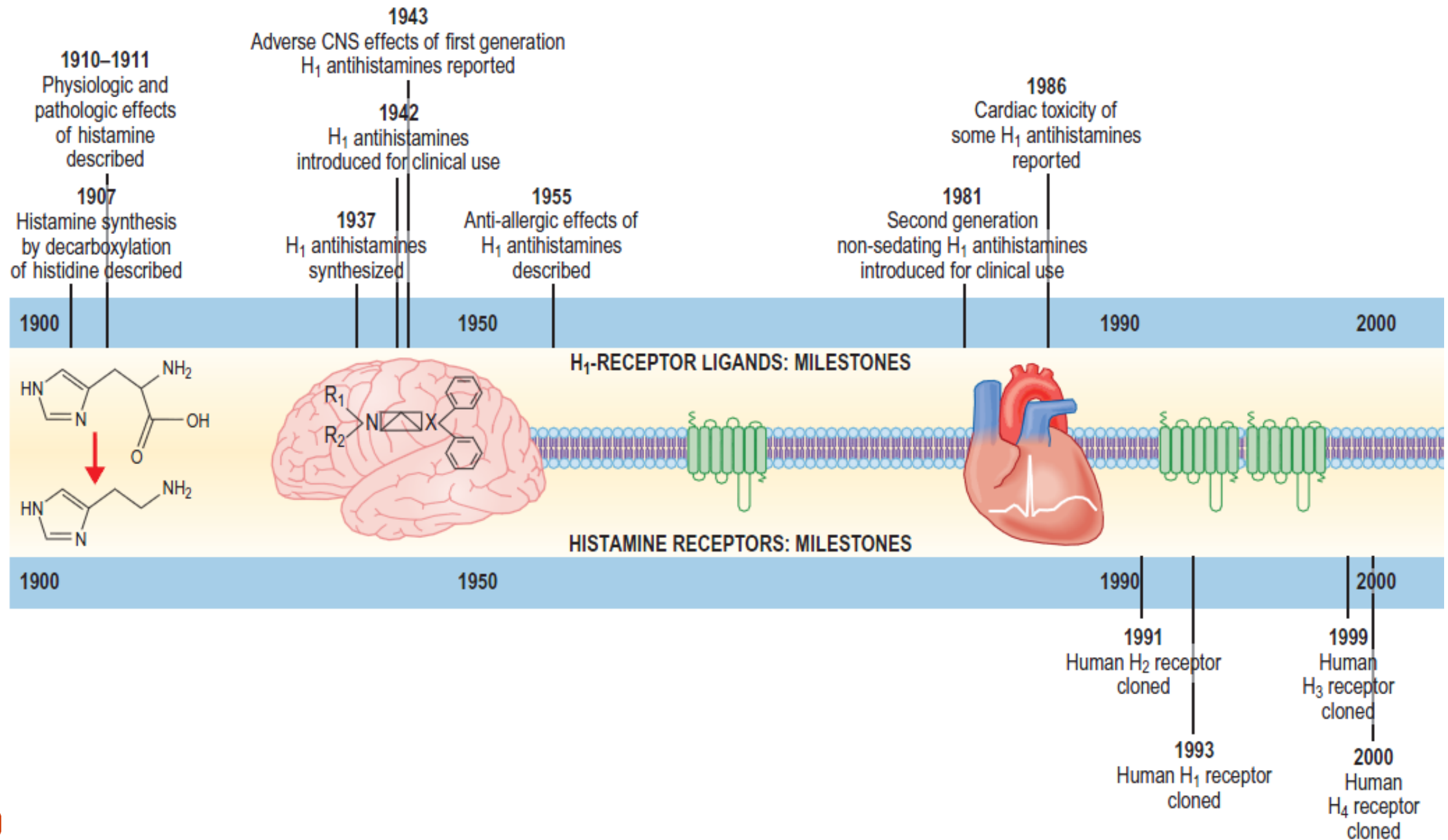
**What is the best time for their prescription and why? •**

**What is the indication for H1-antihistamine use? •**

**What are the H1-antihistamines side effects? •**

# Introduction

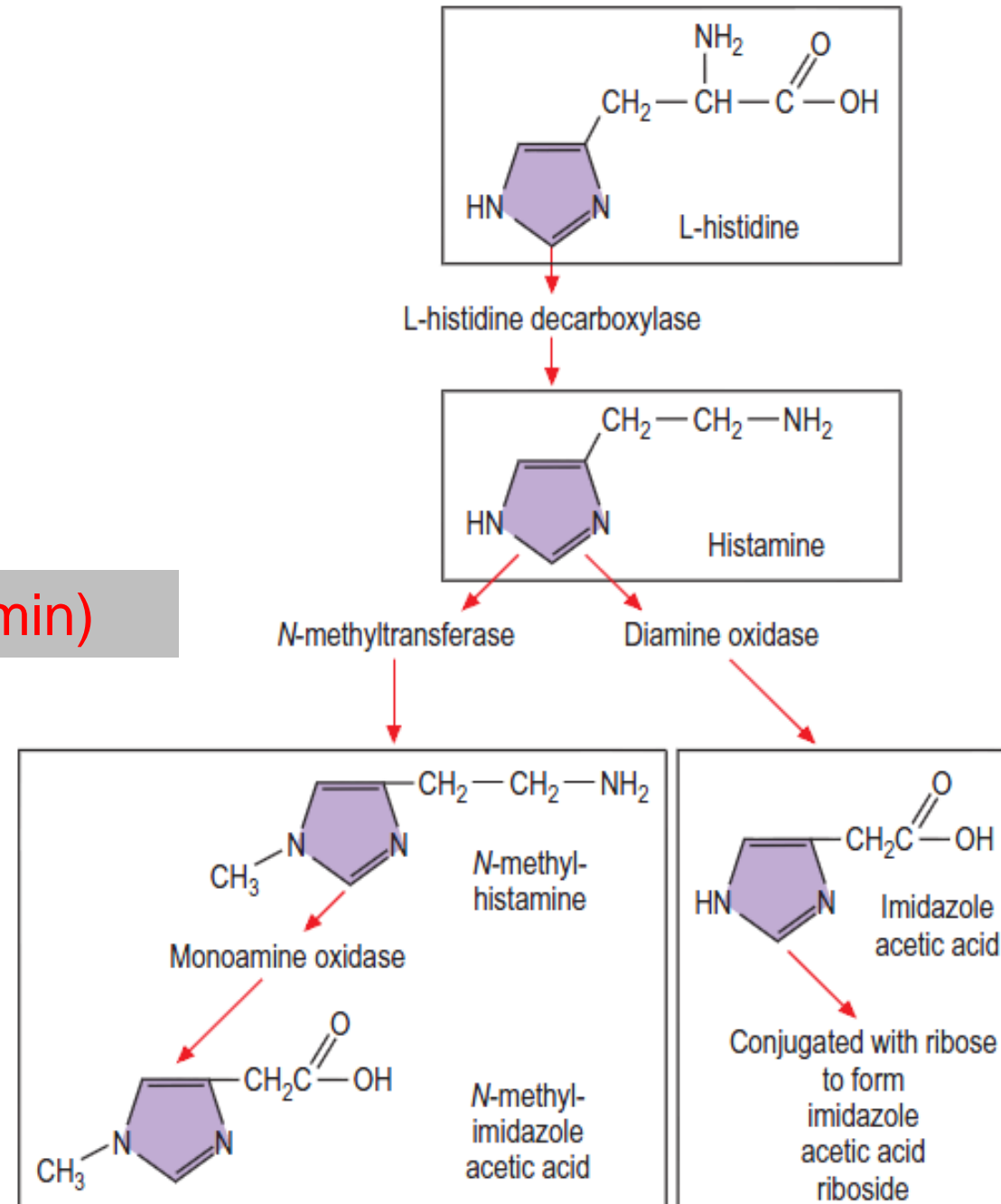
- Histamine was isolated and characterized more than 100 years ago
- Medications targeting its receptors have been used for 70 years.
- Histamine has a major role in human health and disease
- Exerting diverse biologic effects through 1 of its 4 receptors, H1-, H2-, H3-, or H4-receptor.



# Introduction

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

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

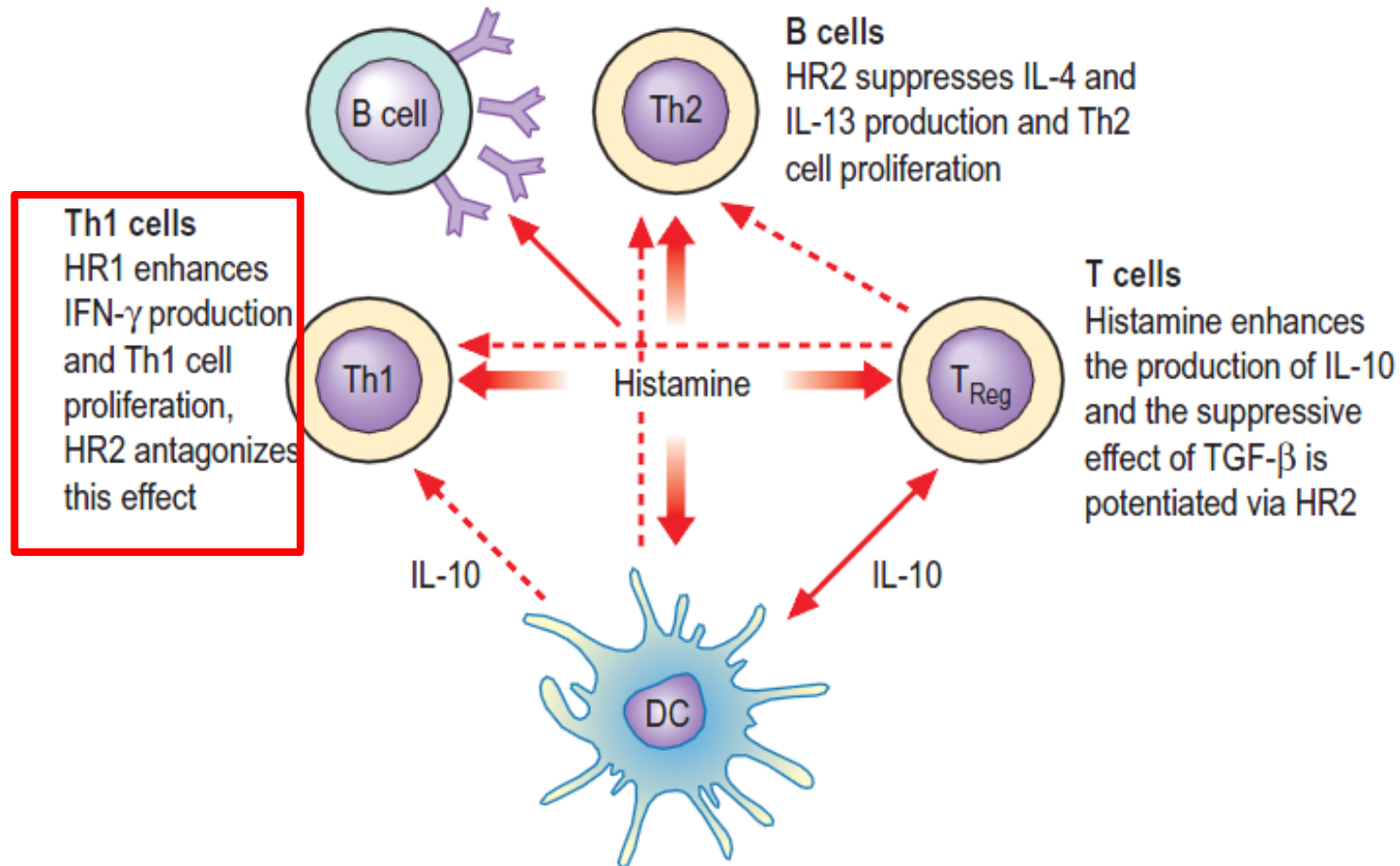
- Mast cells
- endothelial cells of the vessels
- cells of sensitive nerve fibers
- bronchial smooth muscles

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

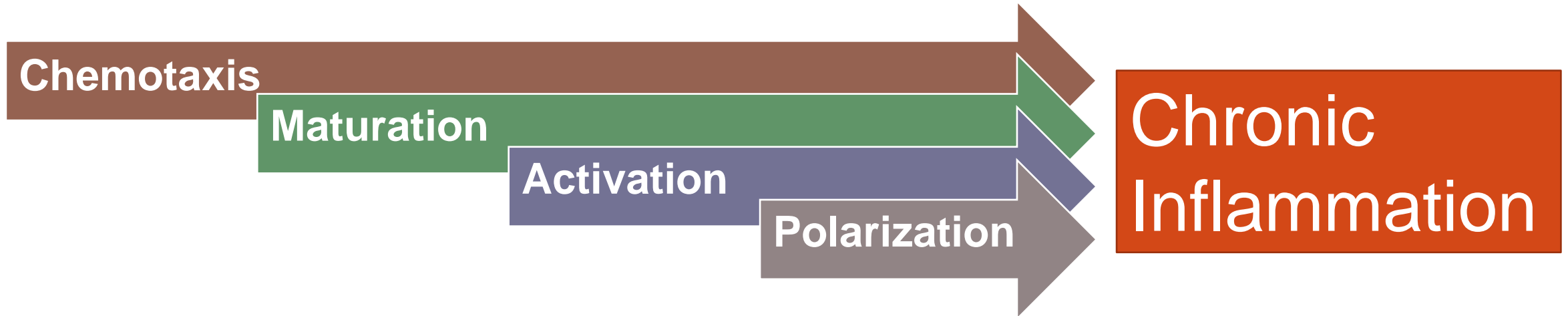


Dendritic cells

HR1 increases antigen-presenting capacity and Th1 priming.

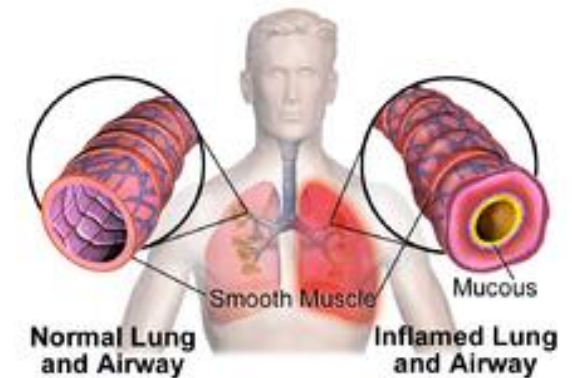
HR2 induces IL-10 production, suppresses antigen presentation and aids development of IL-10-secreting Y cells

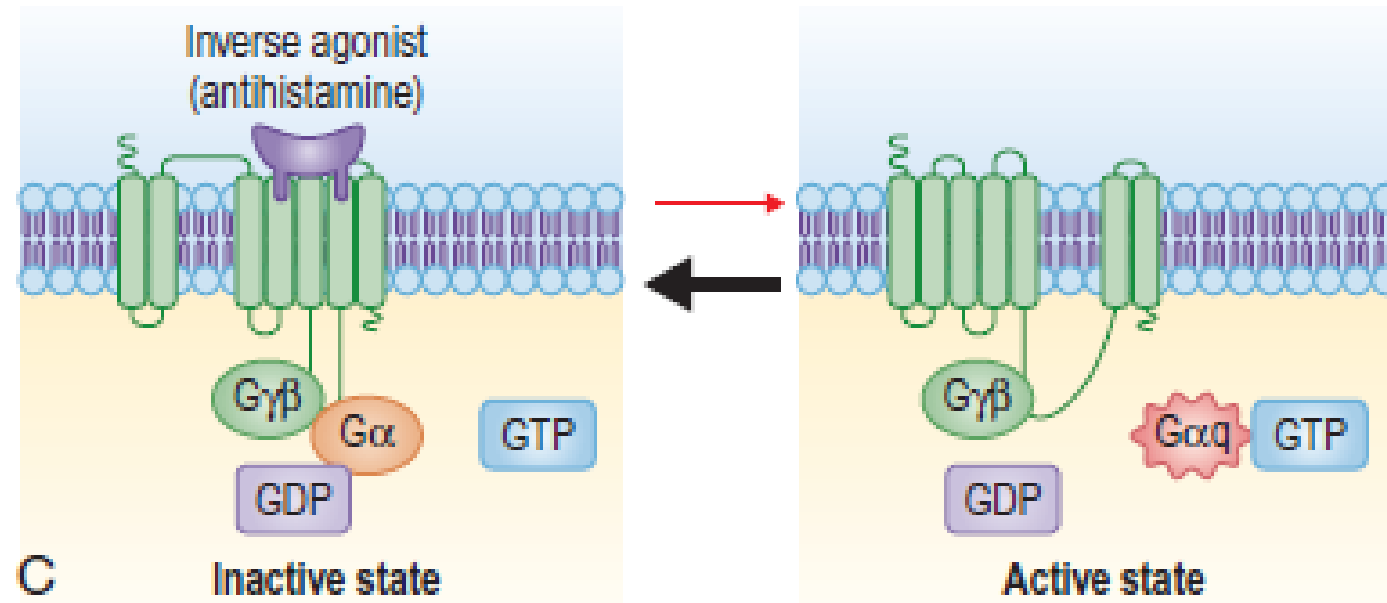
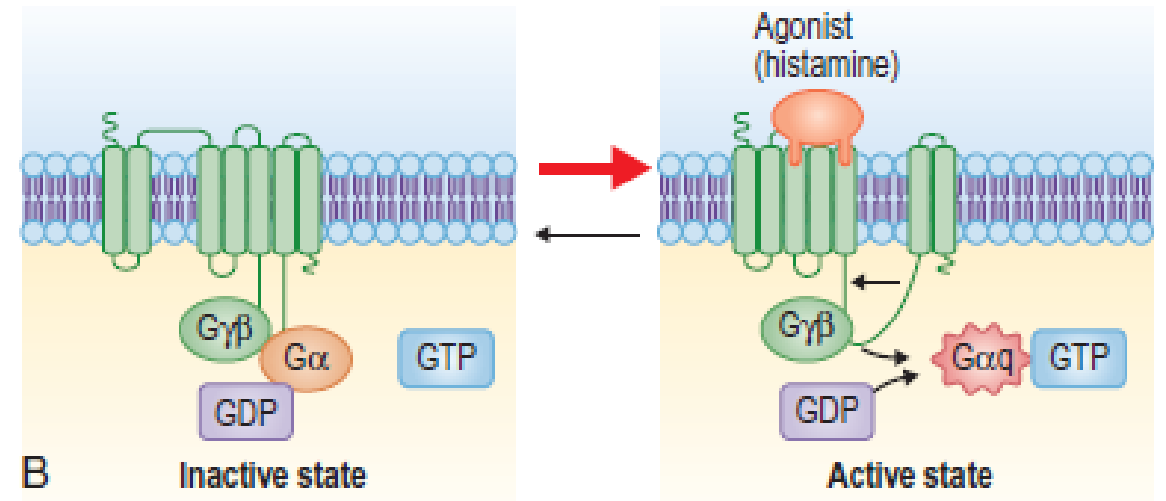
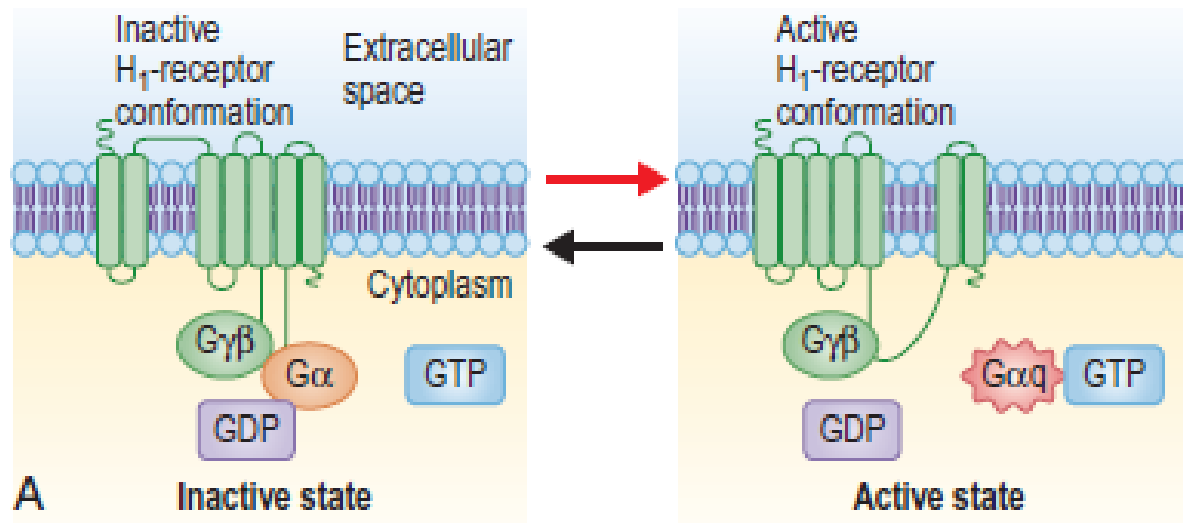
# Histamine effect on mast cells and eosinophils

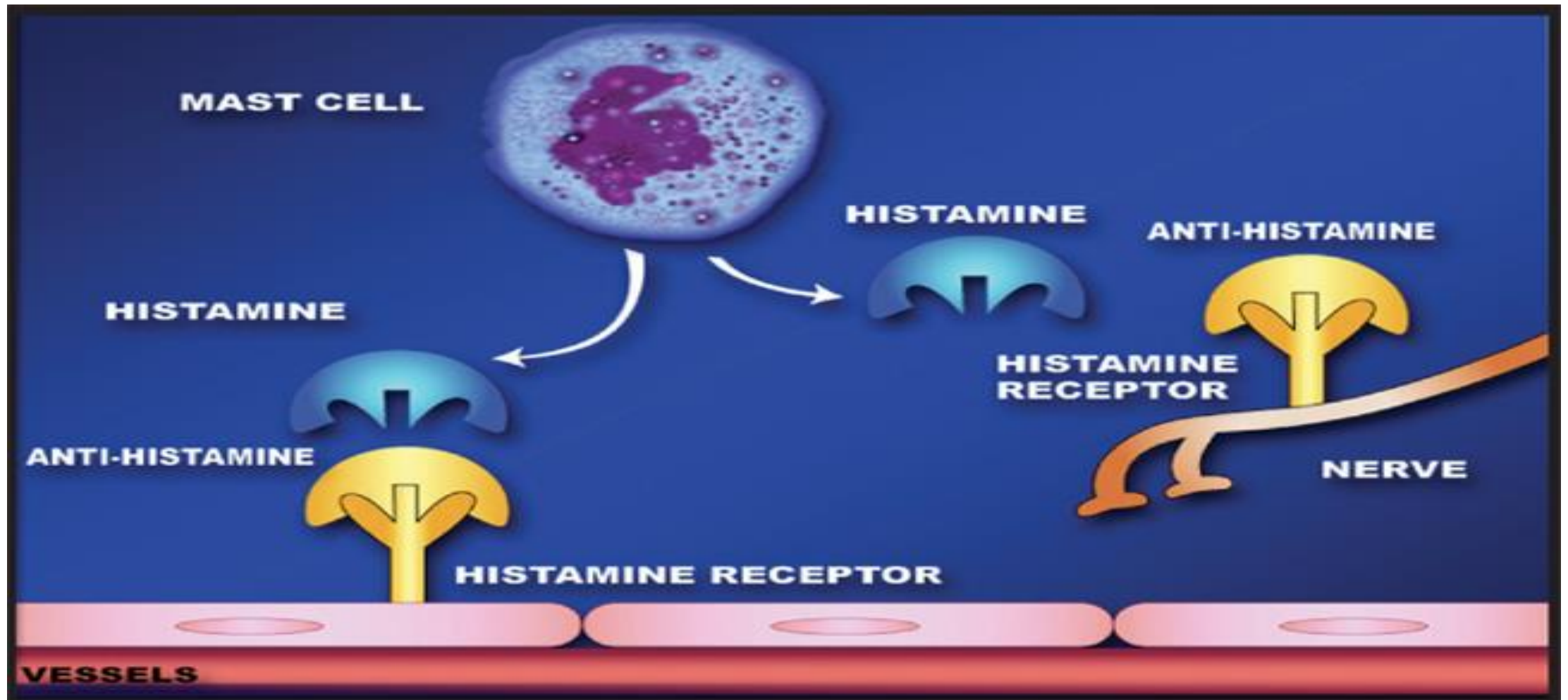


# Histamine effects (H1-receptor)

- 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.







# 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<sub>1</sub>-antihistamines: chemical and functional classification

Chemical class	Functional class	
	First-generation	Second-generation
Alkylamines	Brompheniramine, chlorpheniramine,	Acrivastine
Piperazines	hydroxyzine	Cetirizine, levocetirizine
Piperidines	Azatadine, ciproheptadine, ketotifen	Astemizole, desloratadine, ebastine, fexofenadine, levocabastine, loratadine, olopatadine, terfenadine
Ethanolamines	clemastine, dimenhydrinate, diphenhydramine,	–
Ethylenediamines	Antazoline, pyrillamine, tripeleminamine	–
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

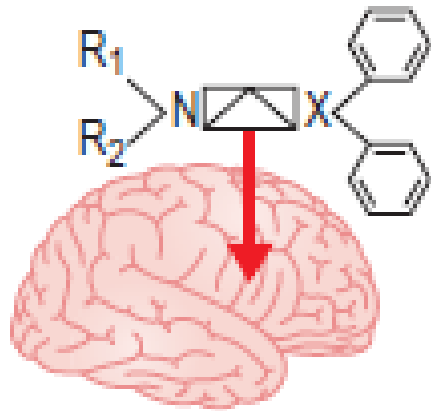
# Cross the blood–brain barrier

- 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

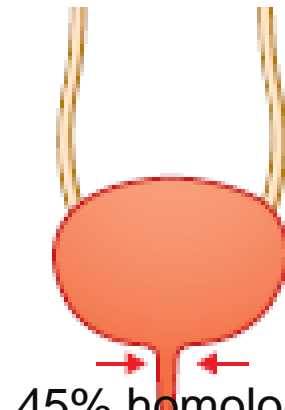
## Potential Adverse Effects of First (Old)-Generation H<sub>1</sub> Antihistamines



CNS H<sub>1</sub> receptors

↓ Alertness, cognition,  
learning, memory,  
and psychomotor  
performance

↑ Impairment with or  
without sedation



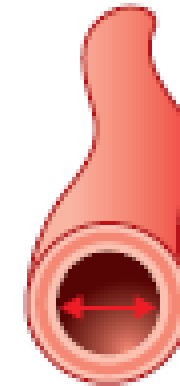
45% homology  
Muscarinic receptors

↑ Dry mouth  
↑ Urinary retention  
↑ Sinus tachycardia



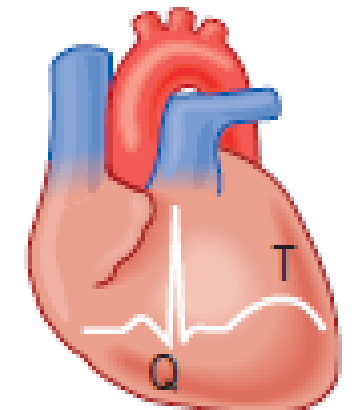
Serotonin receptors

↑ Appetite  
↑ Weight gain



α-Adrenergic receptors

↑ Dizziness  
↑ Postural hypotension



Cardiac ion channels  
(I<sub>Kr</sub>, I<sub>Na</sub>, 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 within 1-3 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%)

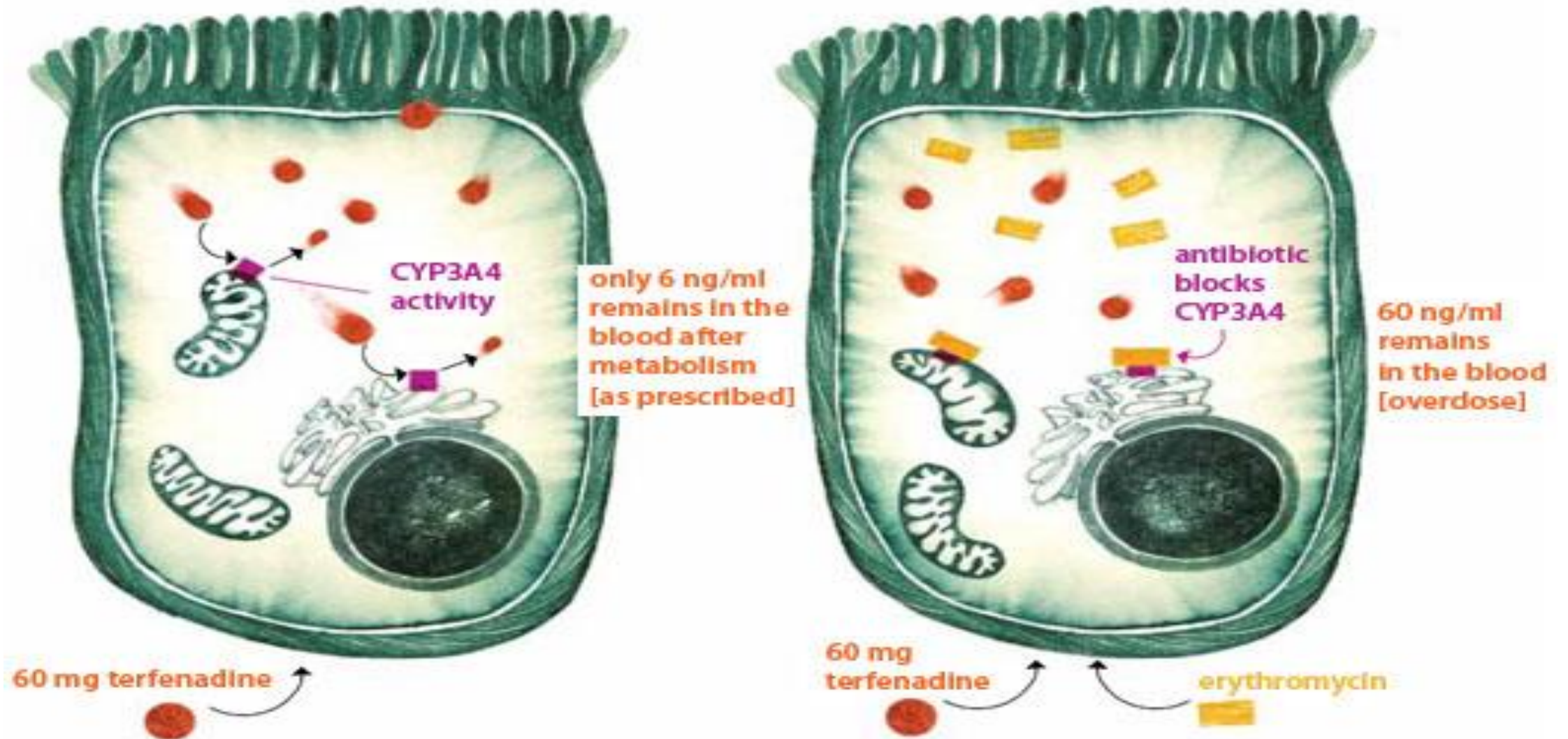


# Pharmacodynamics

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

## 2<sup>nd</sup> 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

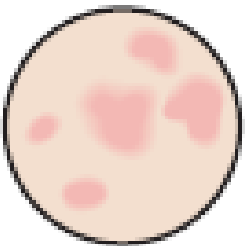

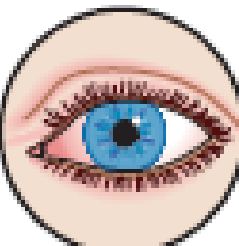
- a rapid onset of action of 3 to 15 minutes.
- Some are reported to treat nasal symptoms in addition to conjunctival symptoms.
- In allergic conjunctivitis, a more favorable benefit/risk ratio than all other classes of medications, including NSAIDs, decongestants, and glucocorticoids

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# 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, Pyrillamine
  - 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<sub>1</sub>-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<sub>1</sub>-antihistamine
- Preferably a second-generation
- Topical ophthalmic, rapid onset of action of 3 to 15 min
- More favorable H<sub>1</sub> antihistamines benefit/risk ratio than NSAIDs, decongestants, and glucocorticoids



Mata kucing yang disebabkan karena alergi konjungtiva.

# Allergic conjunctivitis



Mata kanan yang menyedihkan karena alergi konjungtiva.

- 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**