Drugs affecting the immune system

Antiallergic drugs, immunosuppressants
Immunostimulators

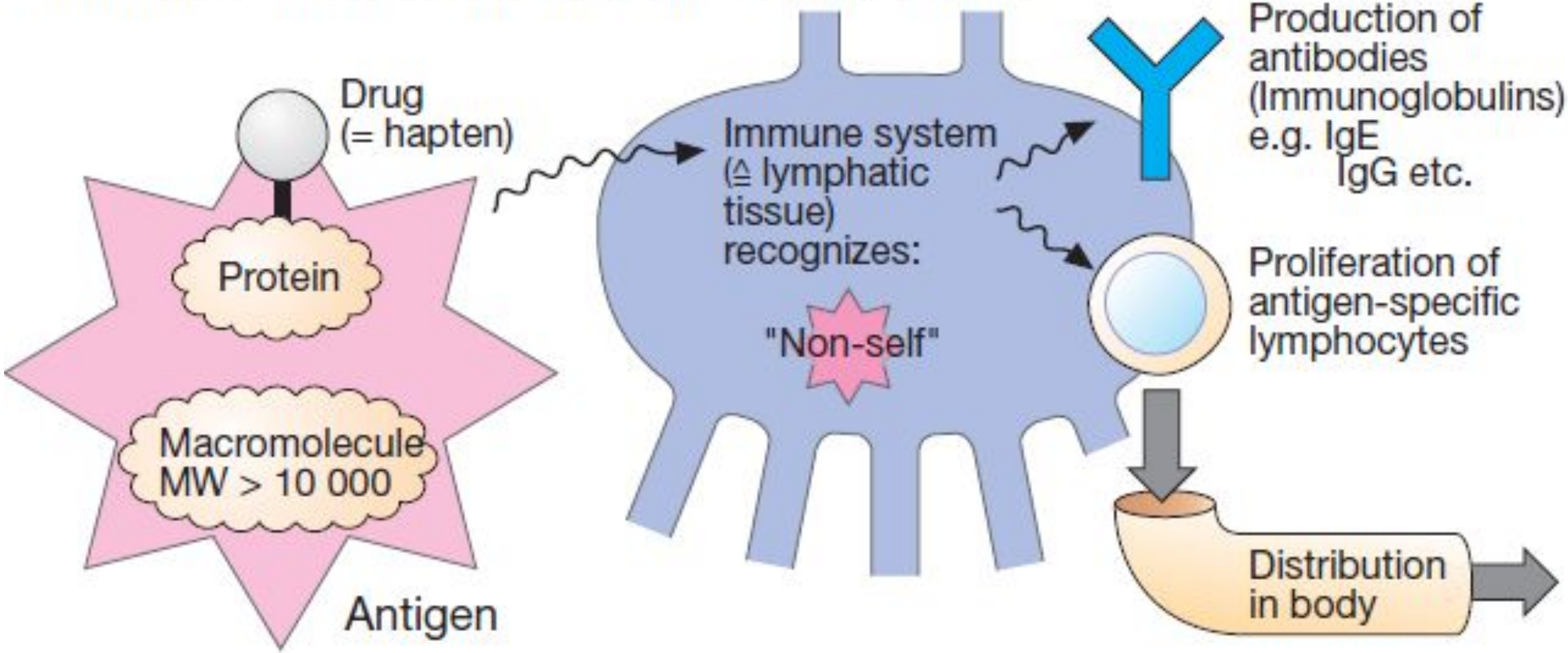
Pathologically excessive immune responses to an antigen that cause damage to the tissue of a sensitized macroorganism are called allergic (hypersensitivity) reactions. Such reactions are relatively common.

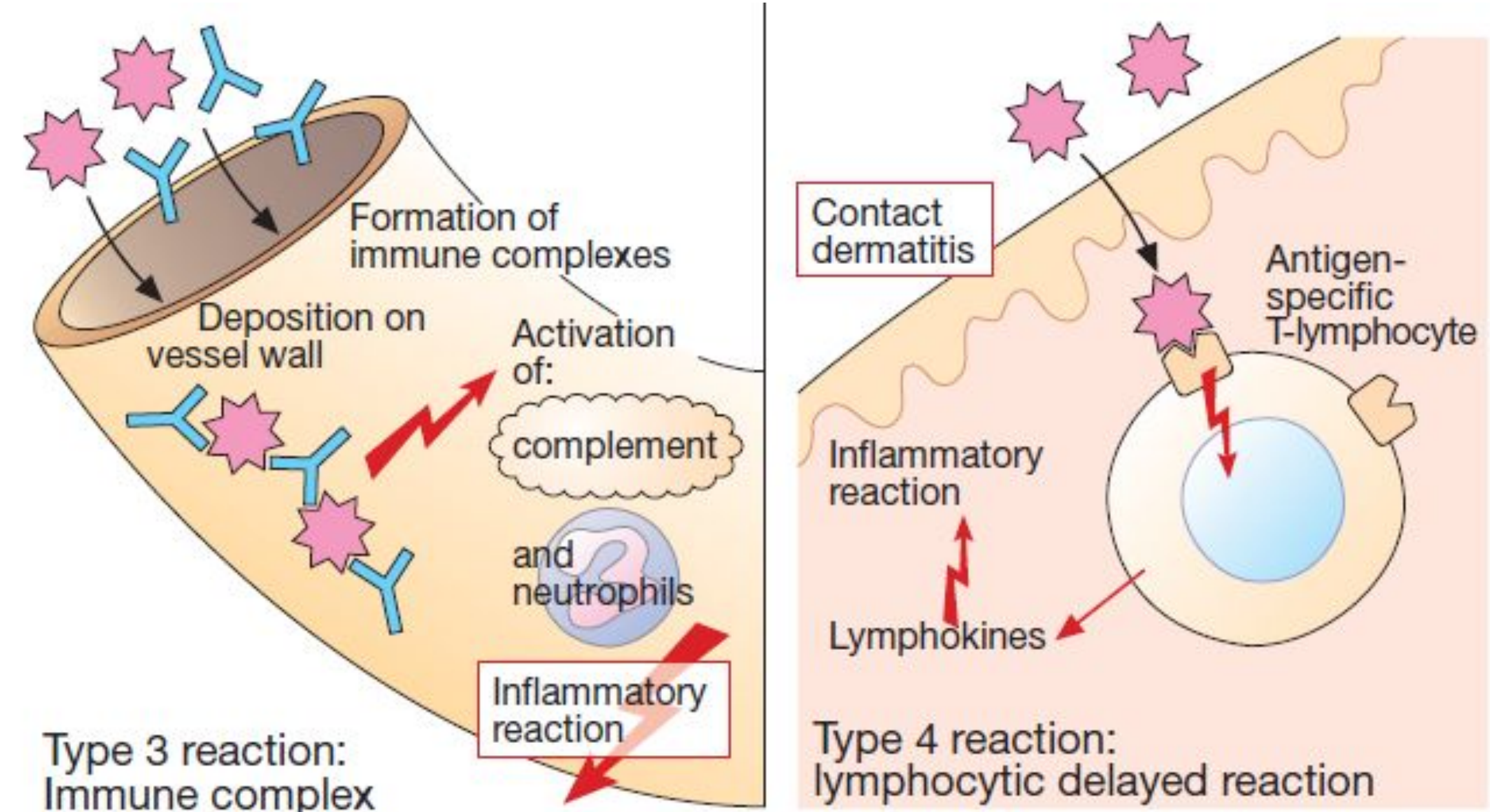
There are 2 main mechanism of immunogenesis:

- Humoral, that occurs due to antibody production;
- Cellular one that involves many immunocompetent cells.

Hypersensitivity reactions can be divided into the following types: **immediate types and delayed type of hypersensitivity**.

Reaction of immune system to first drug exposure




Formation of immune complexes
Deposition on vessel wall
Activation of:
complement
and neutrophils
Inflammatory reaction
Type 3 reaction: Immune complex
Contact dermatitis
Antigen-specific T-lymphocyte
Inflammatory reaction
Lymphokines
Type 4 reaction: lymphocytic delayed reaction

Immediate type of hypersensitivity (allergy) is manifestered minutes or hours after subsequent exposure to the antigen. It occurs due to the interaction between antigens and antibodies. Antibodies are produced by plasmocytes. They are fixed on the high-affinity receptors on the cells (mast cells, basophils). Interaction between an allergen and antibodies leads to tissue damage. Biologically active substances release from cells.

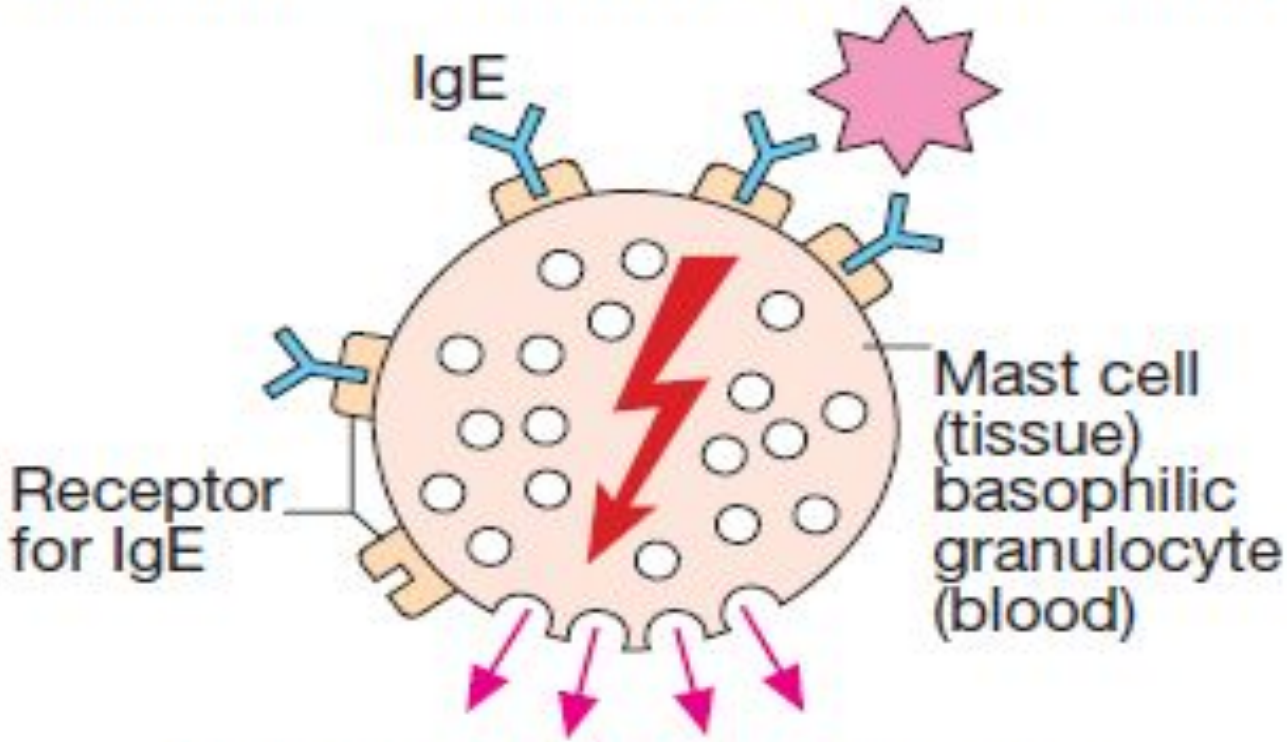
Among reactions of immediate type there are allergic bronchospasm, rhinitis, conjunctivitis, urticaria, anaphylaxis, drug-dependent thrombocytopenic purpura, serum sickness, Arthus's phenomenon and others.

Anaphylactic reactions are the most dangerous.

The interaction of the Antigen with 2 JgE on the surface of the mast cell or basophile is accompanied by:

- The opening of Ca-channels and entry of Ca++ into the cell;
- Activation of phospholipase A2 with increasing of membrane permeability and formation of prostaglandins and leukotrienes;
- Degranulation of mast cells (basophils), release of mediators of allergy (histamine, serotonin, bradykinin) into the surrounding tissue;
- Tissue damage, development of swelling, bronchospasm, collapse, skin rashes, itching, etc.

Immune reaction with repeated drug e



Type 1 reaction:
acute anaphylactic reaction

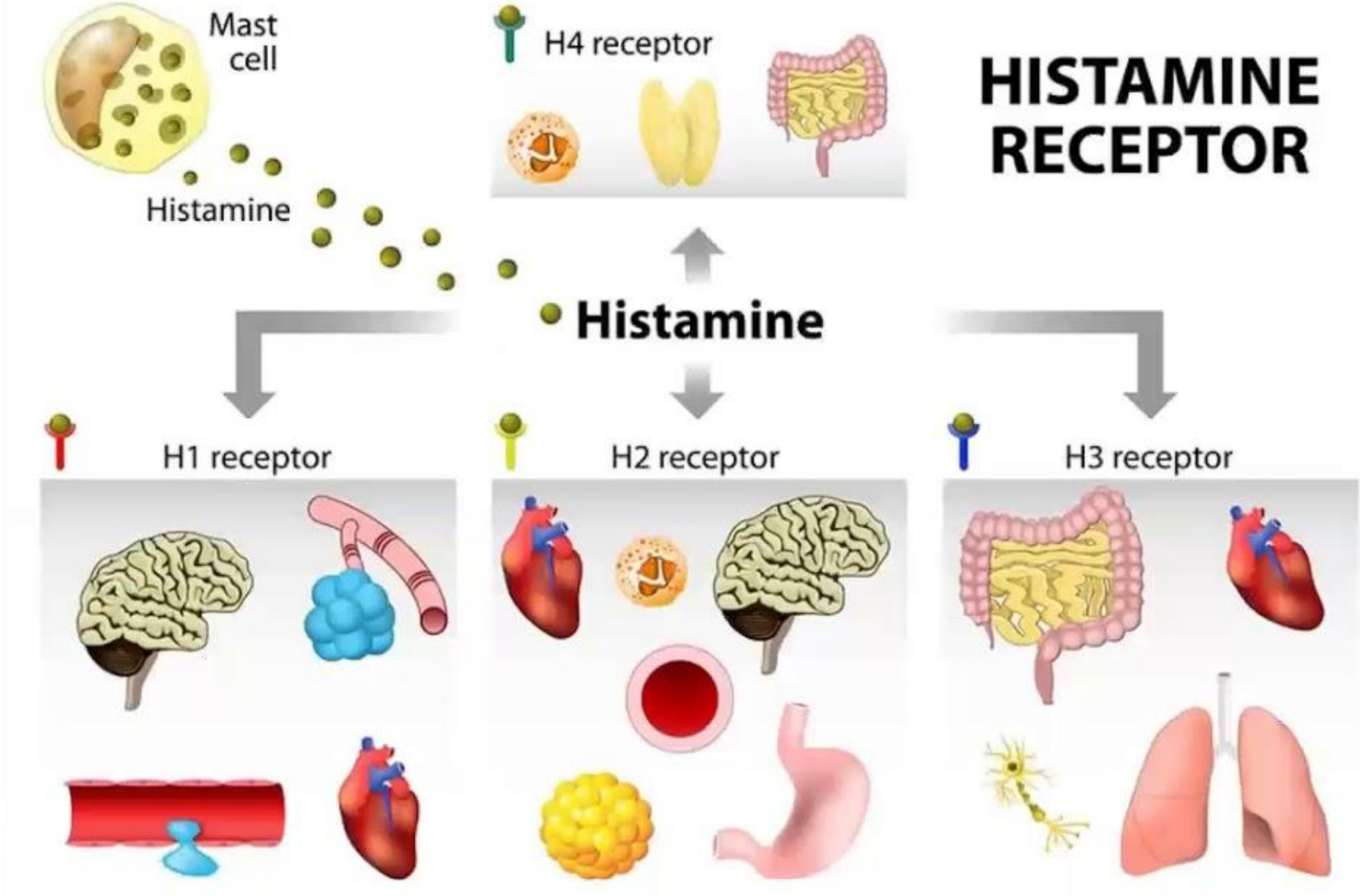
Delayed type of hypersensitivity becomes apparent after 2-3 days and later. It is the result of cell immunity and depends on the presence of sensitizing T-lymphocytes. On the surface of such T-L there are special receptors which recognize antigens, localized on macrophages, and interact with them. Cytokines release from T-L and damage cells.

Tuberculin reactions, contact dermatitis, graft-versus-host reaction and some types of immune pathology are the result of delayed type of hypersensitivity.

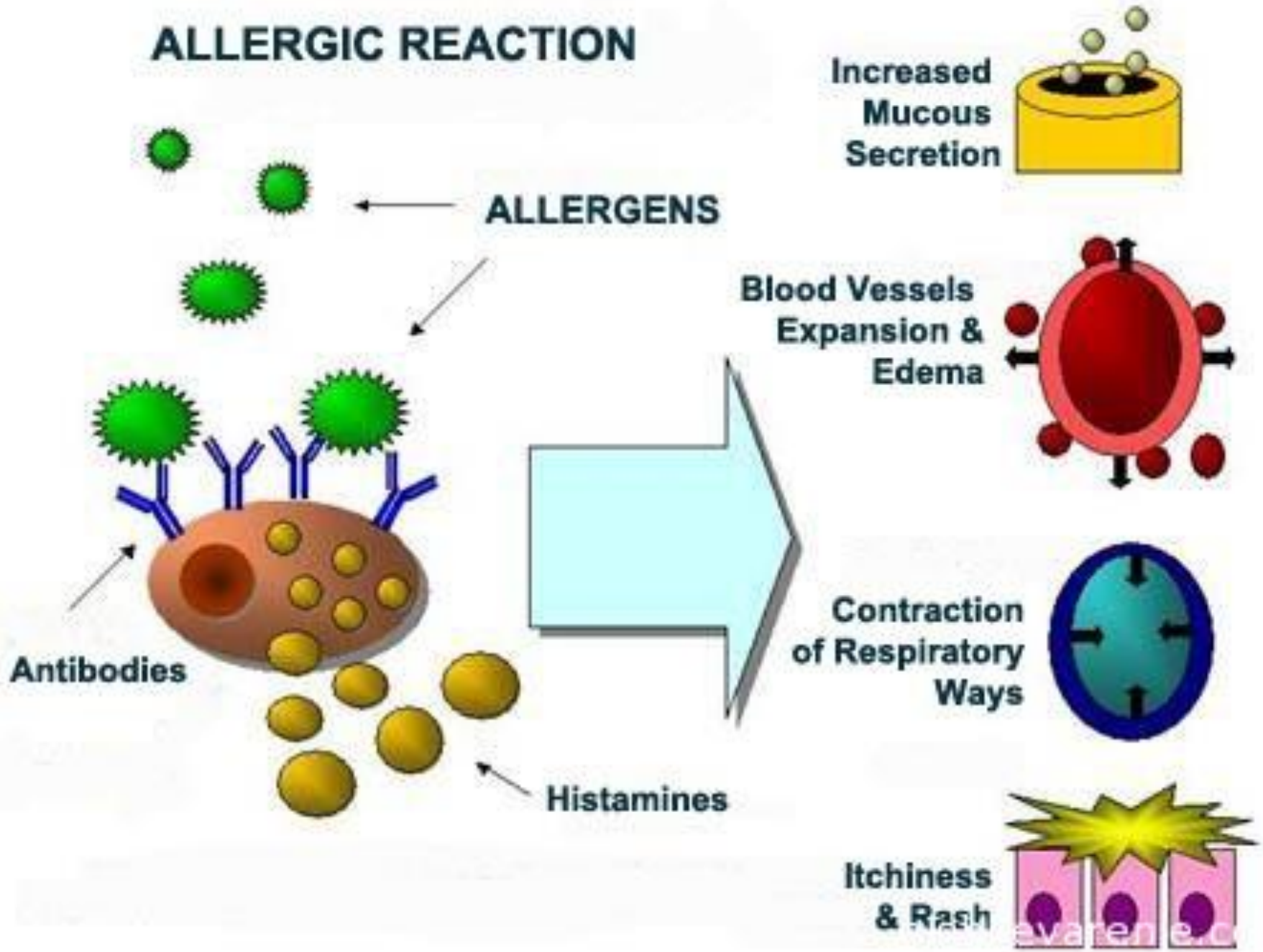
- Treatment of allergic disease should be started with specifying the origin of the allergen (plant pollen, medical drugs, certain food products, animal hair). Avoidance of contact with allergen produces the best result.
- Specific hyposensitization may be used. Low doses of the identified allergen are introduced and this decreases the specific sensitivity.
- Non-specific hyposensitization may be used if antigen is unknown.

Histamine is one of the main mediators of allergic reactions. He stimulates 4 main types of histamine receptors.

type	**localization**
H1	Smooth muscles of bronchi, arteries, veins, capillaries, the heart, neurons of CNS
H2	Parietal cells of gastric mucosal membrane, the heart, arterial smooth muscles, myometrium, neurons of CNS, mast cells
H3	CNS neurons, gastrointestinal tract, cardiovascular system, upper respiratory tract
H4	Intestine, spleen, thymus, immunoactive cells (T-cells, neutrophils, eosinophils)


Mast cell
Histamine
H4 receptor
HISTAMINE RECEPTOR
Histamine
H1 receptor
H2 receptor
H3 receptor

The stimulation of H1 receptors	The stimulation of H2-R
• Increase in tone of smooth muscles of the bronchi, gastrointestinal tract, uterus. • Decrease in the tone of smooth muscle of arteries. • Increase in tone of smooth muscle of veins. • Increased vascular permeability and the development of tissue edema. • The decrease in systemic vascular resistance and blood pressure. • Inhibition of AV conduction	↑ secretion of gastric glands.


ALLERGIC REACTION
ALLERGENS
Antibodies
Histamines
Increased Mucous Secretion
Blood Vessels Expansion & Edema
Contraction of Respiratory Ways
Itchiness & Rash

Classification of anti-allergic drugs

1. Drugs that prevent the formation and release of histamine and other mediators from sensitized mast cells and basophils:

- ❑ Adrenergic agonists (epinephrine, salbutamol, fenoterol);
- ❑ Dimethylxanthine (aminophylline);
- ❑ M-blockers (ipratropium bromide)
- ❑ Specific stabilizers of membranes of mast cells (cromoglicici acid, ketotifen);
- ❑ Glucocorticoids (Prednisolone, Dexamethasone, Beclomethasone)

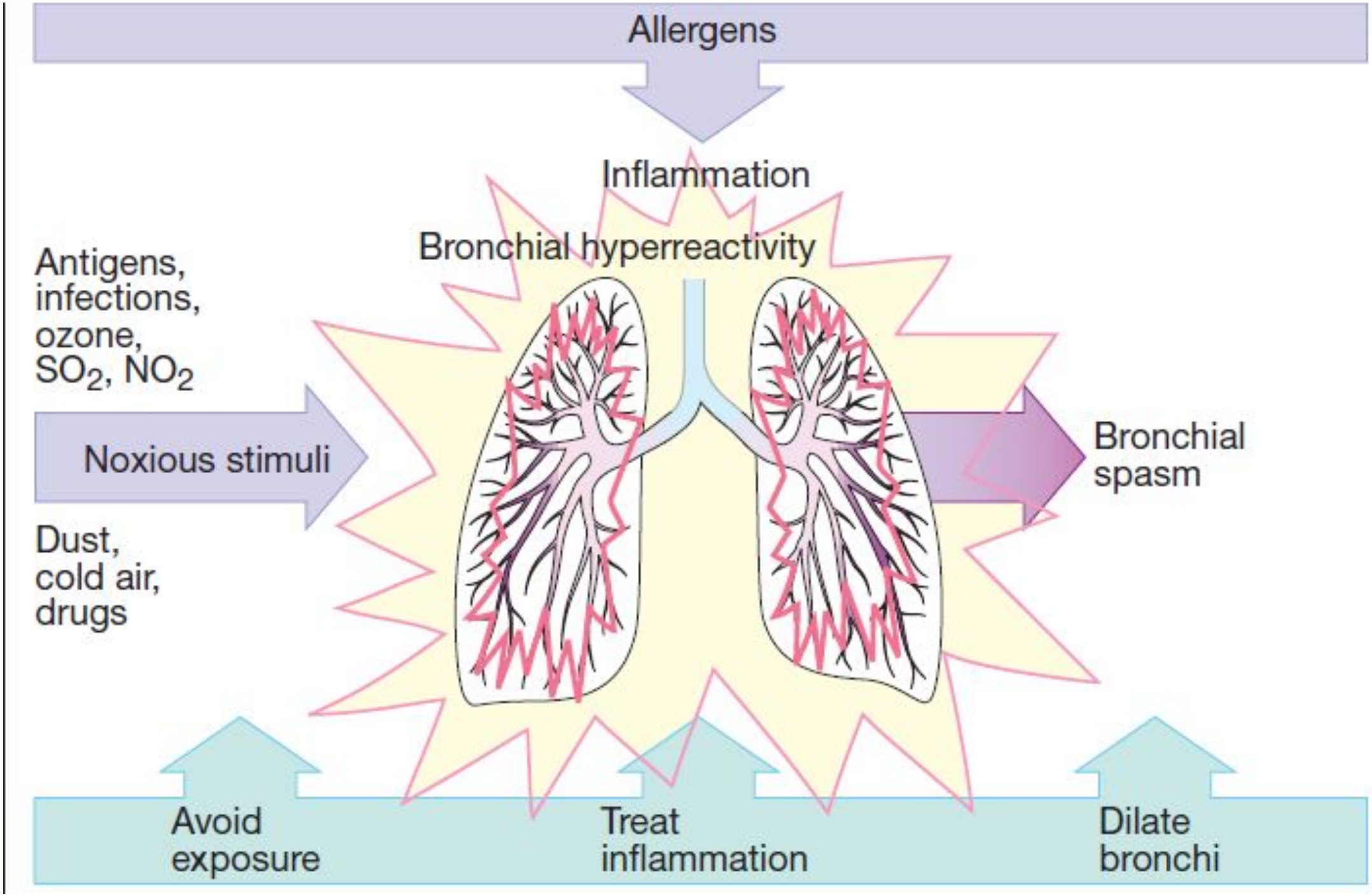
2. Drugs reducing the interaction of biologically active substances (mediators of allergy) with the tissue receptors:

- ❑ blockers H1-histamine receptors (diphenhydramine, etc.);
- ❑ blockers of LT-receptors (montelucast)

3. Drugs eliminating the symptoms of allergic reactions:

- ❖ anaphylactic shock - epinephrine, phenylephrine, prednisolone
- ❖ bronchospasm – salbutamol, fenoterol, aminophylline, ipratropium bromide

4. Drugs reducing inflammation and tissue damage – NSAIDs and SAIDS


Allergens
Inflammation
Bronchial hyperreactivity
Antigens,
infections,
ozone,
SO_2, NO_2
Noxious stimuli
Dust,
cold air,
drugs
Bronchial
spasm
Avoid
exposure
Treat
inflammation
Dilate
bronchi

Mechanism of anti-allergic action of β-adrenoceptors agonists:

They stimulate β2-AR on the membrane of mast cells and increase activity of adenylyl cyclase

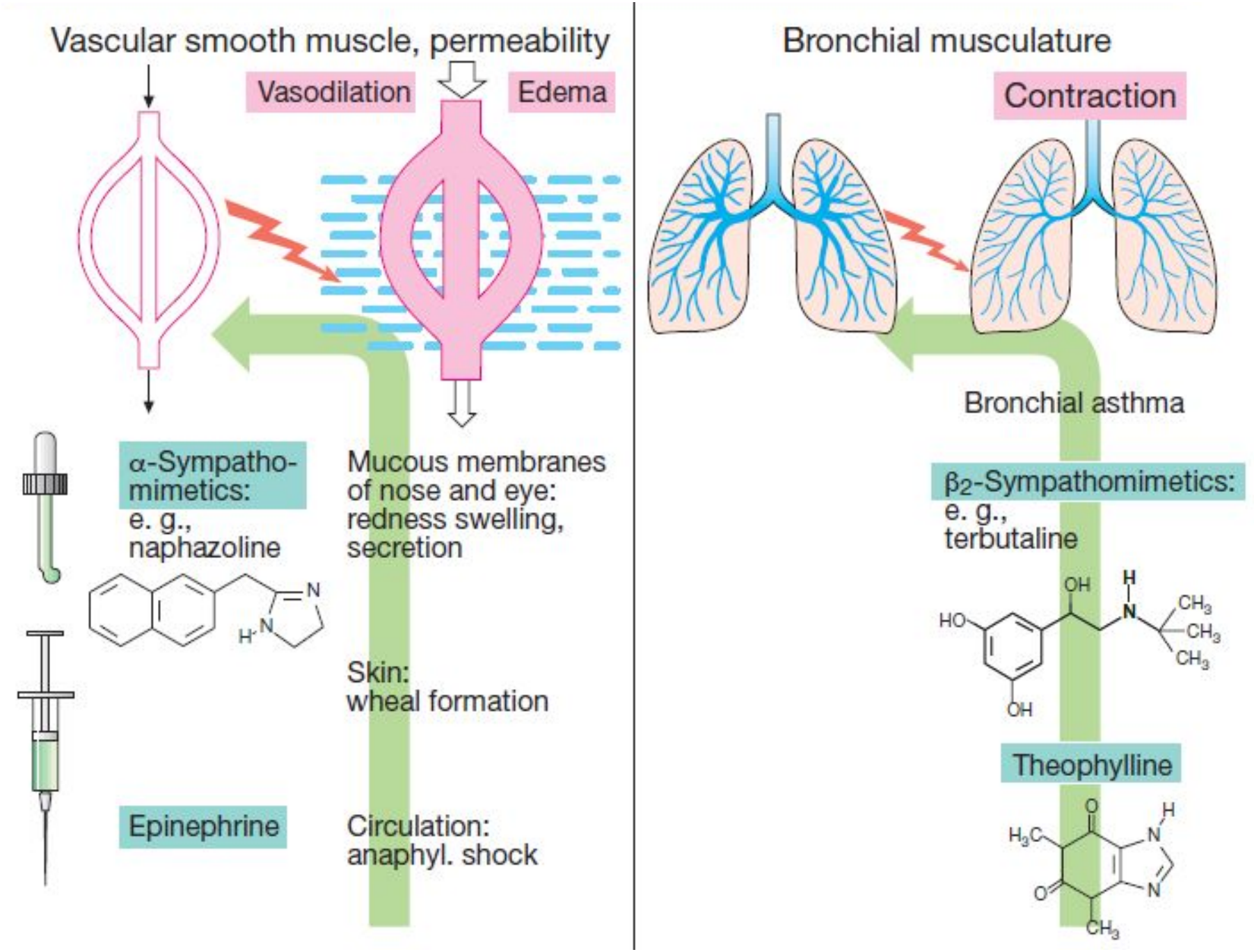
→increase in cAMP levels

→closing of the Ca channels→ decrease in the number of active Ca in the cell

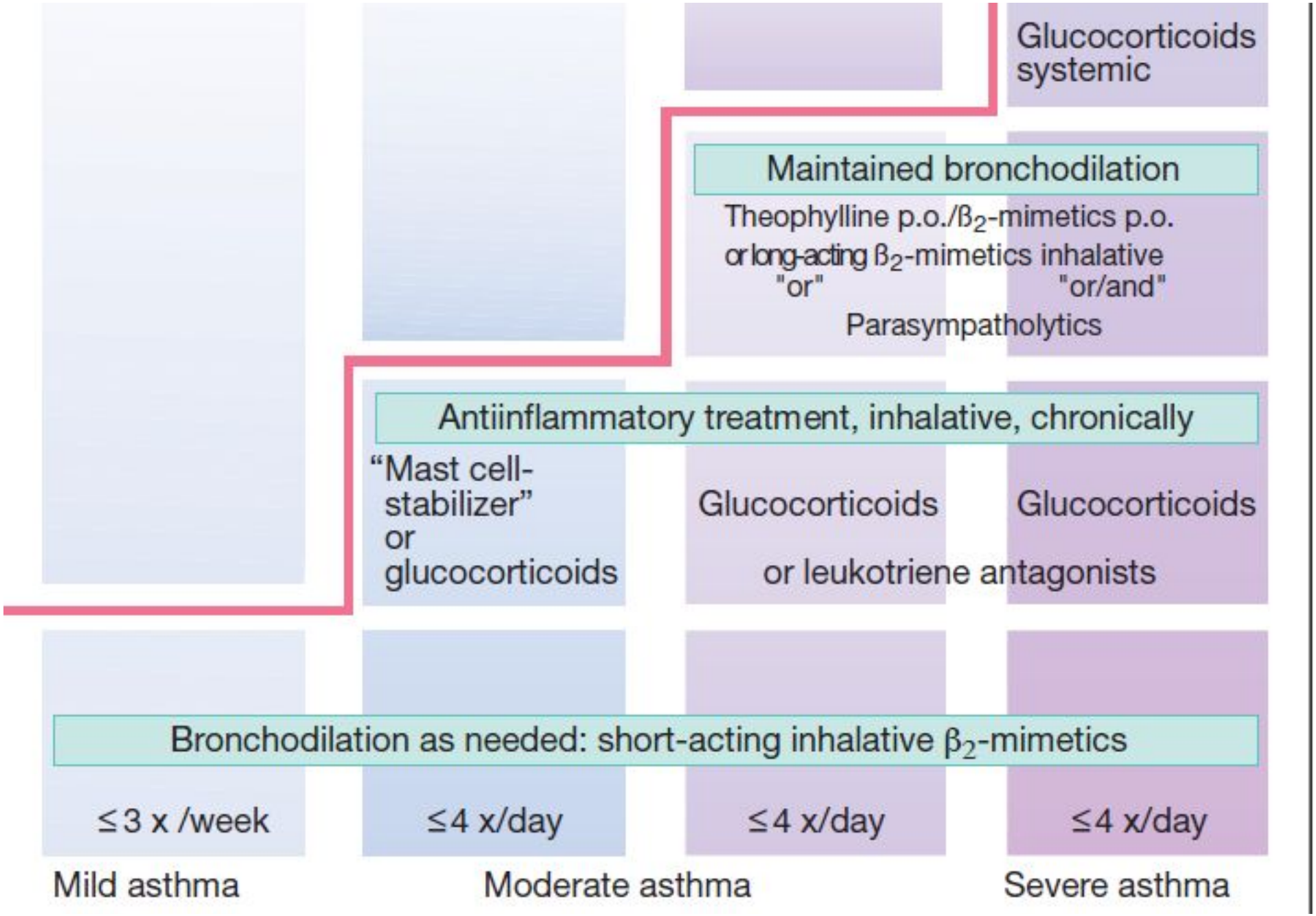
→inhibition of degranulation of mast cells

→decrease in the release of mediators of Allergy

- Salbutamol and fenoterol expand bronchi and help expectorate sputum. They are administered via inhalers for the relief of bronchospasm (effect in 2-3 min.). Salmeterol, Formoterol are used orally or via inhalers in order to prevent bronchospasm.
- Epinephrine is also used in a case of bronchospasm. It stimulates α-AR and increase blood pressure. Epinephrine is used for relief of anaphylactic shock.


Vascular smooth muscle, permeability
Vasodilation
Edema
α-Sympatho-
mimetics:
e. g.,
naphazoline
Mucous membranes
of nose and eye:
redness swelling,
secretion
Skin:
wheal formation
Epinephrine
Circulation:
anaphyl. shock
Bronchial musculature
Contraction
Bronchial asthma
β2-Sympathomimetics:
e. g.,
terbutaline
Theophylline

- **Methylxanthines (aminophylline, theophylline)** block adenosine receptors on the membrane of mast cells, inhibit IgE landing on mast cells. They increase the catecholamines' levels and reduce the process of degranulation.
- They inhibit phosphodiesterase and increased cAMP level, reduce level of Ca and decrease the process of degranulation.
- They also increase the level of T-suppressors and decrease excessive allergic reaction. They have myotropic bronchodilator effect.
- Indications for use: -relief of an attack of BA (IV) - prevention of bronchial spasm (tabl.)

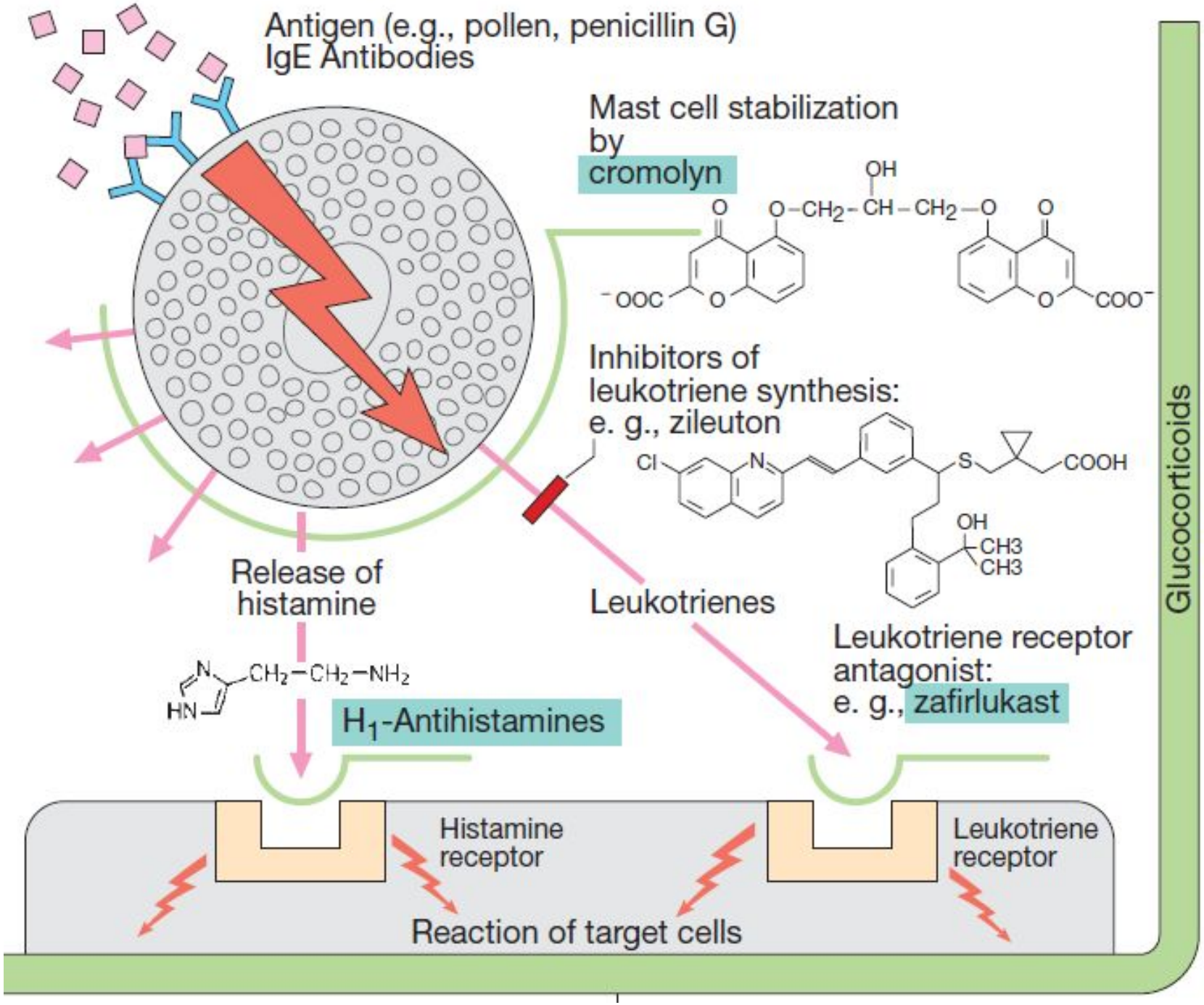

Glucocorticoids systemic
Maintained bronchodilation
Theophylline p.o./ß2-mimetics p.o.
or long-acting ß2-mimetics inhalative
"or"
"or/and"
Parasympatholytics
Antiinflammatory treatment, inhalative, chronically
"Mast cell-stabilizer" or glucocorticoids
Glucocorticoids
Glucocorticoids
or leukotriene antagonists
Bronchodilation as needed: short-acting inhalative β2-mimetics
≤3 x /week
≤4 x/day
≤4 x/day
≤4 x/day
Mild asthma
Moderate asthma
Severe asthma

Cromoglicici acid (Sodium cromoglycate):

1. Blocks chloride channels in the membrane of the mast cells⟶ closing the Ca channels⟶ Stabilization of the membranes of mast cells and granules, ↓degranulation.
2. ↓ release of mediators of allergy (histamine, SRS-A).
3. Increases the sensitivity of β2-AR to catecholamines
4. Reduces the need for inhaled corticosteroids.

- It is used for the prophylaxis bronchial asthma attacks. The drug is administered via inhaler.
- The onset of action develops after 2 weeks Pronounced effect develops within 4-5 weeks.
- It is poorly soluble in water, it is not absorbed in the digestive tract. It can be used for prevention allergic rhinitis (drops) and food allergic reactions.

- **Ketotifen** is known to inhibit release of allergic mediators from mast cells. It also blocks H1-histamine receptors. It decreases the formation of IgE.
- K. is administered orally for the prevention of bronchial asthma attacks, hay asthma, rhinitis and other allergic reactions of the immediate type. The drug acts slowly and reaches its maximum effect in 3-4 weeks.
- The adverse effects: sedation, thrombocytopenia.


Antigen (e.g., pollen, penicillin G)
IgE Antibodies
Mast cell stabilization
by
cromolyn
Inhibitors of
leukotriene synthesis:
e. g., zileuton
Release of
histamine
Leukotrienes
Leukotriene receptor
antagonist:
e. g., zafirlukast
H1-Antihistamines
Histamine
receptor
Leukotriene
receptor
Reaction of target cells
Glucocorticoids

- Glucocorticoids reduce the formation of IgE (reduce the sensitization of the body).
- They block phospholipase A2, inhibit degranulation and release of histamine, serotonin and other allergy mediators, reduce the formation of leukotrienes. They reduce the synthesis of histamine, reduce the sensitivity of histamine receptors, increases the metabolism of histamine (promotes the synthesis of histaminase in the liver).
- They eliminate such manifestations of allergy symptoms as a decreasing of blood pressure and bronchospasm (symptomatic effect).
- Glucocorticoids are used in all allergic reactions of immediate type.

Glucocorticoids:

- A. *Systemic:* **hydrocortisone, prednisolone , dexamethasone, triamcinolone**

- B. *Inhalational:* **beclomethasone dipropionate, budesonide, fluticasone propionate**

- **Montelukast** blocks leukotriene receptors and causes anti-inflammatory effect. Such effect manifests as a reduction of vascular permeability, a decrease in the mucosal edema of the bronchi, suppression of the secretion of viscous sputum. Bronchodilation occurs due to the blockade of LTD4-R.
- It is used orally. Its clinical effect develops slowly (over 24 h). It is used for the prophylaxis of bronchial asthma.
- Adverse effects: headache, gastritis, skin allergies, myalgia.

- **Antihistamines (blockers of histamine H1-R)** block tissue receptors sensitive to histamine. They do not really affect the release of free histamine or histamine synthesis.
- They remove such effects of H. as increase in smooth muscle tone of bronchi, intestine, uterus; decrease in blood pressure, increase in capillary permeability followed by edema; hyperemia and pruritis.

Classification

1 generation: diphenhydramine, promethazine pheniramine, chloropyramine, clemastine, quifenadin, mebhydrolin

2 generation: loratadine, astemizole, cetirizine.

3 generation (active metabolites of the 2nd): desloratadine, fexofenadine, levocetirizine, ebastine.

Indications for use

- Urticaria
- Hay asthma
- Allergic rhinitis and conjunctivitis
- Angioneurotic edema
- Drug allergy
- Food allergy

Drugs for relief of anaphylactic shock: epinephrine, prednisone, diphenhydramine.

Comparative characteristics of the H1-blockers

- The drugs of 1-generation are dissolved in fats, pass through the BBB, have central effects. Their action begins during 20-60 minutes, duration of action is on average 4-6 hours (clemastin -12 hours). They are administered orally and parenterally.
- But! mebhydrolin does not pass through the BBB, does not have a sedative effect. It acts 24-48 hours.

- Drugs of the 2nd generation poorly pass through the BBB and do not have a sedative effect.
- They are prescribed orally, the action begins in 1-2 hours, lasts 20-24 hours (astemizol-48 hours).
- They're cardiotoxic.
- Some drugs of the 3rd generation are the active metabolites of the drugs of the 2nd generation. Their effect does not depend on metabolism.

Drug	Activity	Duration of effect	Influence on CNS	Block		
				N-CHR	M-CHR	A-R
Diphenhydramine	++	4-6 h	++	+		
Chloropyramine	++	4-6 h	++		+	
Promethazine	+++	4-6 h	++		+	+
Clemastine	+++	8-12 h	+			
loratadine	+++	24 h	+			
Cetirizine	+++	24 h	+			

The effect on the Central nervous system:

- Sedative
- Hypnotic
- Potentiating
- Antiemetic

Indications:

- ✔ insomnia;
- ✔ premedication before anesthesia;
- ✔ fever with antipyretics;
- ✔ vestibular disorders (motion sickness)

Possible adverse effects

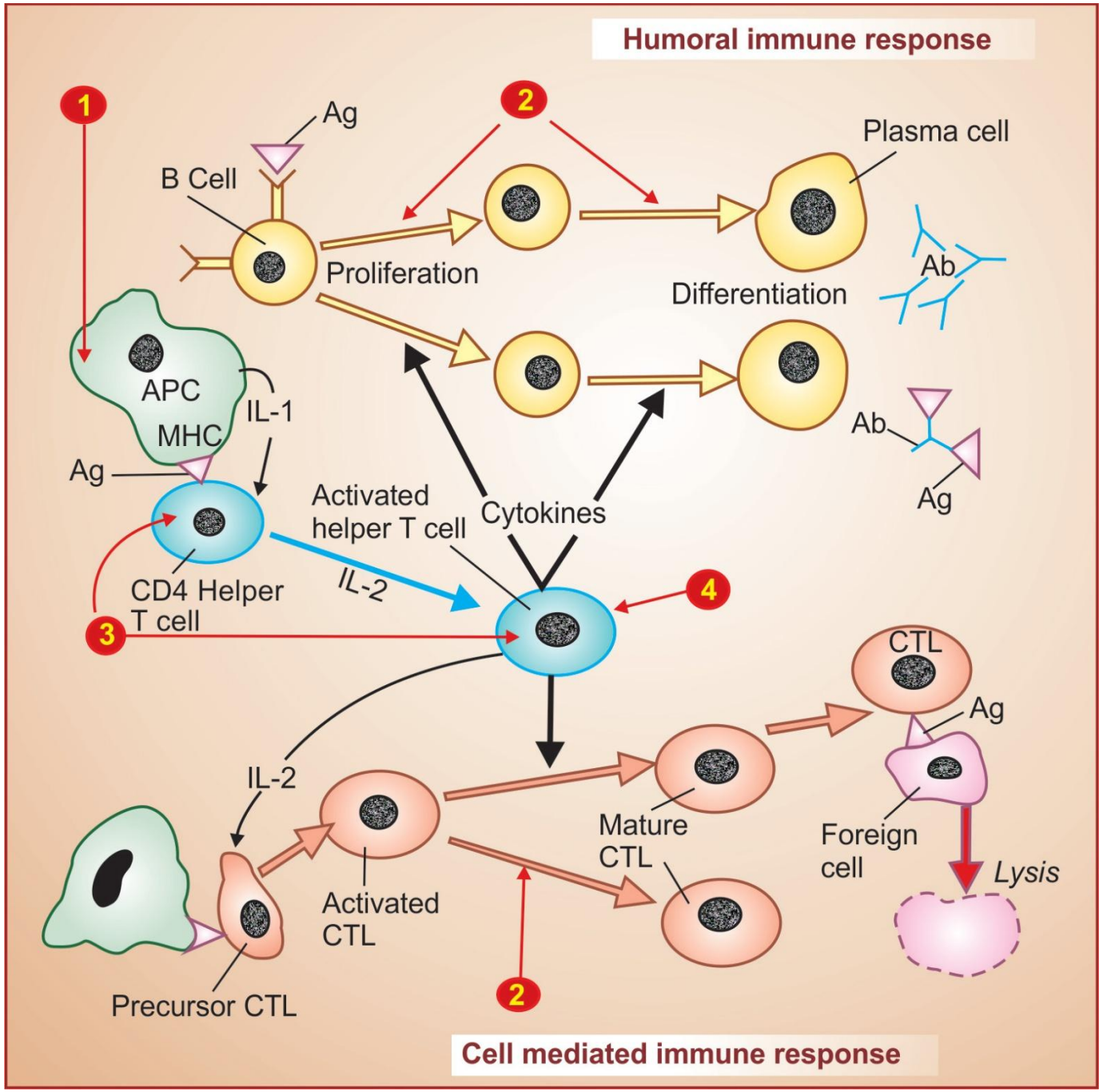
- The first generation drugs cause drowsiness, lethargy, confusion, decrease in speed of psychomotor reactions, discoordination of movements
- Diphenhydramine can cause excitement (in children and the elderly even in a therapeutic dose)
- Headache, dizziness, dry mouth (M-blocking effect of promethazine and chloropyramine)
- Increase of appetite, increase in the body weight
- A decrease in the efficiency of the drugs of I generation

Drugs for the treatment of reactions of delayed type of hypesensitivity

1. Drugs suppressing immunegenesis (Immunosuppressants):

- Glucocorticoids (prednisolone, etc.)
- Cytotoxic agents (azathioprine, 6-mercaptopurine, cyclophosphamide,)
- Antibiotics (cyclosporine, tacrolimus)

2. Drugs diminishing tissue damage: SAID, NSAID


Humoral immune response
1
2
Ag
B Cell
Plasma cell
Proliferation
Differentiation
Ab
APC
MHC
IL-1
Ag
Ab
Ag
Activated
helper T cell
Cytokines
CD4 Helper
T cell
IL-2
3
4
CTL
Ag
IL-2
Mature
CTL
Foreign
cell
Lysis
Activated
CTL
Precursor CTL
2
Cell mediated immune response

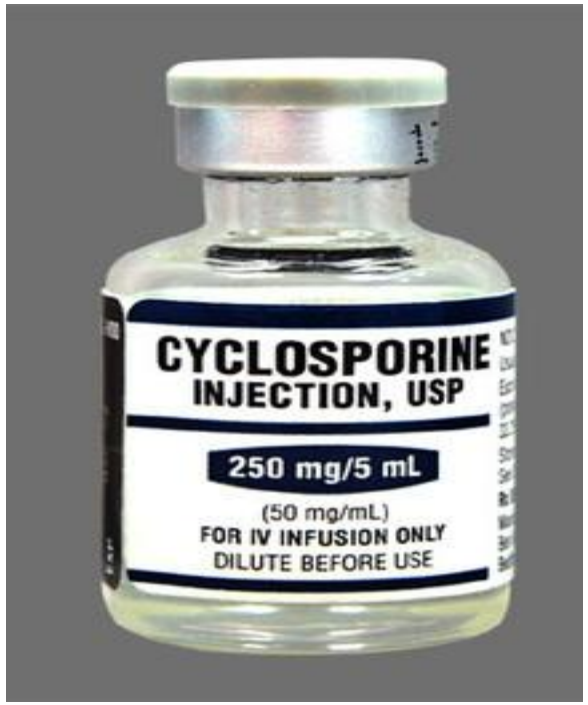
Immunosupressing action of **glucocorticoids** results from the inhibition of lymphocyte proliferation (especially T-L). Antigen recognition is also suppressed. Activity of macrophages is decreased. The production and activity of interferon and a number of interleukins are reduced. Cytotoxicity of some T-L population (T-K) is decreased. The formation of migration inhibitory factors is suppressed. Large doses provide lowing of specific antibody production and anti-body complex formation. Glucocorticoids have anti-inflammatory effect also. They are used for the treatment of collagenosises.

- Cytostatics inhibit cell division of lymphoid tissue, reduce the formation and activity of immune cells, inhibit the immunopathological mechanisms for the development of connective tissue.
- Indications: rheumatoid arthritis; lupus erythematosus and other diseases of connective tissue (reserve drugs).
- Complications: hematotoxicity, hepatotoxicity, nephrotoxicity, teratogenicity.

- **Azathioprine** is an antimetabolite that is converted into 6-mercaptopurine and disrupts the metabolism of purines. It inhibits the proliferation of tumor cells.
- It has an immunosuppressive effect in low doses, inhibits the proliferation of t-lymphocytes and their activity.
- Indications: Autoimmune diseases, organ transplantation (reserve medicine).
- Side effects: inhibition of bone marrow function, leucopenia, anemia, thrombocytopenia, excessive bleeding, nausea, vomiting, diarrhea, jaundice.

- **Cyclosporine** inhibits macrophages and reduces the production of IL-1. It reduces the differentiation and activity of T-lymphocytes, inhibits the activity of T-helpers, but keeps the activity of T-suppressors, promotes natural immunosuppression. It suppresses the rejection of transplanted tissues and organs. The drug reduces production of IL-2 and gamma interferon.
- Indications: Organ transplantation; autoimmune diseases (rarely)
- Side effects: Hepato-and nephrotoxicity.

- **Tacrolimus** inhibits the activation of T-lymphocytes and production of IL-2. It is 100 times more active than Cyclosporine.
- Indications: organ transplantation
- Side effects: nephrotoxicity; neurotoxicity; increased blood sugar levels; increased blood pressure



Immunostimulants

Natural:

- Vaccines, preparations of bacterial lysates (Imudon),
- Preparations of thymus: Timalin, Taktivin
- Preparations of interferons (α,β,γ),
- Adaptogens: Immunal (preparation of Echinacea), preparations of Chinese Magnolia vine, Ginseng

Synthetic drugs: Levamizol, Dibazol, Methyluracil, Azoximer bromide (Polyoxidonium)

Preparations of Chinese Magnolia vine, Echinacea, Ginseng, Siberian Ginseng

Mechanisms of action of immunostimulants

- ✔ Immunomodulators stimulate non-specific immunity: Increase activity of immunocompetent cells (T-and B-lymphocytes and macrophages); production of cytokines, antibody formation.
- ✔ They stimulate non-specific immunity: increase the production of interferon, lysozyme, phagocytosis completeness, complement system activity.

Indications for use

- Chronic purulent infections
- Malignant neoplasms
- Radiation sickness
- Chemotherapy and radiation therapy
- Leukopenia
- Poorly healing wounds and ulcers
- Immunodeficiency after the use of antibiotics, glucocorticoids

Thymus preparations

- Activate the system of T-lymphocytes,
- Normalize the ratio of T-and b-lymphocytes,
- Normalize the reaction of cellular immunity,
- Increase phagocytosis
- Stimulate the production of lymphokines.

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