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Drugs used in diseases characterized by bronchial obstruction

Department of Pharmacology

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Bronchial asthma

chronic inflammatory disease of airways
affecting 300 million people all across the globe
prevalence in CZ: 8 %, in children over 10 %

Characteristics:

bronchial hyper-reactivity
obstruction (often reversible)
inflammation

Symptoms:

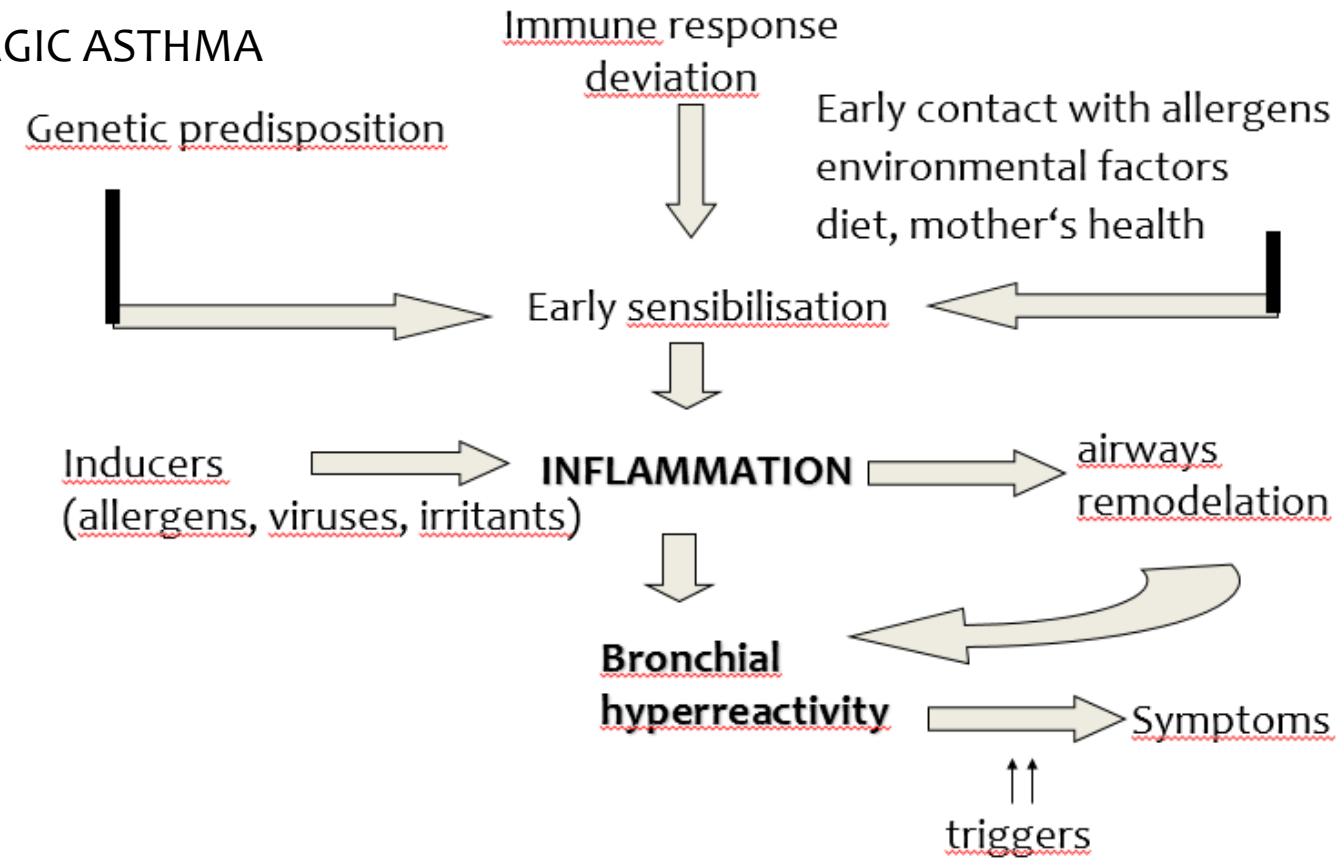
shortness of breath (bronchoconstriction, mucous plug, oedema, airway remodeling due to the inflammation)

difficult and prolonged **expiration** → wheezing, whistling

cough (especially at night or in early morning)

Bronchial asthma

ALERGIC ASTHMA



NON-ALERGIC ASTHMA

- allergy not present
- excercire-induced, aspirin-sesitive, infectious, work-related, endogenous

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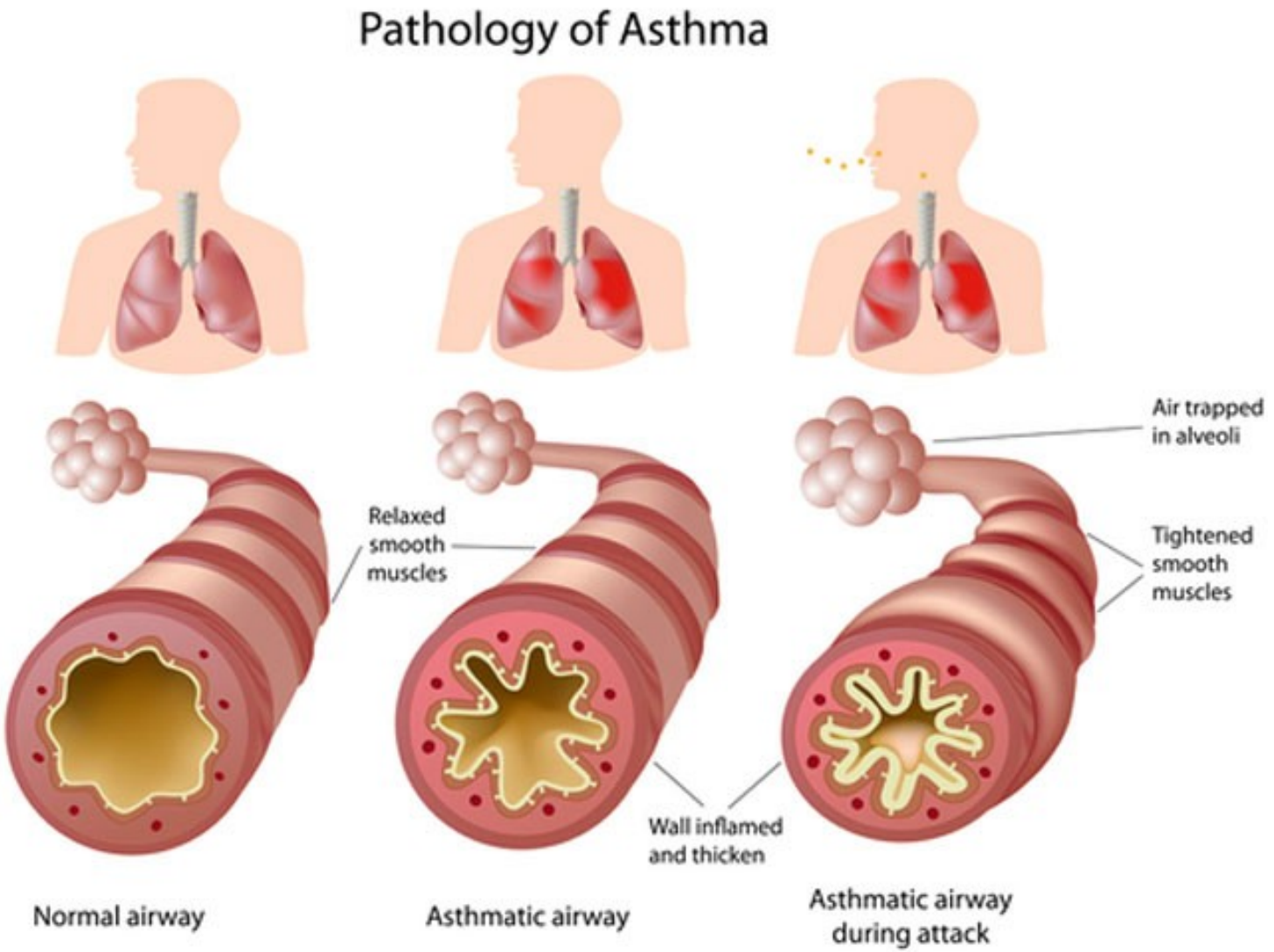

https://www.canstockphoto.com/anatomy-of-asthma-6231875.html

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Diagnose

Anamnesis – personal, familiar

Clinical examinations - auscultation, signs of atopy, eosinophilia,

PEF – Peak Expiratory Flow

FEV 1 – Forced Expired Volume

Laboratory tests- eosinophilia, IgE

Allergy testing

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 ≤ 60 %

Managment of asthma

the disease itself cannot be fully treated, the goal is to keep asthma under control

Goals:

minimalize both acute and chronic symptoms

reduction of exacerbations (lessen SABA administration)

improvement of the quality of life (physical activity)

avoid adverse effects of the treatment

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Chronic obstructive pulmonary disease (COPD)

affecting 600 million people all across the globe
prevalence: 8 %
risk factors: smoking, polluted air, dust and chemical vapors at workplace, genetic predisposition

Characteristics:

chronic inflammation caused and maintained by long-term exposure to harmful agents (irritating gases and particles)
poorly reversible, progressing bronchial obstruction
production of mucus

Symptoms:

cough (usually whole day, hardly ever only during night)
expectoration
shortness of breath

Managment of COPD

we can only slow the progression
reduction of risk factors is necessary (mainly top quit smoking)

Goals:
symptom reduction

improvement in physical condition and overall health state

prevention of complications and exacerbations

Administration

oral, parenteral (injections, infusions)

inhalation

- local administration, high drug concentration at the site of action

- fast onset of the effect

- minimal penetration to systemic circulation → ↓ risk of side effects

Drugs used in diseases characterized by bronchial obstruction

BRONCHODILATATORS

- β_2 sympathomimetics
- parasympatholytics
- glucocorticoids
- methylxanthines
- roflumilast (COPD only)
- antileukotrienes
- imunoprofhylactics
- monoclonal antibodies

asthma only

- noselective sympathomimetics (epinephrine, life-saving medication)
- adjuvant medication (antitussics, drugs facilitating expectoration)

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β_2 sympathomimetics

MoA: selective β_2 stimulants

- inhibition of mediator release from mast cells + stimulation of ciliary beat frequency

- diagnostics – post-bronchodilator test (salbutamol)

- mostly **inhaled,** may be also given orally (mainly in kids)

- not completely selective in their binding to β receptors
long-term use = down-regulation of receptors

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β_2 sympathomimetics

Indication: **asthma**, COPD

AE: nervousness, tremor, cephalgia, palpitation, hypokalemia (mainly when given orally)

CI: hypertension, dysrhythmia, pregnancy

β_2 sympatomimetics

Short-acting = SABA (also rapid-acting = RABA)
fast onset of effect, which lasts 4 – 6 hours, inhalation

salbutamol

fenoterol

Long-acting = LABA
effect lasts for up to 12 hours, inhaled or administered orally

salmeterol

clenbuterol

formoterol (RABA)

indakaterol (U-LABA)

vilanterol (U-LABA)

Parasympatholytics

MoA: competitive antagonism of M receptors

- in a form of inhalation
- can be combined with β_2-sympathomimetics or glucocorticoids

Indication: COPD, asthma

AE: if entering the systemic circulation (low risk, they contain quaternary nitrogen in their structure) – anticholinergic effects

CI: glaucoma, prostate hypertrophy, pregnancy

Parasympatholytics

ipratropium

- used in asthma as well – in patients resistent to β2 sympathomimetic treatment (approx. 1/6 of patients)
short acting (SAMA)

aclidinium (LAMA)

tiotropium (U-LAMA)

glykopyrronium-bromide (U-LAMA)

umeclidinium (U-LAMA)

COPD only

Glucocorticoids

MoA: inhibition of phospholipase A2
by lipocortin

Effects I:

↓ cytokine, PG a LT secretion

↓ lipolytic and proteolytic enzyme secretion

↓ endothelial permeability

block of cell migration

↓ bronchial hyperreactivity,

Glucocorticoids

Effects II:

reduction of edema
prevention of chronic irreversible changes
(hypertrophy and hyperplasia of bronchial smooth muscles, subendothelial fibrosis and thickening of mucous basal membrane)

increase in sensitivity of β_2 adrenergic receptors to β_2-SM

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MoA at the cellular level

glucocorticoid + cytoplasma receptor

↑ production of specific mRNA

↑ production of some proteins (lipocortins)

MoA at the cellular level

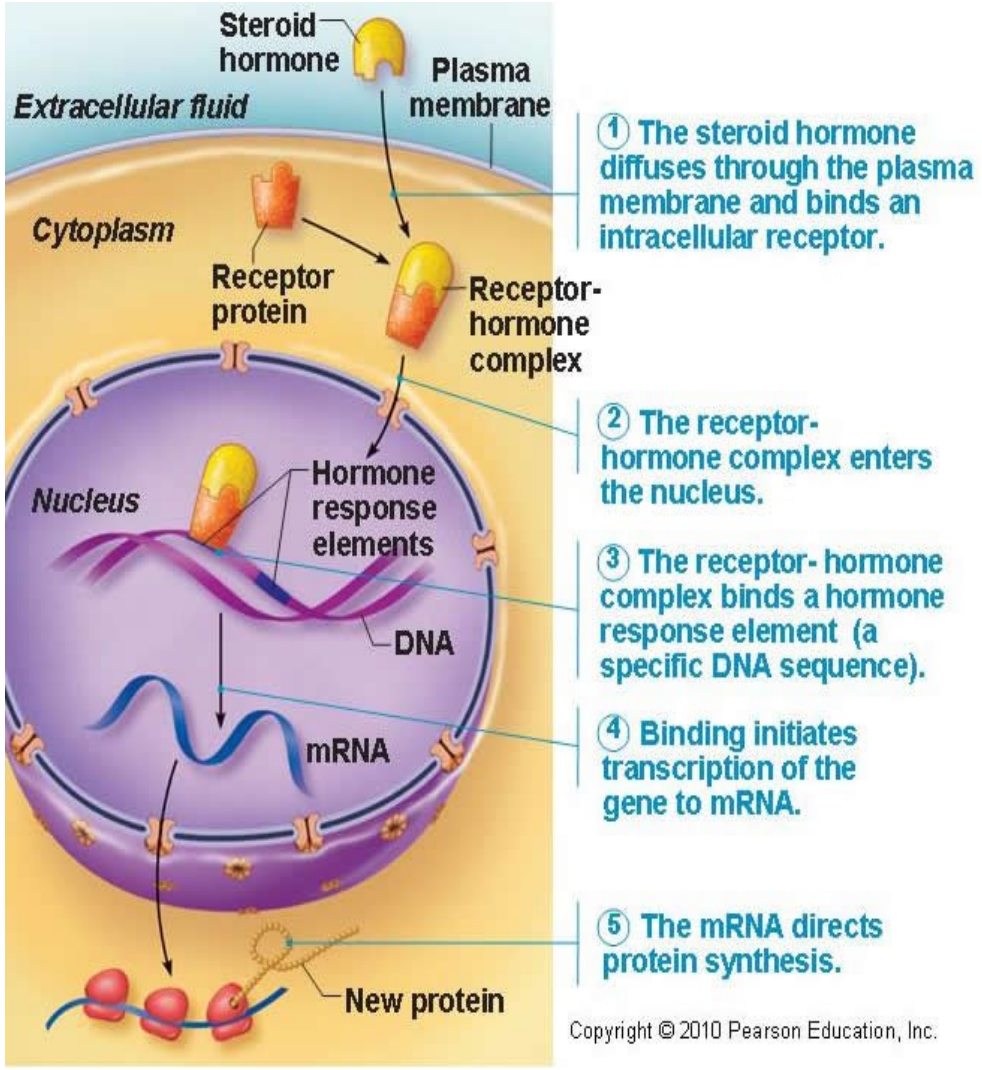
After entering the cell they bind to specific receptors in cytoplasm causing change of conformation = activation of receptors

Complexes of corticoid + receptor are transported to cell nucleus and bind to DNA elements.

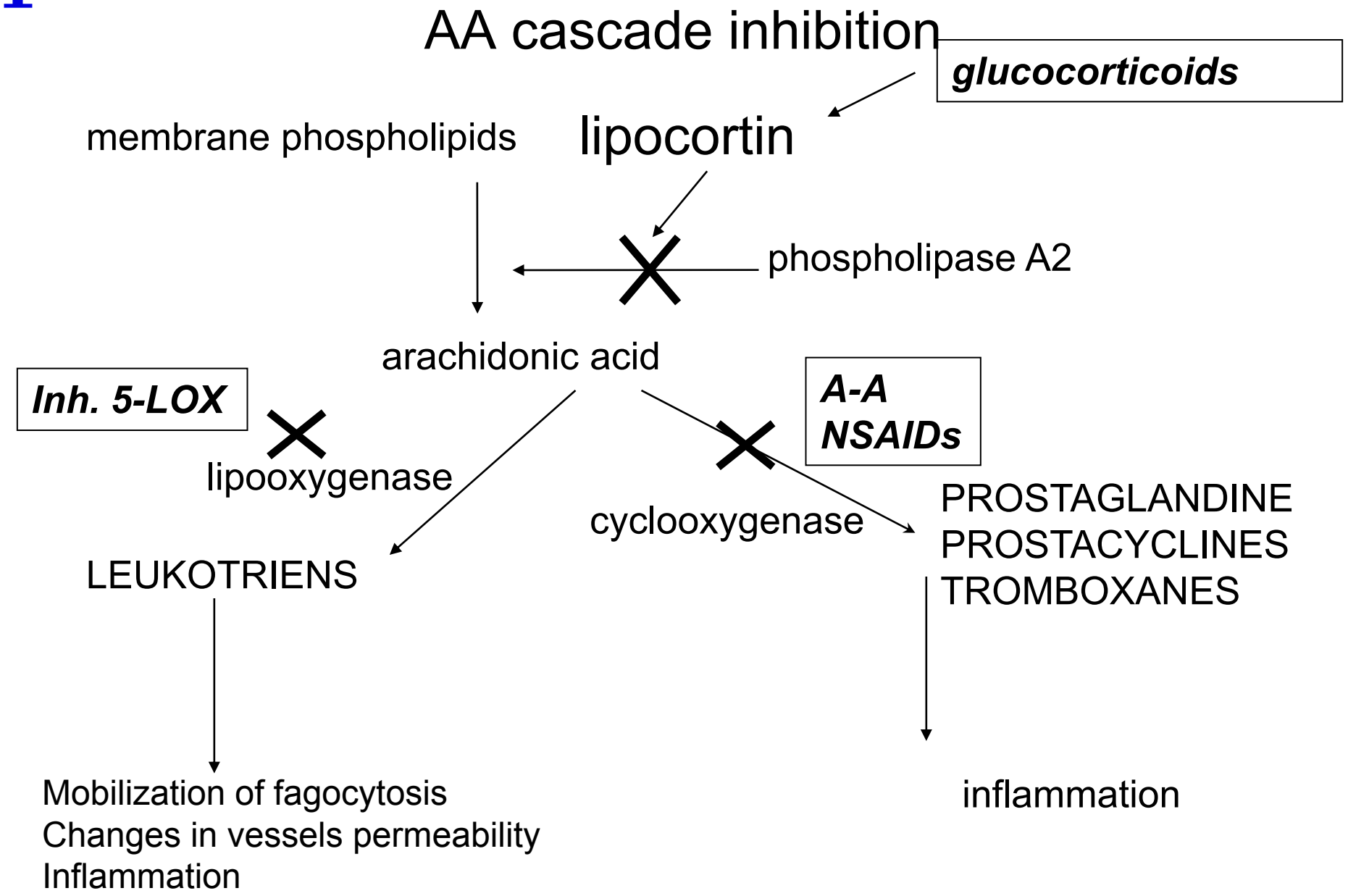
The result is increased transcription of genes either inducing or inhibiting synthesis of other proteins

GLC receptors are present in all tissues!!!

Proteins called **lipocortins** are able to suppress phospholipase A



Antiinflammatory effect of GC



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Glucocorticoids

given by inhalation

lower risk of systemic adverse effects

AE: affected vocal cords – croaky voice, oral **candidiasis (thrush)**

beclomethasone
budesonide
***f*luticasone**
ciclesonide
mometasone

systemic administration

orally, via injection – acute conditions, doses are gradually decreased, in severe persistent asthma – if nothing else is effective

prednisone
triamcinolone
hydrocortisone (injection)

Methylxanthines

MoA: phosphodiesterase 1 – 4 inhibitors
adenosine receptors antagonists

sustained-release drug forms

Effects:

– bronchodilatation

– cardiostimulation (+chrono, +inotropic eff.)

– diuretic eff.

– CNS and respiratory center stimulation

– stimulation of hydrochloric acid secretion

Methylxanthines

Effects:

- substrates of CYP450 – be cautious if patient is a smoker!

CI: pregnancy, epilepsy, cardiovascular disease

AE: tachycardia, palpitations, sleeplessness

Methylxanthines

theophylline

- combination therapy with β_2 SM is convenient

- becoming obsolent, therapeutic drug monitoring needed

- variable pharmacokinetics, low therapeutic index

aminophylline

- a complex of theophylline and ethylendiamine (better solubility)

- COPD, emphysema

roflumilast

selective long-acting inhibitor of phosphodiesterase 4

reduces the inflammation in bronchi in COPD

Antileukotrienes

MoA: antagonism of LT-receptors / inhibition of lipoxygenase

LT receptor antagonists:
treatment of persisting asthma, allows lowering of glucocorticoid dose
1-2x a day, orally

montelukast

Inhibitors of LOX:
need for frequent application
not registered in CZ (**zileuton** – USA)

Imunoprophylactics (mast cells stabilizers)

MoA: stabilisation of mast cell membrane → ↓ Ca^{2+} influx → ↓ degranulation of mast cells and thereby ↓ histamine release
influence on lymphocyte function

prevention of asthma attack, they **do not affect already present bronchospasm**

Use: as preventive, long-term, maintenance therapy – mild and moderate asthma
when combined with other antiasthmatics, they allow lowering of their dose

CI: pregancy (1. trimester)

nedokromil, **ketotifen** (H1 antihistamine), **cromoglycate**

Monoclonal antibodies

Anti-IgE

omalizumab

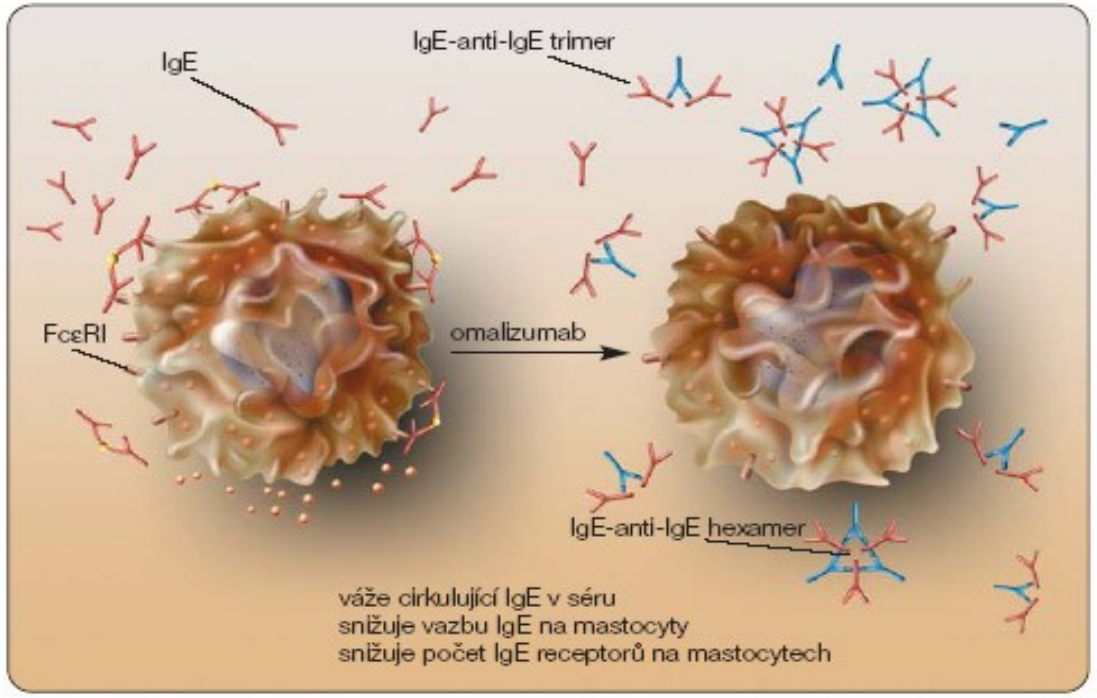
antibodies against a part of IgE, which binds to mast cells

Indication: severe persistent allergic asthma, which cannot be otherwise controlled

administered subcutaneously in specialized centers only

Anti-IgE

omalizumab



Obr. 3 Mechanismus působení omalizumabu

http://www.remedia.cz/Okruhy-temat/Respiracni-onemocneni/Omalizumab-terapeuticka-perspektiva-v-lecbe-tezkeho-bronchialniho-astmatu/8-1o-gD.magarticle.aspx

Monoclonal antibodies

Anti-IL-5

mepolizumab, reslizumab

add-on treatment for severe refractory eosinophilic asthma in adult patients

Other options

Bronchial thermoplasty

- bronchoskopic procedure, during which a therapeutic radiofrequency energy is delivered to the airway wall, resulting in reduction of smooth mucle cells

Allergen immunotherapy

- induces tolerance to the triggering allergen

Devices for inhaled medications

MDI = metered dose inhalers
drugs as solutions, propellants

BAI = breath-actuated inhalers

DPI = dry powder inhalers
spinhaler, diskhaler, turbohaler

nebulizers (liquid → aerosol)

Devices for inhaled medications

spacers for children and elderly

patient must be educated how to use their inhaler
→ up to 41 % of patients use incorrect technique

inhalers often combine two drugs (bronchodilator + glucocorticoid
or two bronchodilators)

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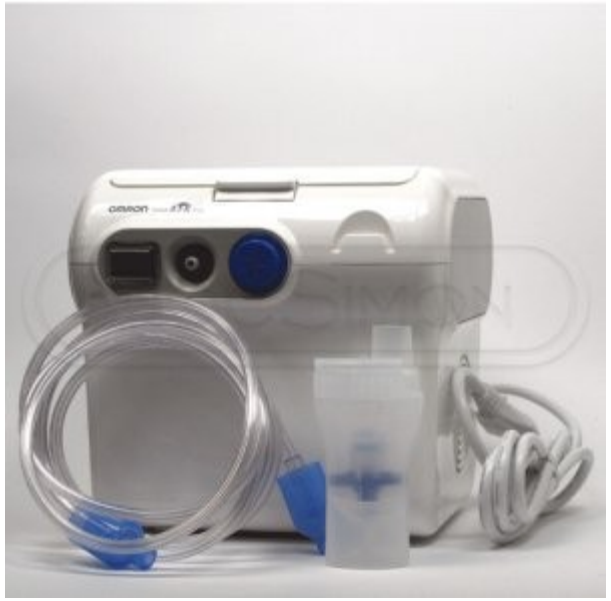

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Adjuvant medication in diseases characterized by bronchial obstruction and another drugs affecting respiratory system

antitussives

drugs facilitating expectoration

H_1 antihistamines (mainly II. a III. generation)