MUNI
MED

Antihistaminines

MUNI MED

Histamine

- autacoid (local hormone)
- endogenous amine (hydrophilic)
- in tissues is formed from histidine

Location: in granules in mast cells, basophiles (histaminocytes) → bound to heparan sulphate and acidic protein

in almost all tissues, highest levels in lungs, GIT, skin

Main roles in the body:

neurotransmitter – **CNS**

mediator of allergic/inflammatory reactions – **mast cells, basophilles**

regulation of gastric acid release (↑) - **stomach**

Histamine

is released from mast cells granules by exocytosis
(activation of phospholipase C a ↑ Ca^{2+})

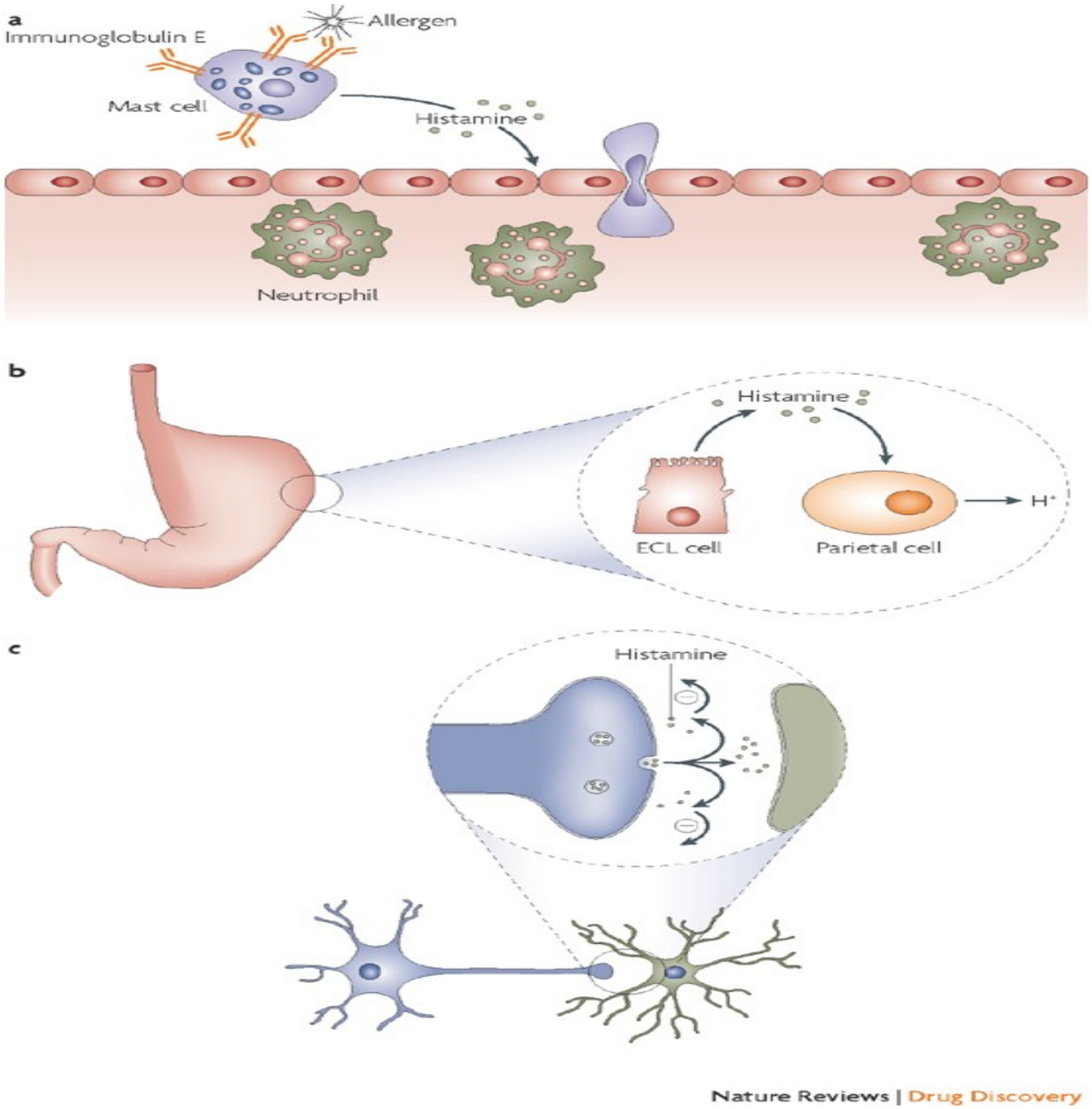
Stimuli:

imunological: antigen + IgE

physical, chemical or mechanical cell damage

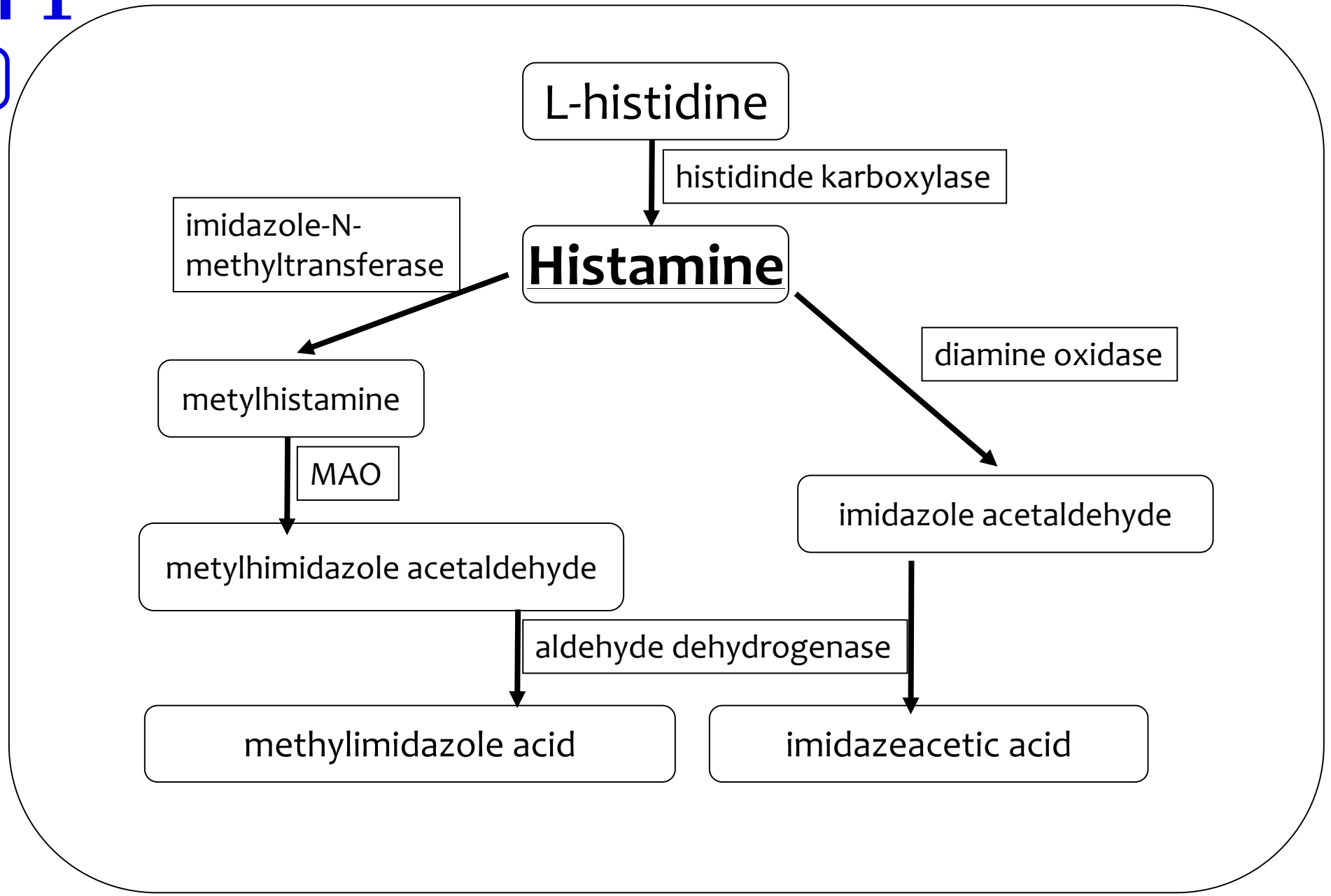
drugs

MUNI
MED



doi:10.1038/nrd2465

Histamine metabolism



Histamine receptors

4 subtypes (H_1 – H_4)

G protein-coupled receptors

their stimulation results in increase in cellular concentration of Ca^{2+} ions

MUNI MED

H_1 receptors

postsynaptic, G_q-protein ↑ phospholipase C →
↑ IP3 and DAG → ↑ Ca^{2+}

Location:

endothel, smooth muscles (vessels, bronchi, uterus, GIT),
peripheral neuron ending, CNS (!!!)

Effects:

smooth muscle contraction (bronchi, uterus, ileum)

vasodilatation of minor vessels (↓BP, reddening of skin)

increase in vessel permeability (swelling)

irritation of peripheral neuron endings (itching, even pain)

excitation of CNS

H_2 receptors

postsynaptic, G_s-protein ↑ activity of adenylate cyclase → ↑cAMP

Location:

stomach mucosa, heart, vessels, immune system

Effect:

in stomach: gastric acid, pepsine, intrinsic factor secretion

slower and longer vasodilatation

+ inotropic, + chronotropic effect

H_3 receptors

presynaptic, G_i protein → inhibition of N-type Ca^{2+} channels
→ ↓ cellular Ca^{2+}
feedback inhibition of histamine release

heteroreceptors, ↓ release of other neurotransmitters

Location:

mainly in CNS (but in PNS tissues as well)

Effects:

sedation
negative chronotropic effect
bronchoconstriction

H_4 receptors

possibly isoform of H_3

Location:

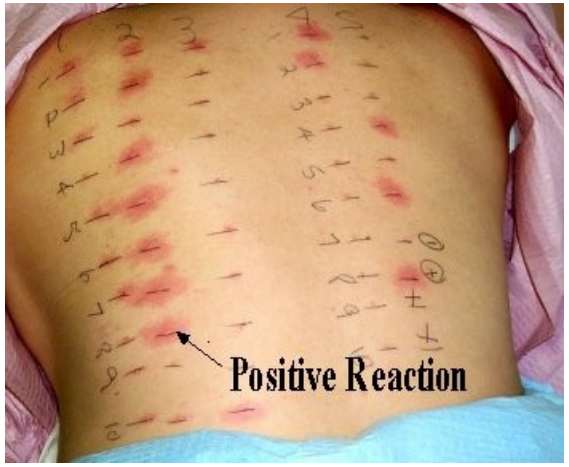
eosinophiles, basophiles, bone marrow, thymus, intestine, spleen

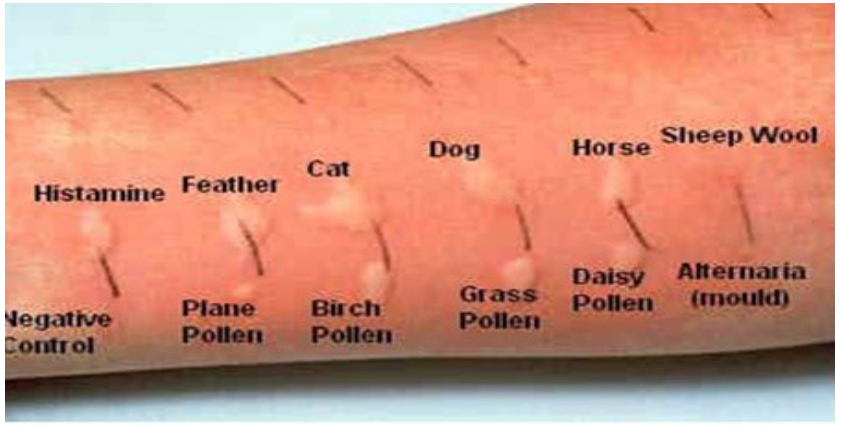
Effects:

influencing activity of immune system
important for chemotaxis

Histamine in clinical practise

limited use (ineffective when given orally)
diagnostics in allergology





Skin Allergy Test

histamine analogue → **betahistine**

Lewis reaction

typical response to intradermal histamine administration:

skin reddening (vasodilatation of arterioles)

wheal (capillary permeability)

flare (redness in the surrounding area due to arteriolar dilatation mediated by axon reflex)

used in allergy testing – positive control

it is used to evaluate the potential antiallergic effect of H1 antihistamines

MUNI
MED

How to antagonize effects of histamine?

Treat the symptom

vasoconstrictiors, sedatives, antacides, tocolytics etc.

Treat the cause

inhibition of synthesis (glucocorticoids)

inhibition of release (cromoglycate, nedokromil, β_2-SM, glucocorticoids)

receptor antagonism:

- non-specifically, indirectly (epinephrine)
- specifically, directly (H1, H2, H3 - antihistaminines)

Allergy

has a high incidence, 10-30% (and growing)

genetic factors

various theories about its origin

<u>Mechanism of alergic reaction:</u>

early contact with allergen

allergen binds to IgE antibody

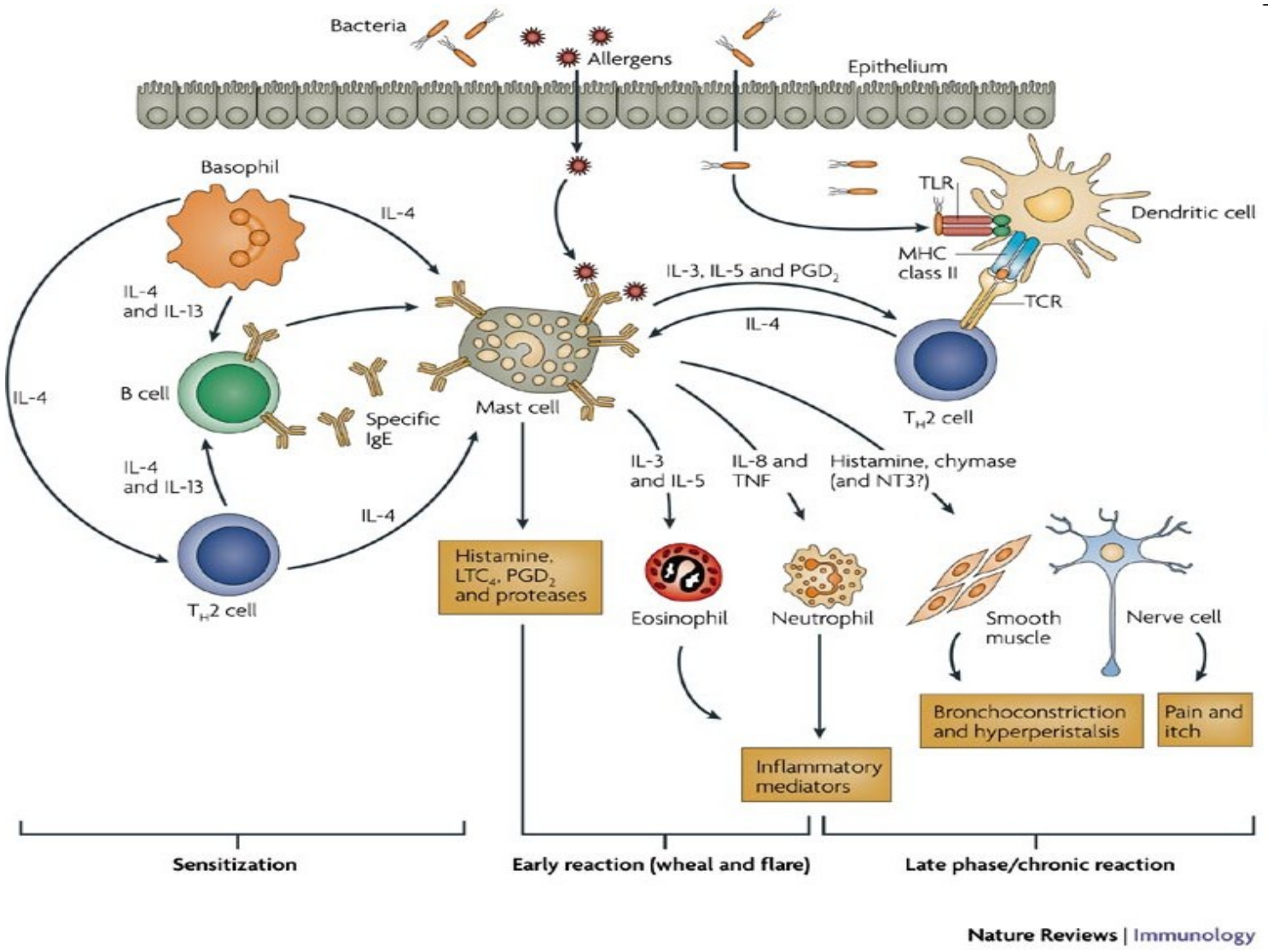
degranulation of cells containing histamine

activation of phospholipase C

→ mobilization of intracellular Ca^{2+}

→ mediators are released: HIS, PG, LT, PAF, cytokines

MUNI MED



Stephan C. Bischoff. Nature Reviews Immunology 7, 93-104, February 2007

Allergy treatment

always as an addition to taking enviromental control measures and avoiding allergen

H_1- antihistamines

glucocorticoids

mast cells stabilizers

immunotherapy

epinephrine (anaphylactic shock)

MUNI MED

H_1 antihistamines

MoA: antagonization of H_1 receptor
they antagonize the allergy symptomes caused by histamine

high selectivity to H_1 rp. → low affinity to H_2 rp.
3 generations

AE:
antimuskaric, antiserotonergic a antiadrenergic effects of older drugs of this group (sedation, fluctuating blood presure,...)

block of Na^+ channels → locally anaesthetic and antipruritic effect

MUNI MED

H_1 antihistamines pharmacokinetics

Dosage forms:
oral, topical, parenteral (i.m., infusion)

easy and quickly absorbed from GIT

distributed evenly in the body

metabolized in liver (some in form of prodrug)

excreted in urine, stool

drugs of I. generation cross the blood-brain barrier → central effects (sedation)

cross the placenta and are distributed into milk!

MUNI
MED

H_1 antihistamines - I. generation

relatively old drugs

in general lower selectivity to H_1 receptors

they cross the **blood-brain barrier**

effect lasts **approx. 4 - 6 h**

rather common adverse effects

dimetinden (Fenistil®)

promethazine

bisulepin (Dithiaden®)

moxastine – for motion sickness (Kinedryl®)

cyproheptadine – treatment of serotonin syndrome

ketotifen

H_1 antihistamines
AE of I. generation

sedative, even hypnotic eff.– driving, heavy mashinery operation (!)

paradoxical reaction (children, elderly) = excitation (sleeplessness, nervousness, tachycardia, tremor, ...)

indigestion (nausea, vomiting, diarrhea x constipation)

skin symptoms → phototoxicity

anticholinergic effects

increas in appetite (antiserotoninergic effect)

ortostatic hypotension (weak block of α-adrenergic rp.)

H_1 antihistamines
II. and III. generation

- low distribution to CNS – minimal sedative effect

- better properties – higher selectivity towards rp., less AE

- effect lasts for **12 – 24 hours,** given 1 - 2 times a day

II. generation

- cetirizine
- loratadine
- fexofenadine
- azelastine
- levocabastine

III. generation

- levocetirizine
- desloratadine
- bilastine
- rupatadine

Novel H_1 antihistamines III. generation

bilastine

high selectivity towards H_1-receptors, antiinflammatory properties

not metabolized by liver or intestinal wall, low potential for drug-drug interaction

rupatadine

long-term effect

dual effect (H_1 antagonist + blocks PAF receptors)

H_1 antihistamines
AE of II. generation

arrythmogenic→ QT interval prolongation (some drugs even withdrawn)

possible sedation when overdosed (cetirizine)

Interactions:

are metabolised by CYP3A4 → be cautious of inhibitors of this isoform (macrolide ATB, azole antifungals, verapamil, grapefruit juice...)

H_1 antihistamines
Indications I

treatment of symptoms of **allergic diseases**
- allergic rhinitis
- urticaria, drug and food allergy

add-on treatment of anafylactic reactions

pruritus of various ethiology (e.g. itching in allergic and non-allergic dermatitis + insect bites)

tinitus, Meniére‘s disease

H_1 antihistamines
Indications II

migraine

nausea a vomiting
movement sickness (moxastine, embramine)
vertigo

prophylactic premedication before some drugs (e.g. monoclonal antibodies)

sleeplessness, when hypnotics are not tolerated

anxiety (hydroxyzine → mild anxiolytic effect)

MUNI
MED

H_1 antihistamines
Contraindications

- alcohol dependency
- hypersensitiveness to that substance
- serious hypotension
- simultaneous administration of sedative drugs (I.generation)
- activities which require full attention (I.generation)
- patients with history of arrythmias (II. generation)

H_3 antihistamines

betahistine

MoA: H_3 antagonist, H_1 agonist
analogue of histamine

improves microcirculation of the inner ear by vasodilatating capillaries

indications: tinitus, vertigo, Menière‘s disease

MUNI
MED

Drugs used in diseases characterized by bronchial obstruction

Department of Pharmacology

MUNI MED

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:

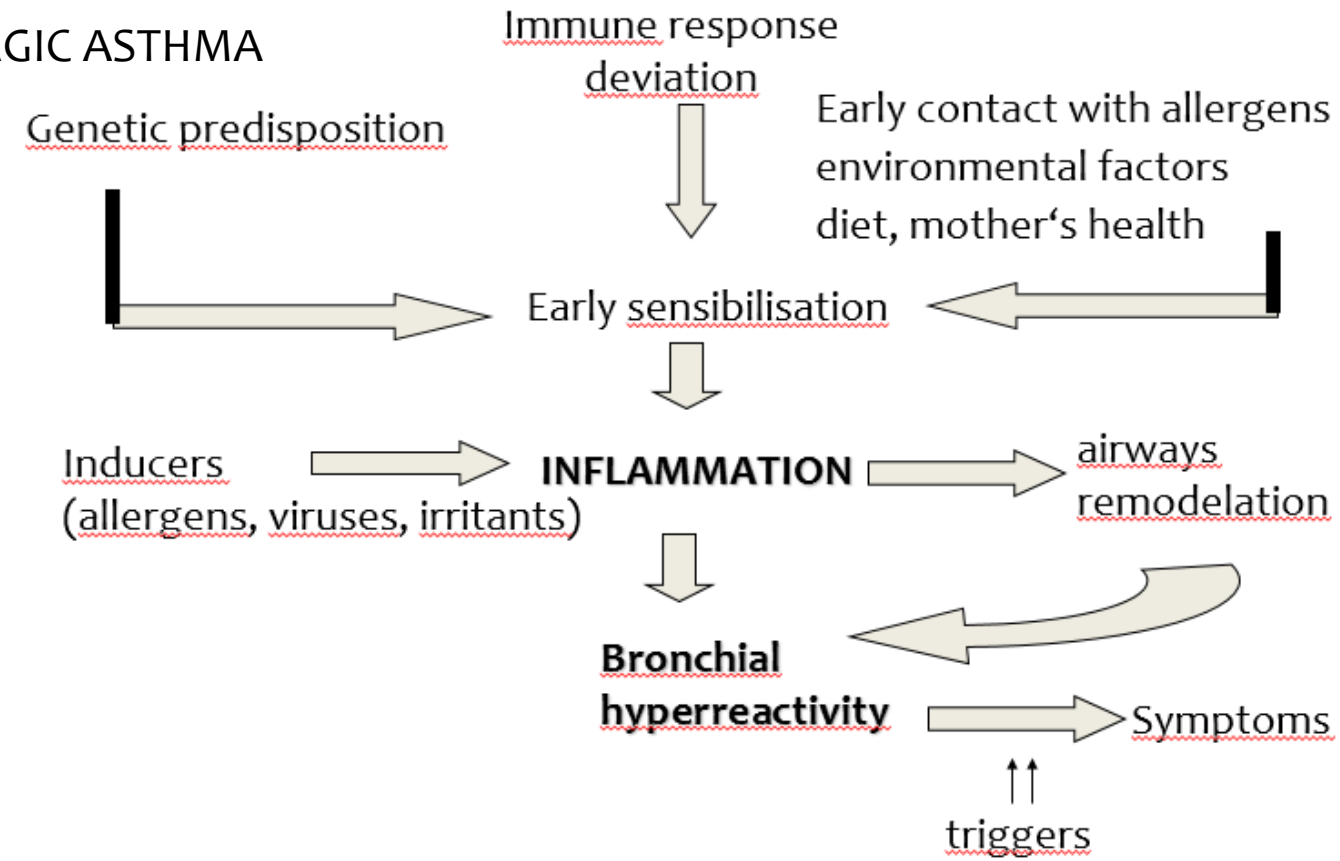
shortness of breath (bronchoconstriction, mucous plug, oedema, airway remodeling due to the inflammation)

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

cough (especially at night or in early morning)

Bronchial asthma

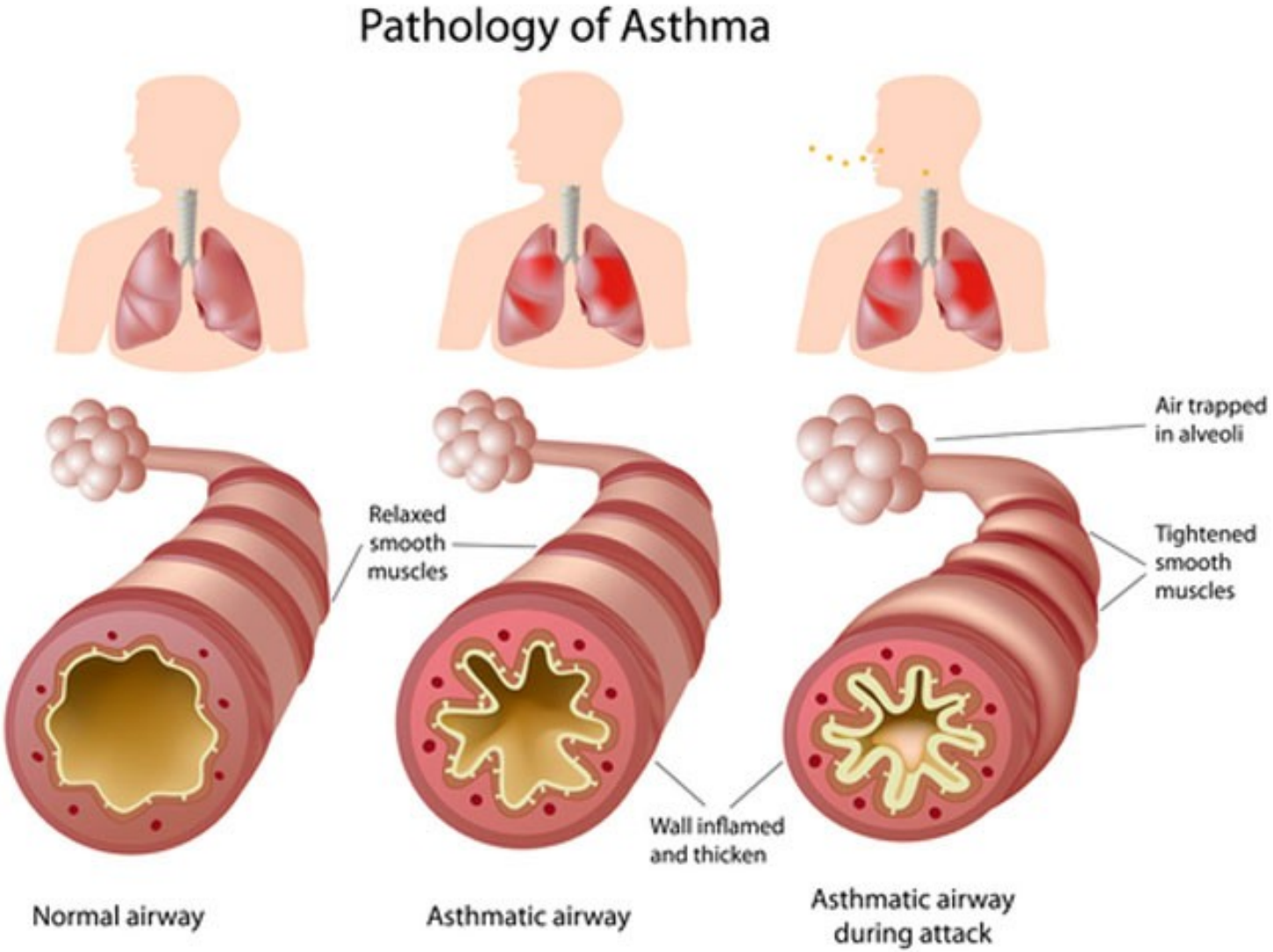
ALERGIC ASTHMA



NON-ALERGIC ASTHMA

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

MUNI
MED



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

MUNI
MED

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

MUNI MED

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)

MUNI MED

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

MUNI
MED

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

MUNI MED

MoA at the cellular level

glucocorticoid + cytoplasma receptor

↑ production of specific mRNA

↑ production of some proteins (lipocortins)

MoA at the cellular level

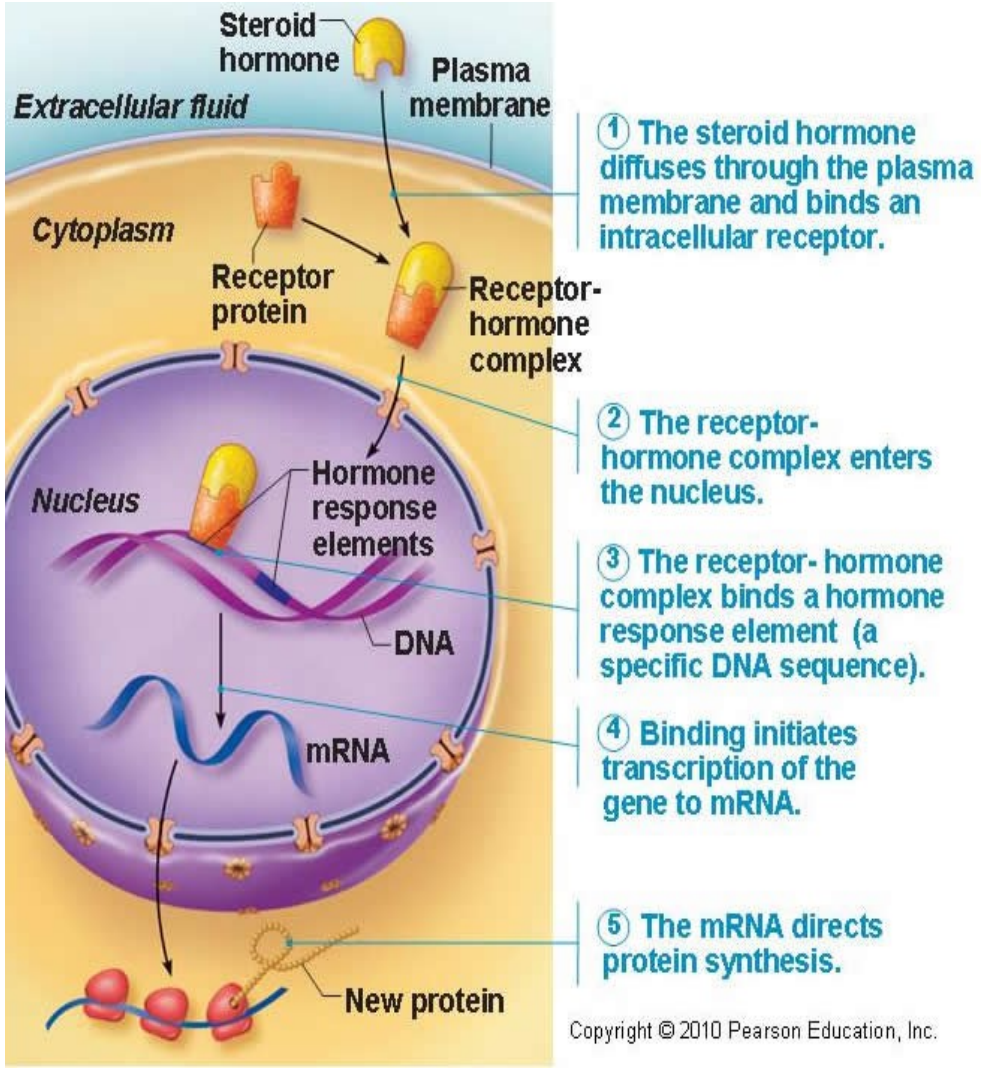
After entering the cell they bind to specific receptors in cytoplasm causing change of conformation = activation of receptors

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

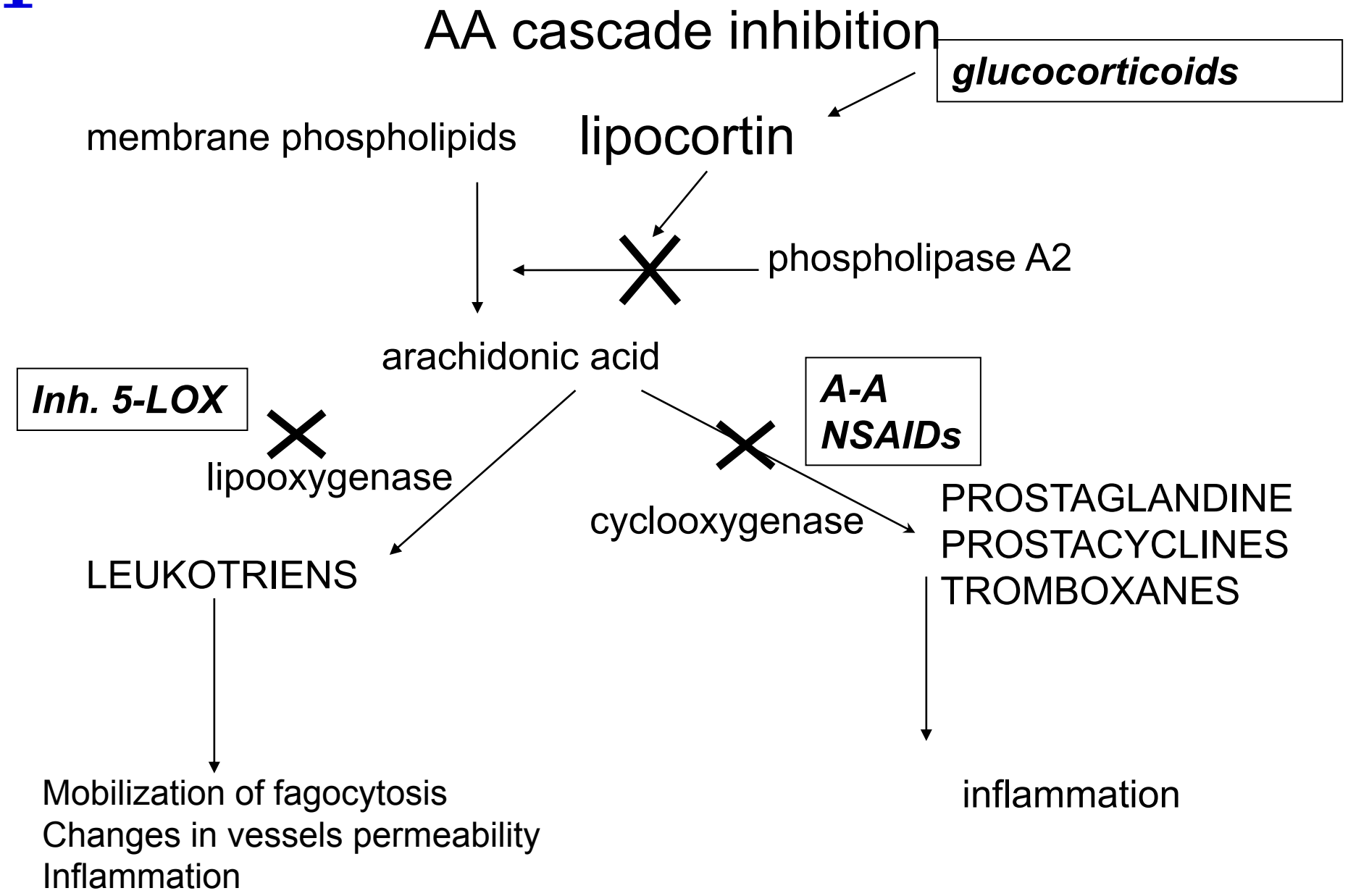
The result is increased transcription of genes either inducing or inhibiting synthesis of other proteins

GLC receptors are present in all tissues!!!

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



Antiinflammatory effect of GC



MUNI
MED

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

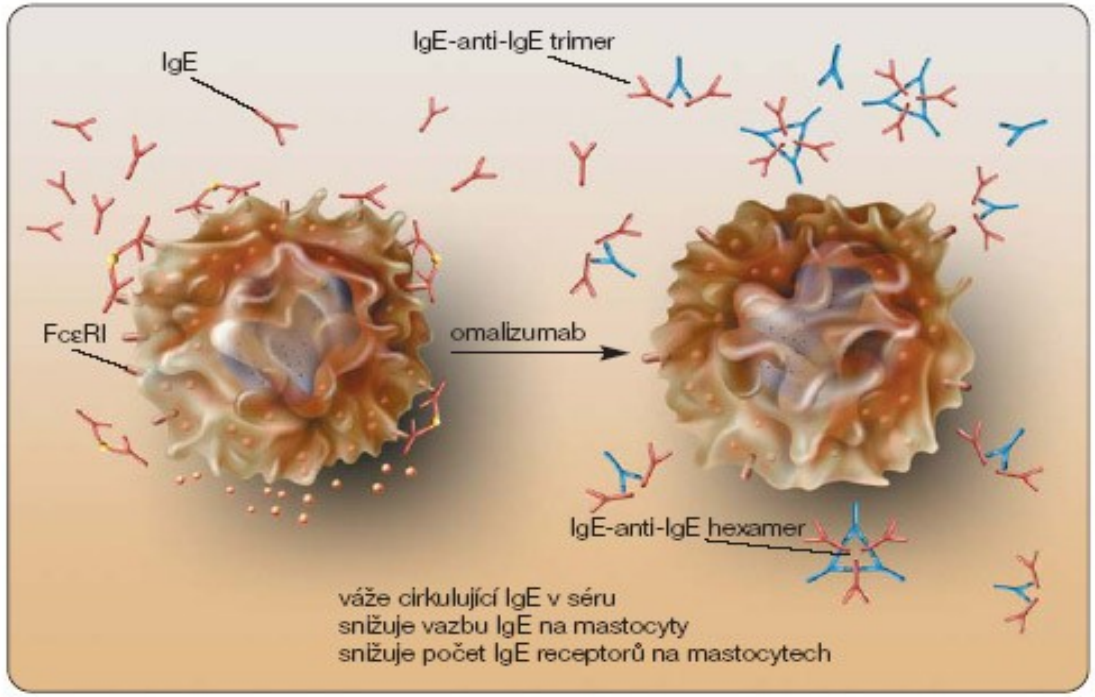
antibodies against a part of IgE, which binds to mast cells

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)

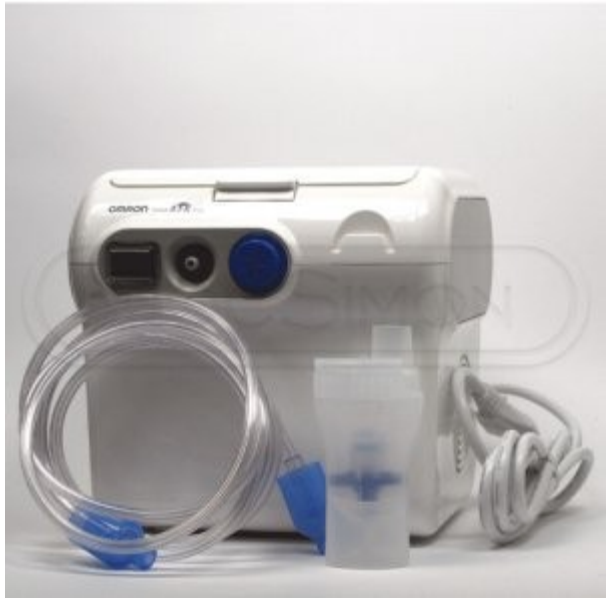
Devices for inhaled medications

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)

MUNI
MED



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)