

ANTIASTHMATICS

This study material is exclusively for students of general medicine and stomatology in Pharmacology II course. It contains only basic notes of discussed topics, which should be completed with more details and actual information during practical courses to make a complete material for test or exam studies. Which means that without your own notes from the lesson this presentation IS NOT SUFFICIENT for proper preparation for neither tests in practicals nor the final exam.

Asthma bronchiale

= chronic respiratory tract inflammation

prevalence in CZ:

children 10-15 %, adults 3-5 %

Asthma bronchiale

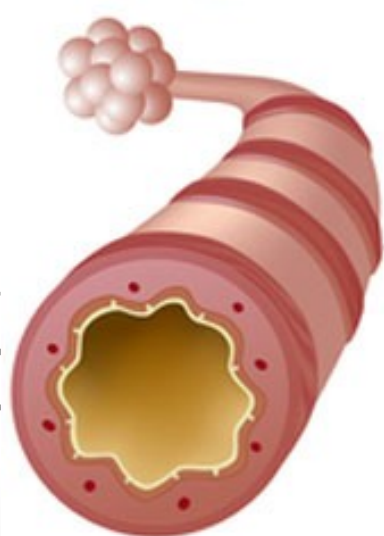
- Constriction of bronchial smooth muscles
- Edematous changes on bronchial mucosa
- Increased mucus production and secretion



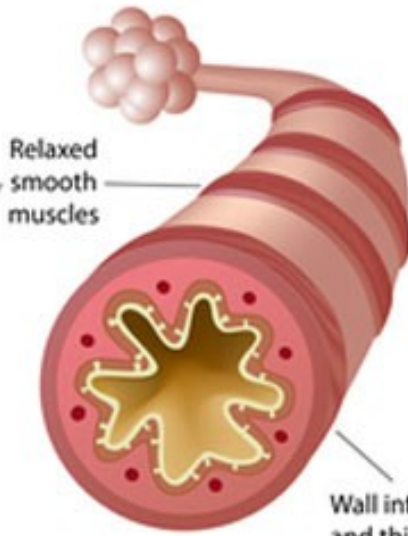
Symptoms

- **breathlessness** caused by bronchoconstriction, oedema, bronchial inflammation and mucus
- **difficult expiration, prolonged expiration, whistling, creaking.**
- **cough**

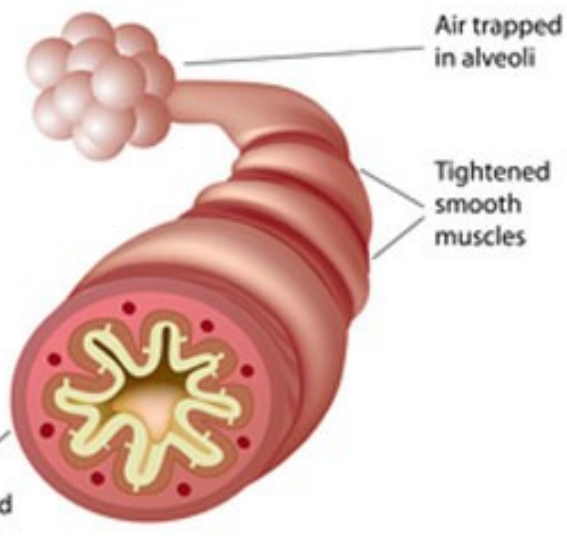
Pathology of Asthma



Normal airway

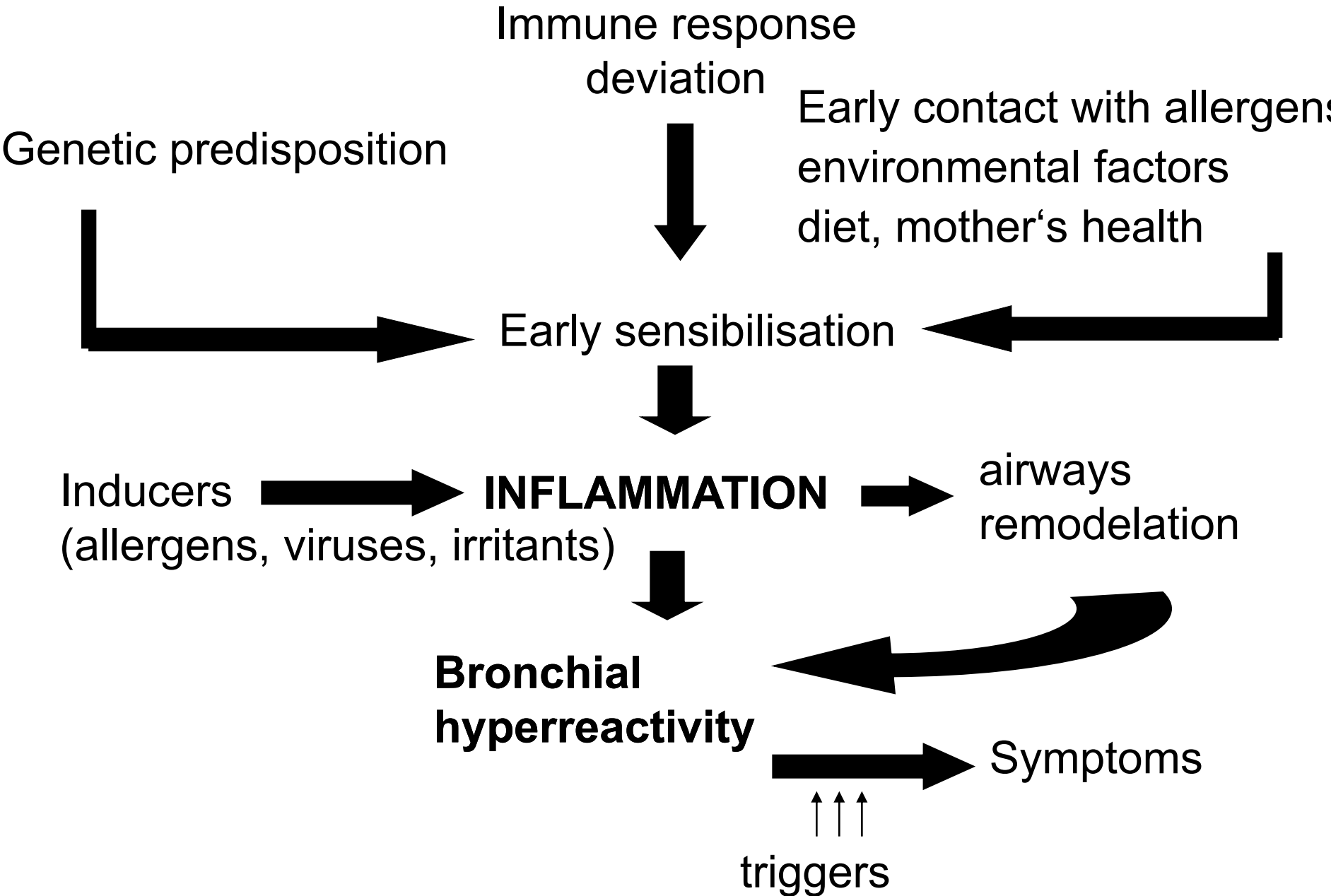


Asthmatic airway



Asthmatic airway during attack

Patophysiology



Diagnose

Anamnesis – personal, familiar

Clinical examinations - auscultation, signs of atopy,
eosinophilia,

PEF – Peak Expiratory Flow

FEV – Forced Expired Volume

Laboratory tests- eosinophilia, IgE

Allergy testing

Asthma bronchiale classification

| | allergic | non-allergic |
|------------------|-----------------------------|--|
| inducer | contact with allergen | infection psychogennic phys. activity irritation aspirin |
| ↑ of probability | young patients | older patients |

Classification with regard to seriousness

- **Intermittent** – sign up to once a week, night symptoms up to twice a month, pulmonary function normal
- **Mild persistent**– signs no more than once daily, night symptoms up to twice a month, PEF at least 80 %
- **Moderate persistent**– signs once a day and are not permanent, night sign no more than once a week, PEF 60-80 %
- **Severe persistent**– permanent signs, daily, obstruction, PEF \leq 60 %

Administration of antiasthmatics

- Peroral

- Injections

- **Inhalation**

benefits: high drug concentration on the
site of action

fast onset of effect

minimal penetration to systemic
circulation = low risk of systemic AE

Inhalation preparation for antiasthmatics

- Aerosol dispensers – meter dose dispensers
- Aerosol dispenser + spacer – children elders
- Powder (spinhaler, dischaler, turbohaler)
- Nebulizer



Asthma bronchiale pharmacotherapy

- Quick relief drugs – acute attack
- Long-term control medicines – between attacks

Pharmacotherapy

1. Bronchodilators

- β -sympathomimetics
- nonselective sympathomimetics
- antimuscarinics
- methylxanthines

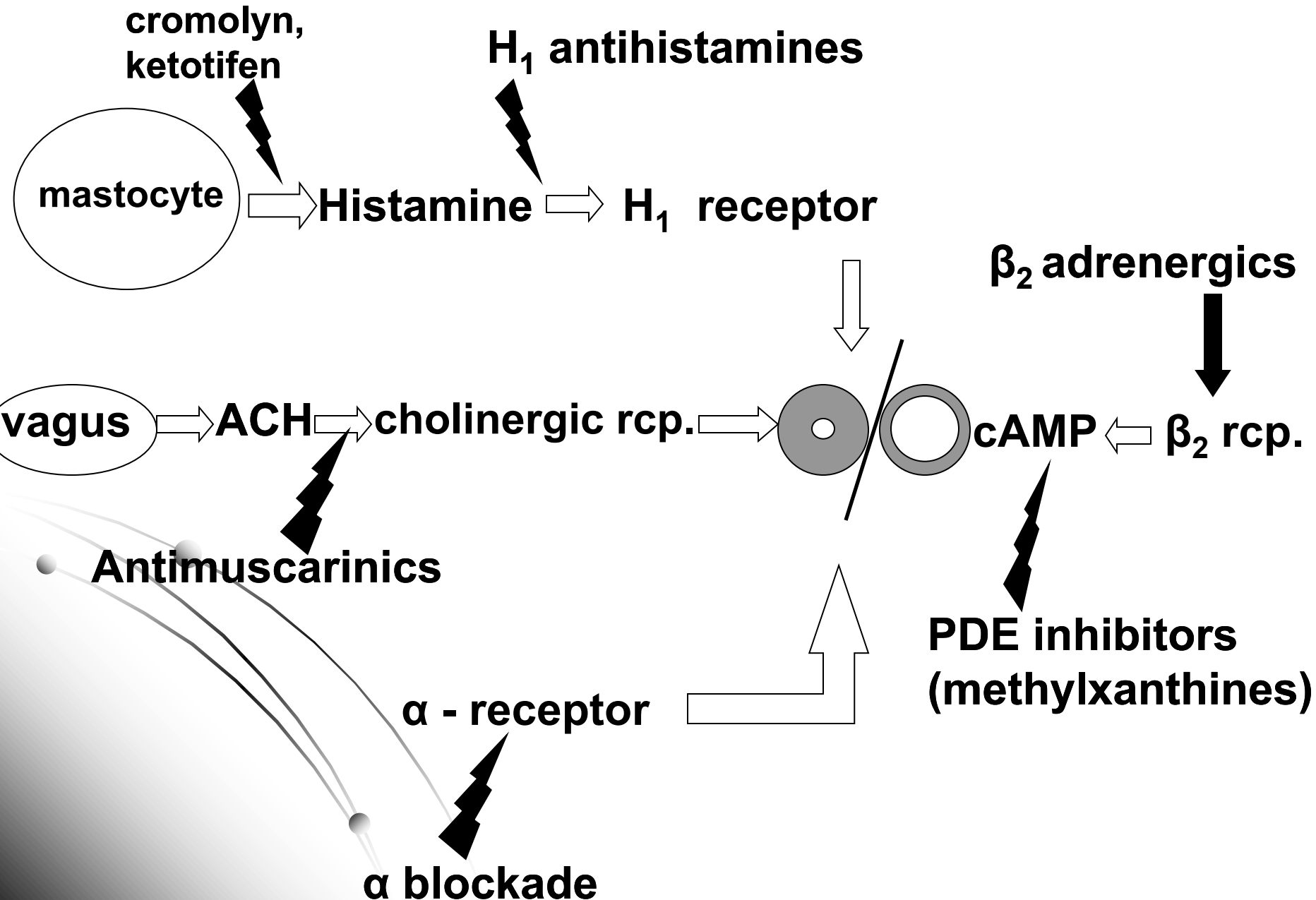
2. Anti-inflammatory agents

- Glucocorticoids
- Immunoprophylactics

3. Adjuvant therapy and other drugs of respiratory system

- Antileucotriens
 - leucotriens' receptors antagonists.
 - 5-LOX inhibitors
- Antihistamines
- Expectorants
- Antitussives
- Hyposensibilisation
- Anti IgE monoclonal antibodies

Bronchodilators target sites on smooth muscle cells



1. Bronchodilators

β - sympathomimetics

- selective stimulation of β_2 -Rc
- adenylyl cyclase stimulation \rightarrow \uparrow cAMP \rightarrow bronchial smooth muscles relaxation
- decrease in inflammation mediators from mastocytes
- increase in ciliar activity

1. Bronchodilators

β - sympathomimetics

- **Short-acting (max. 4 - 6 hrs.)**

salbutamol

fenoterol

terbutaline

hexoprenaline

1. Bronchodilators

β - sympathomimetics

- **Long- acting (12 hrs.)**

prokaterol

formoterol

salmeterol

clenbuterol

bambuterol

1. Bronchodilators

β - sympathomimetics

- AE:
nervousness, tremor, cephalgia,
palpitation
hypokalaemia
- CI:
dysrhythmia, hypertension
(pregnancy)

1. Bronchodilators

Nonselective sympathomimetics

epinephrine— in life-threatening situations

ephedrine

orciprenaline

More of AE

tachycardia, palpitation, dysrhythmia, hyper/hypo tension,
insomnia

1. Bronchodilators

Antimuscarinics

- for inhalation
- blocks cholinergic M receptors
- to increase the effect of β_2 -sympathomimetics

ipratropium

tiotropium

atropine analogues, inhalation in combination with beta-mimetics – or administration after beta-mimetics

when combined with corticoids, then administered after them

- AE: dry mouth, urine retention, constipation
- CI: prostate hypertrophy, glaucoma, pregnancy

1. Bronchodilators

Methylxanthines

- phosphodiesterase inhibitors → ↓ cAMP degradation → smooth muscle relaxation
- bronchodilators, cardiostimulants, diuretics
- retarded DDF (before going to bed)
 - theophylline**
 - aminophylline**
 - ethophylline**

1. Bronchodilators

Methylxanthines

adenosine receptor antagonists

(adenosine \Rightarrow contraction, \uparrow His, LT, Pg)

More effects:

CNS stimulation; +chrono, +inotropic effect, \downarrow blood viscosity and hemoperfusion (pentoxiphillin)
gastric acid secretion increase

AE: similar to those of non-selective sympathomimetics

Pharmacotherapy

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- methylxanthines

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- Immunoprophylactics

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2. Antiinflammatory agents

Glucocorticoids

anti-inflammatory and immunosuppressant activity (PLA₂ inhibition)

- ↓ cytokines, prostaglandins and leukotrienes secretion
- ↓ lipolytic and proteolytic enzymes secretion
- ↓ endothelial permeability

2. Antiinflammatory agents

Glucocorticoids

- **block cell migration and decrease bronchial hyperactivity, suppress oedema**
- **block chronic irreversible changes development (bronchial smooth muscles hypertrofia and hyperplasia, subendothelial fibrosis and thickening of mucous basal membrane)**
- **increase sensivity of β adrenergic receptors to beta mimetics**

2. Antiinflammatory agents

Glucocorticoids

Orally or inhalation

- Inhalation

beclomethasone

budesonide

fluticasone

flunisolide

dexamethasone

mometasone

ciclesonide

AE: hoarseness, cough, oral candidosis (wash out mouth after use)

2. Antiinflammatory agents

Glucocorticoids

- Orally

when inhalation are not sufficient

in challenge doses which are gradually decreased

prednisone

triamcinolone

betamethasone

2. Antiinflammatory agents

Glucocorticoids

AE:

- candidosis, risk of systemic adverse effects
- systemic: Cushing's sy., DM, immunosuppression, osteoporosis, hypertension, gastroduodenal ulcers...

2. Antiinflammatory agents Immunoprophylactics

- mast cells membrane stabilizers
- inhibit histamine release
- influence on lymphocytes

in mild forms of asthma

prevention of asthma attacks, maintenance therapy

cromones (cromoglycate, nedocromil)

ketotifen (H1 antagonist, anti-Ach effect)

CI: 1. trimester of pregnancy

Pharmacotherapy

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3. Adjuvant therapy

Antileucotriens

for mild forms of asthma

in serious asthma in combination with corticoids

a) leucotrien receptor antagonists

montelukast

zafirlukast

b) 5-lipoxygenase inhibitors(5-LOXi)

zileuton

piriprost

docebenone

c) both effects (antag. rcp. + i 5-LOX)

tenidap

3. Adjuvant therapy

Antihistamines

2nd generation antihistamines with minimal sedative and arrhythmogenic effects

desloratadine

levocetirizine

fexofenadine

ketotifen

3. Adjuvant therapy

Expectorants

- Secretolytics

bronchial gland stimulation = liquid mucus

ammonium chloride

potassium iodide

saponines – *Primula, Verbascum*

3. Adjuvant therapy

Expectorants

- Mucolytics- decrease of mucus viscosity

N-acetylcysteine

carbocysteine

ambroxol

bromhexine (pro-drug)

erdosteine

3. Adjuvant therapy

Expectorants

- Secretomotorics
increase ciliar activity

**essential oils: oleum eucalypti, o. menthae
piperitae**

bromhexine (pro-drug)

ambroxol

Others

guaifenesine

emetine

3. Adjuvant therapy

Antitussives

Cough = reflexive activity produced to release or clean up airways

- symptomatic therapy of irritating and exhausting cough
- do not combine with expectorants, namely secretomotorics for antagonistic effects

3. Adjuvant therapy

Codiene antitussives

- Block of cough center

codein

pholcodine

ethylmorphine

dextrometorphan

levopropoxyphen

AE: respiratory center suppression → not for children!

3. Adjuvant therapy

Non-codeine antitussives - peripheral

- Block of sensitive neurons in submucosa
dropropizine
bezonatate
- Block of afferent pathways
prenoxdiazine

3. Adjuvant therapy

Non-codeine antitussives - central

- Block of cough centre, but do not suppress respiratory center

butamirate

(clobutinol – *withdrawn!!!*)

- Block of efferent pathways

myorelaxants

ganglioplegics

I: surgery

Anti IgE monoclonal antibodies

Omalizumab: monoclonal antibody used in bronchial asthma, that was unambiguously caused by IgE.

Mechanism of action: it binds to IgE, which decreases amount of circulating IgE and thus IgE can not bind to their specific receptors and trigger the allergic reaction.

It is administered subcutaneously.

Intended for therapy of severe persisting allergic bronchial asthma, that can not be controlled with high doses of inhalational glucocorticoids and during therapy with long-term acting inhalational β_2 -sympatomimetics.

Disadvantage: high price.

THC ?

Two independent groups of investigators demonstrated a short-term bronchodilator response in healthy male volunteers to inhalation of the smoke of marijuana in concentrations of 1.0% to 2.6% Δ^9 THC, that was not seen after inhalation of placebo.

The bronchodilator response to smoked marijuana was of greater magnitude than that observed after administration of a nebulized β -agonist.

→ THC (and other CB_1 receptor agonist) can have local bronchodilator effects in the airway through stimulation of CB_1 receptors on efferent vagal nerve endings, leading to a parasympatholytic effect.

Perspective use for asthma therapy.

!!! CAVE: THC in form of marijuana smoke: pulmonary toxicity

risk of lung, neck and head cancer