Pharmacology of the respiratory system. Pharmacotherapy of bronchial asthma and COPD

Zoltán Zádori

zadori.zoltan@med.semmelweis-univ.hu

2019

Asthma - symptoms, epidemiology

- chronic, obstructive inflammatory disease of airways

- prevalence: ~ 5 % (300 million people, + 100 million in 15-20 years)

- symptoms: paroxysmal dyspnea, wheezing, esp. during expiration

- pathogenesis: hyperreactivity, smooth muscle contraction, inflammation, increased secretion

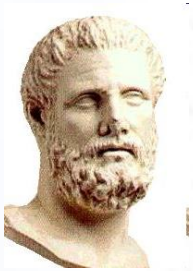
- main types: atopic (extrinsic), non-atopic (intrinsic)

terrifies the patient. At the beginning of February of this year, a patient of mine, a nervous woman, who at one time had herself been a medical student, had her first severe (prolonged) attack of asthma. She had previously only had very slight attacks. She recovered immediately after an injection of adrenaline, but was so distressed that she committed suicide within a few hours, giving as her reason her fear of being an invalid. At the post-mortem (Dr. J. F. Taylor) nothing abnormal was found in the lungs.

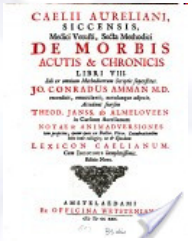
The History of Bronchial Asthma and Allergy.
By E. STOLKIND, M.D.
1933

History of asthma

BC 400 **I-II. c.** **IV-V. c.** **XII. c.** **XVII. c.** **XVIII. c.**



Hippocrates



Soranus **Caelius Aurelianus**

Moses Maimonides

Thomas Willis

William Cullen

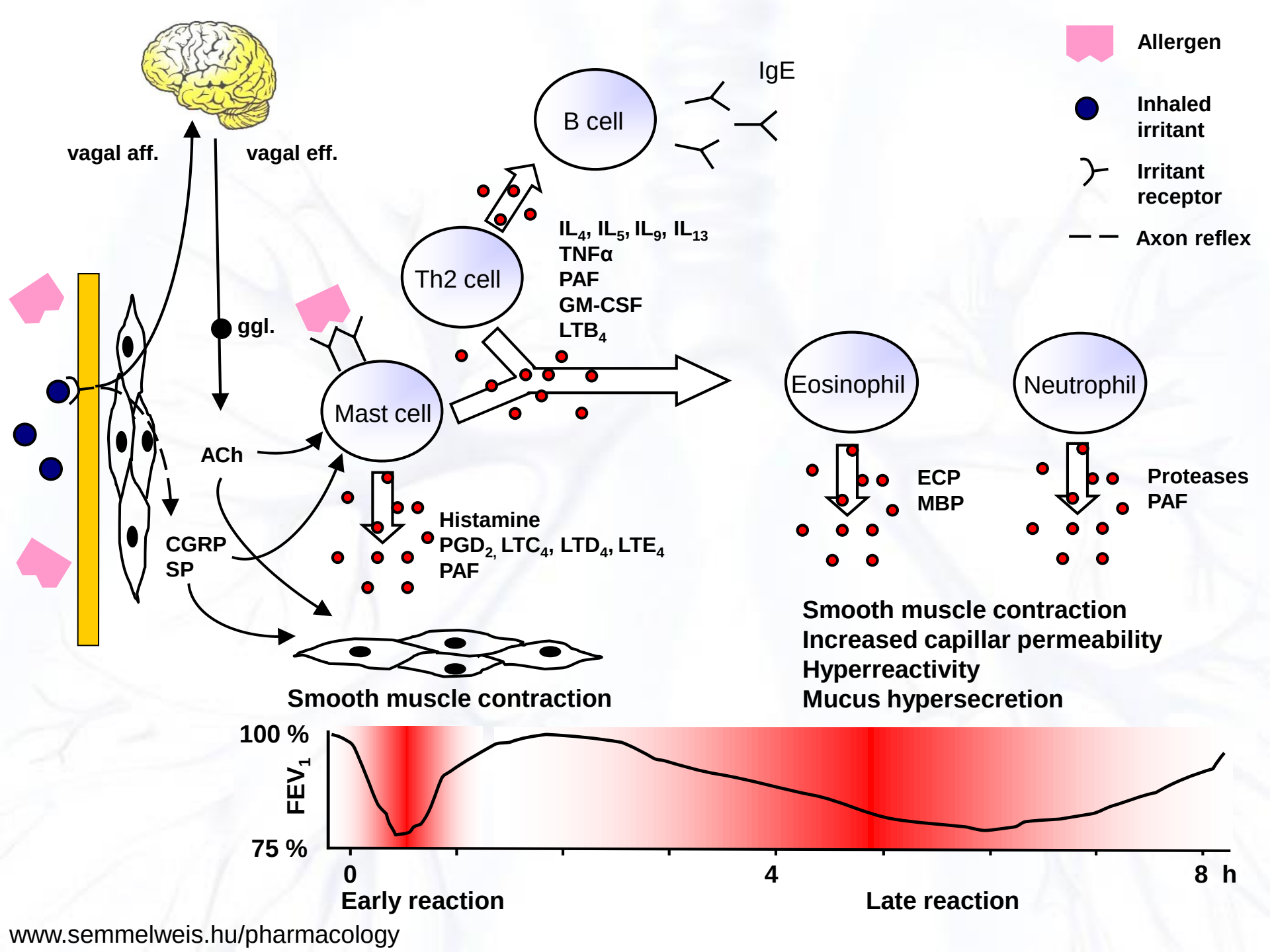
„asthma” (άσθμα) ~ dyspnea

Ø venesection, town → suburbs

importance of the CNS

„De morbis acutis et chronicis” Some characteristics of asthma, treatment strategies

nervous origin, advises opium


Allergen
Inhaled irritant
Irritant receptor
Axon reflex
vagal aff.
vagal eff.
ggl.
B cell
IgE
Th2 cell
IL4, IL5, IL9, IL13
TNFα
PAF
GM-CSF
LTB4
Mast cell
ACh
CGRP
SP
Histamine
PGD2, LTC4, LTD4, LTE4
PAF
Eosinophil
ECP
MBP
Neutrophil
Proteases
PAF
Smooth muscle contraction
Increased capillar permeability
Hyperreactivity
Mucus hypersecretion
Smooth muscle contraction
100 %
FEV1
75 %
0
4
8 h
Early reaction
Late reaction

Classification of antiasthmatic drugs

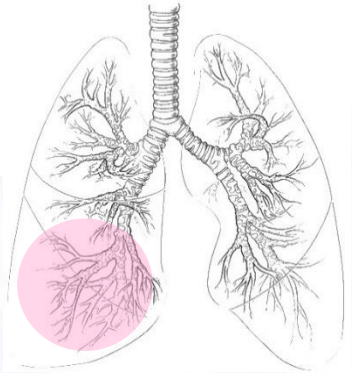
Basic pharmacological

Bronchodilators	Anti-inflammatory drugs
• β_2-AR agonists • Xanthines • Antimuscarinic drugs	• Glucocorticoids • Leukotriene antagonists • Monoclonal antibodies • Degranulation inhibitors

Clinical

„Relievers”	„Controllers”
• Short-acting β_2-AR agonists /SABA/ • Xanthines • Short-acting antimuscarinic drugs /SAMA/	• Glucocorticoids • Leukotriene antagonists • Monoclonal antibodies • Long-acting β_2-AR agonists /LABA/ • Xanthines • Long-acting antimusc. drugs /LAMA/

Bronchodilators 1. β_2-AR agonists

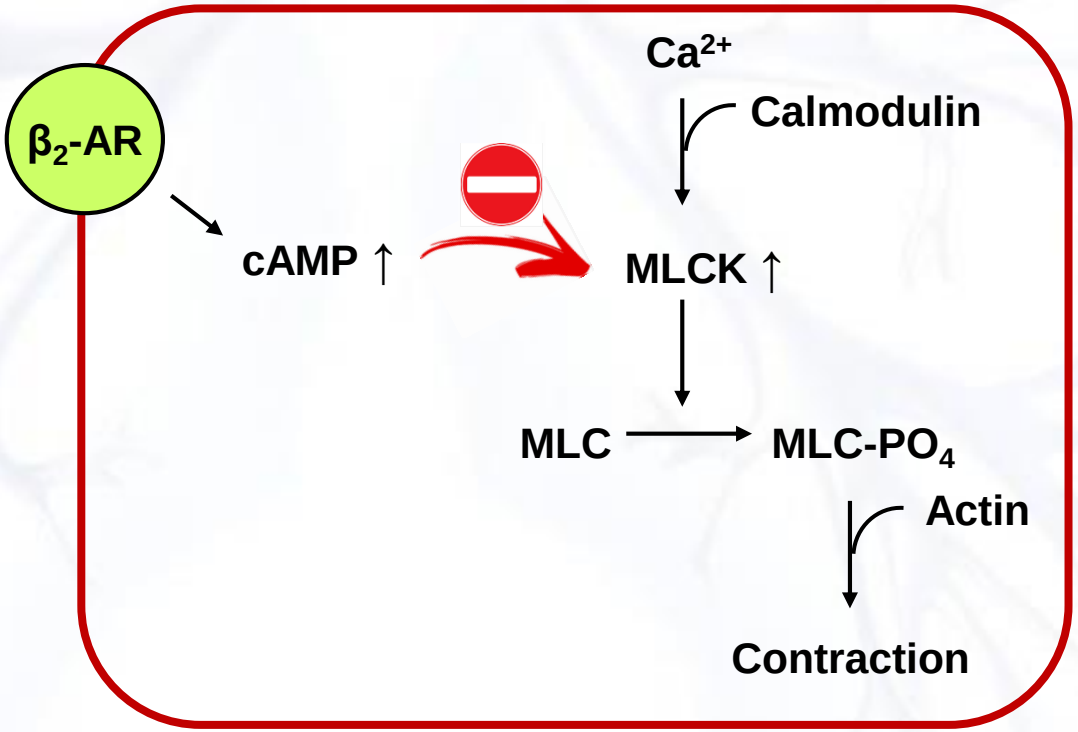


Therapeutic effects

- bronchodilation

- ciliary activity ↑

- release of inflammatory mediators ↓

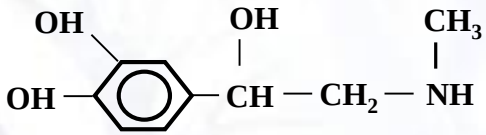


❖ Non-selective β_2-AR agonists (not relevant as antiasthmatics)

B.C. 200 Ephedrine (Ephedra sinica, ma huang,麻黄)

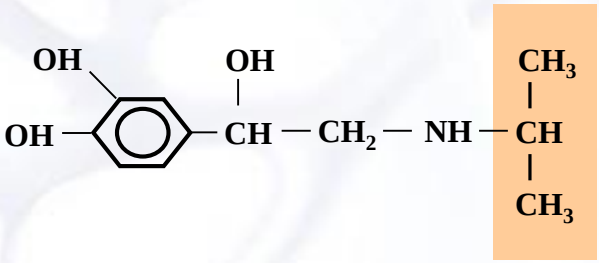
α_1	α_2	β_1	β_2
++	++	+++	+++

1905 Epinephrine



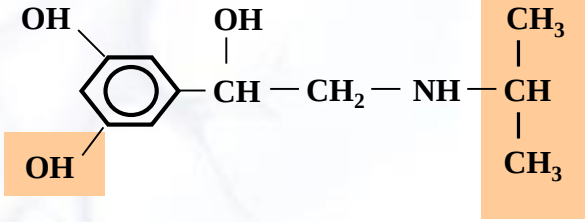
Disadv.: - cardiac effects
- short duration of action
- cannot be given orally

1940s Isoprenaline (Isoproterenol)



α_1	α_2	β_1	β_2
-	-	+++	+++

1963 Orciprenaline (Metaproterenol)



α_1	α_2	β_1	β_2
-	-	+	+++

Adv.: - better oral bioavailability
Disadv.: - cardiac effects

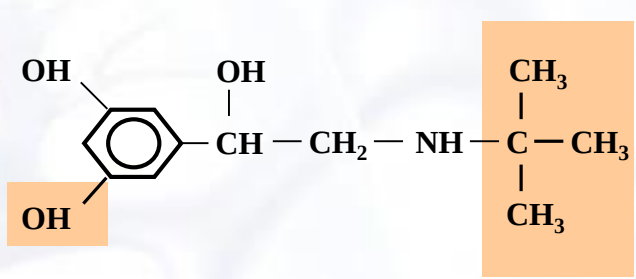
❖ Short-acting β_2-AR agonists /SABA/

α_1	α_2	β_1	β_2
-	-	-	+++

1968 Salbutamol (Albuterol)

1969 Terbutaline

1974 Fenoterol



1999 Levosalbutamol (Levalbuterol)

- onset of action: ~ 5 min, maximal effect: ~ 30 min, duration: 4-6 h

- salbutamol also orally, terbutaline also s.c. and i.v.

- ind.: relievers (on-demand inhalation)

❖ Long-acting β_2-AR agonists /LABA/

Slower onset of action, longer duration > 12 h

/higher lipophilicity → cumulation in membrane/

Salmeterol (1988) - partial agonist

Formoterol (1990) - faster onset of action

Clenbuterol
Bambuterol → → Terbutaline
} oral agents

Indacaterol, Olodaterol, Vilanterol (duration > 24 h)

Clinical use

- controllers in patients with moderate / severe asthma and COPD

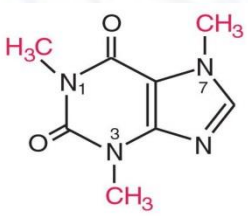
- always in combination with glucocorticoids

Adverse effects of β_2-AR agonists

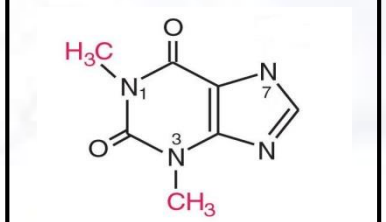
- cardiovascular disturbances (palpitation, tachycardia, angina)
  - direct cardiac effects (β_1,β_2)
  - vasodilation (β_2)
  - presynaptic norepinephrine release (β_2)
- tremor (declines by chronic treatment)
- hypokalemia
- metabolic effects (hyperglycemia, hyperlipidemia)
- reduced arterial PaO_2
- mild loss of appetite, disturbed sleep
- development of tolerance

Bronchodilators 2. Xanthines

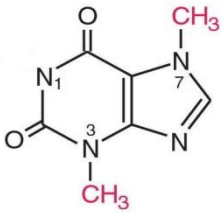
- Methylxanthines - alkaloids (*Coffea arabica, Thea sinensis, Theobroma cacao*)



Caffeine



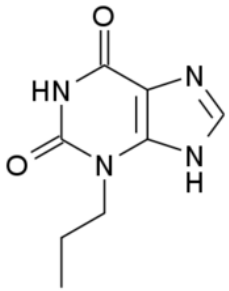
Theophylline



Theobromine

Aminophylline
(2xTheophylline - ethylenediamine)

- Enprofylline (3-propylxanthine)



Albrecht Kossel
1888

Therapeutic effects of theophylline

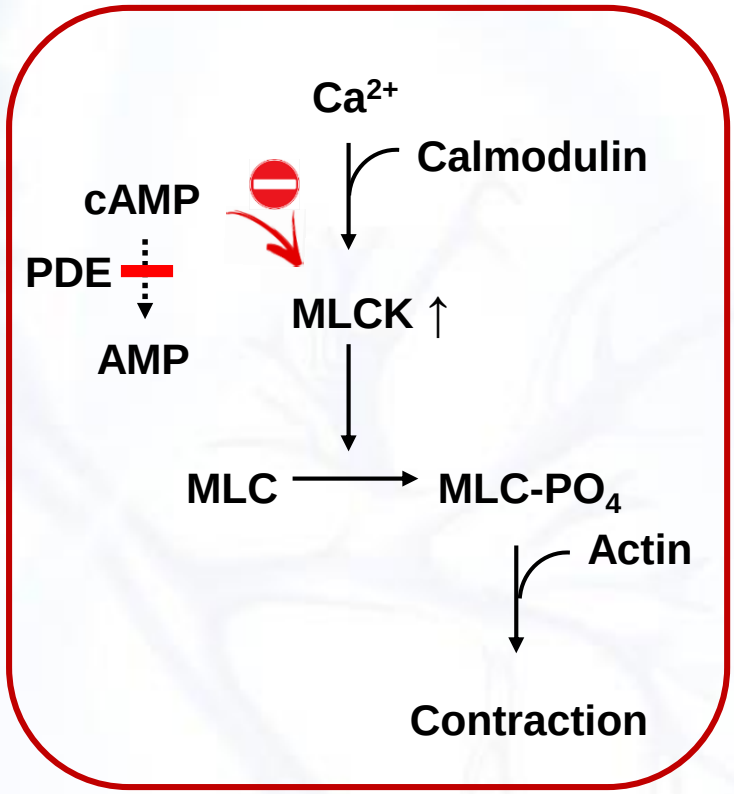
- bronchodilation

  - PDE ↓ → cAMP ↑
  - A_1 rec. ↓

- release of inflammatory mediators ↓

  - PDE_4 ↓, A_1 rec. ↓, HDAC2 ↑

- ciliary activity ↑

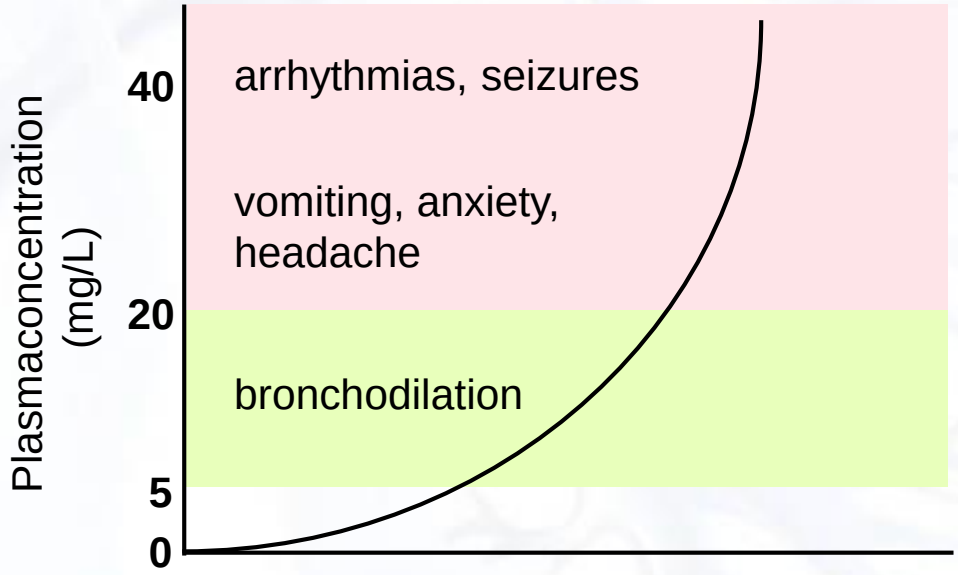


Side effects

- CNS ↑ → anxiety, insomnia, tremor, seizures
- cardiovascular effects
  - at low doses mild elevation of BP ↑ (A rec. ↓)
  - at higher doses „inodilator" effect (CAMP ↑)
- diuretic effect (GFR ↑, tubular sodium reabsorption ↓)
- gastrointestinal secretions ↑ (gastric acid, digestive enzymes)

Pharmacokinetics of theophylline

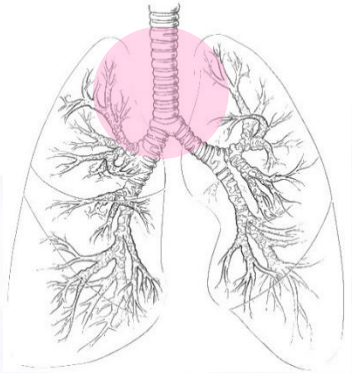
- good oral absorption
- metabolism in the liver /CYP1A2/ (erythromycin, fluoroquinolones !)
- individual differences in metabolic rate and $T_{1/2}$
- narrow therapeutic index



Clinical use of theophylline

- prevention of asthmatic attack (oral, extended-release tablets)
- reliever in acute asthma (aminophylline i.v.)

Bronchodilators 3. mAChR antagonists

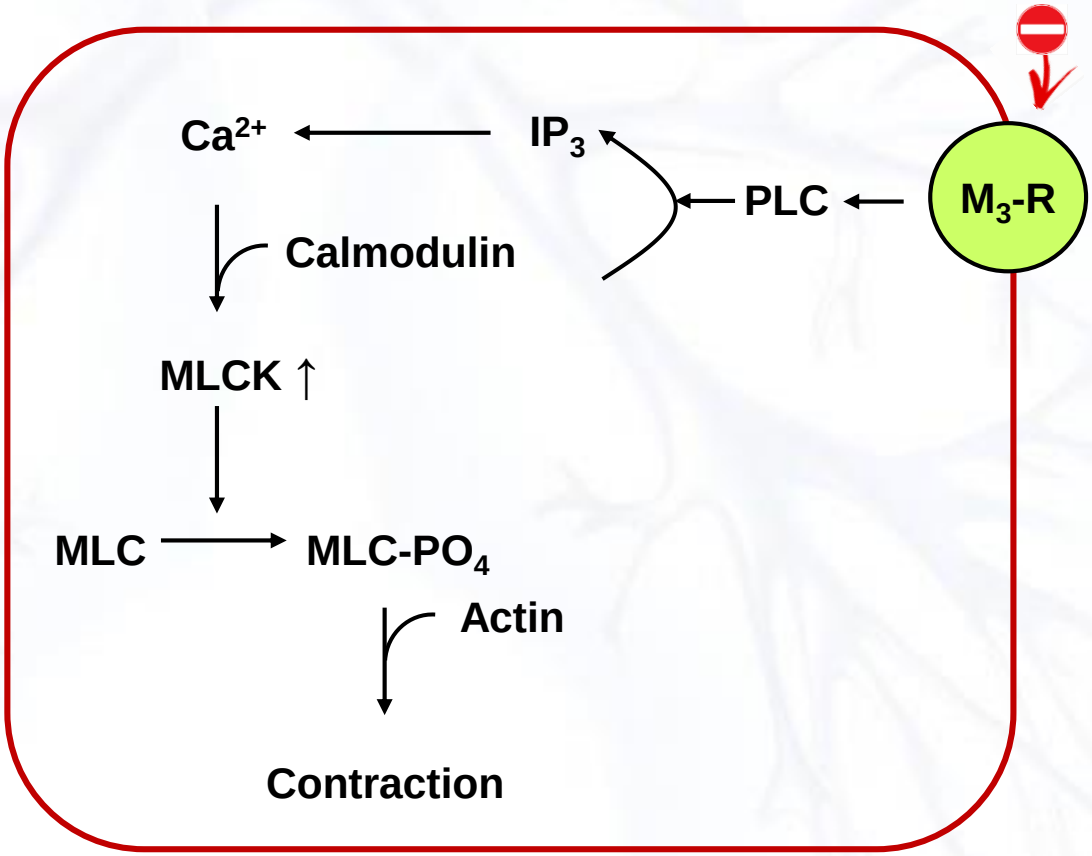


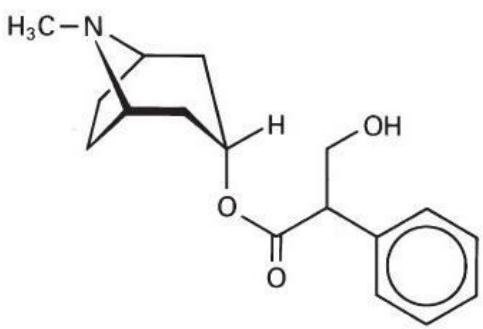
- Atropine (1859)

Therapeutic effects

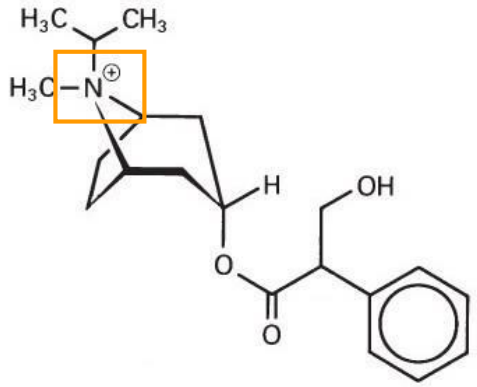
- bronchodilation
- bronchial secretion ↓

Datura stramonium





Atropine



Ipratropium

Ipratropium

- non-selective muscarinic receptor antagonist
- onset: < 15 min, duration: 4-6 h, given 3-4 times daily

Tiotropium, Glycopyrronium, Aclidinium, Umeclidinium

- pharmacokinetic selectivity for M_3 receptors (slower dissociation)
- longer effect ($T_{1/2}$ 11 h - 6 days, except aclidinium), once daily dosage

Adverse effects

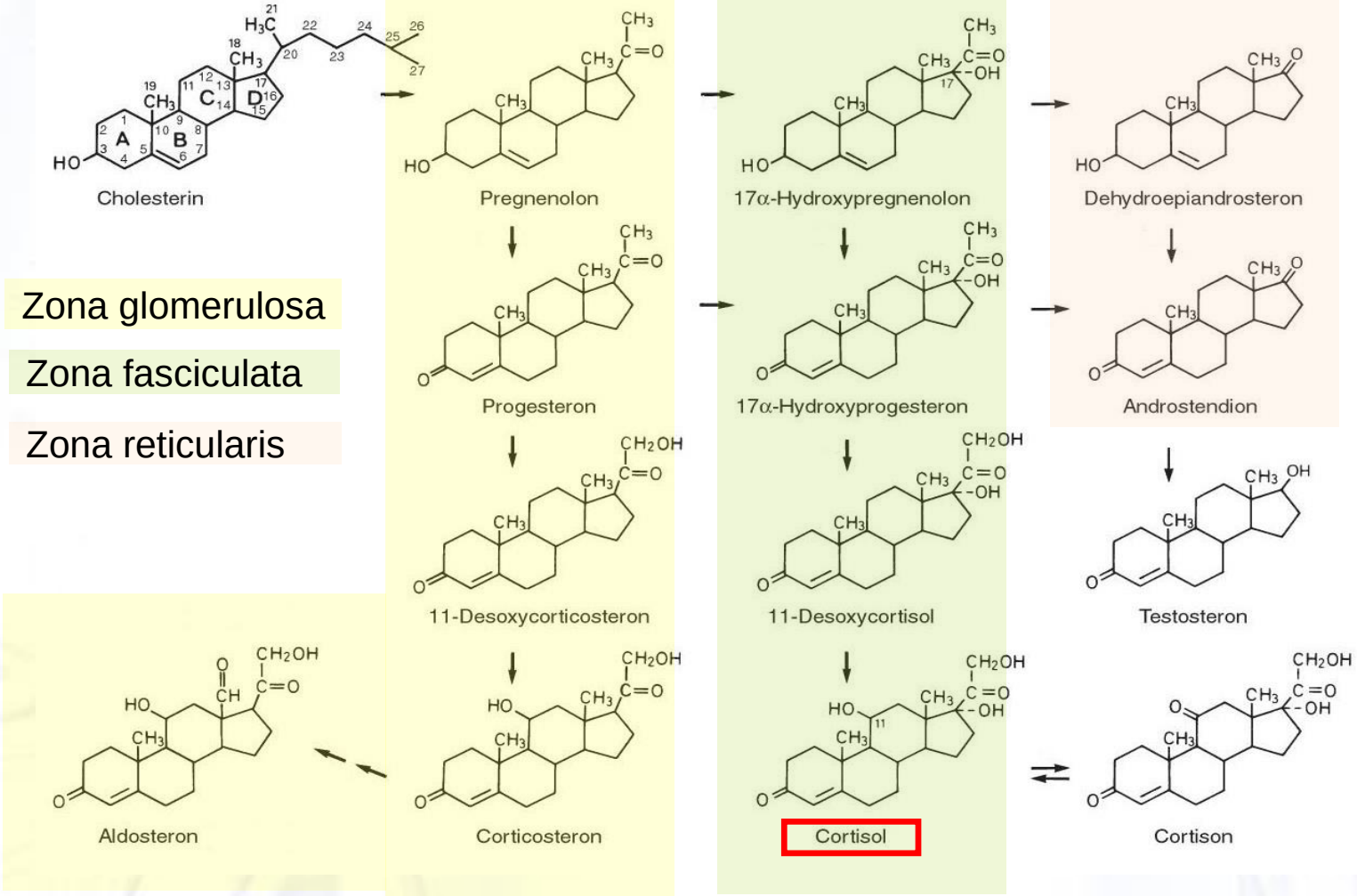
- dry mouth, cough

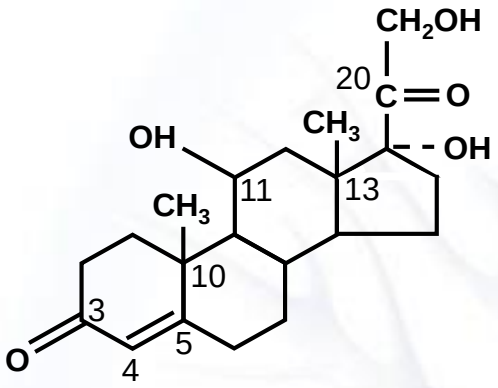
(quaternary structure → less systemic effects)

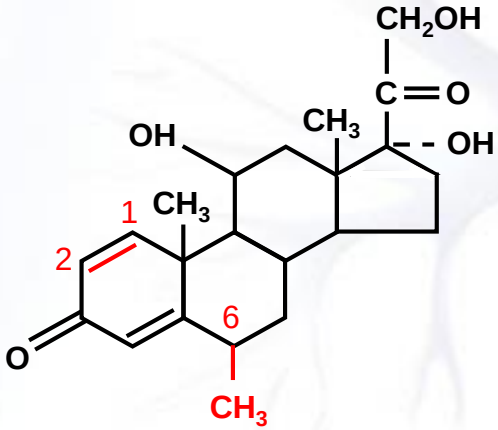
Clinical use

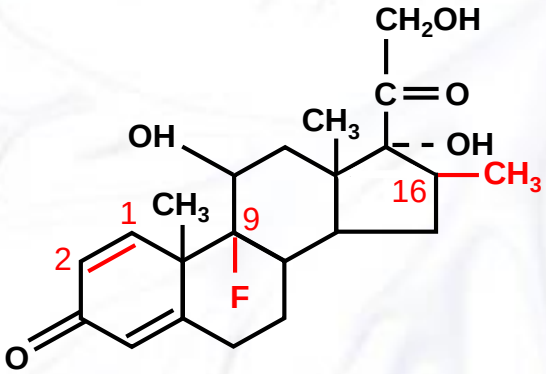
- relievers (ipratropium) or controllers in asthma and **COPD**

Anti-inflammatory drugs 1. Glucocorticoids



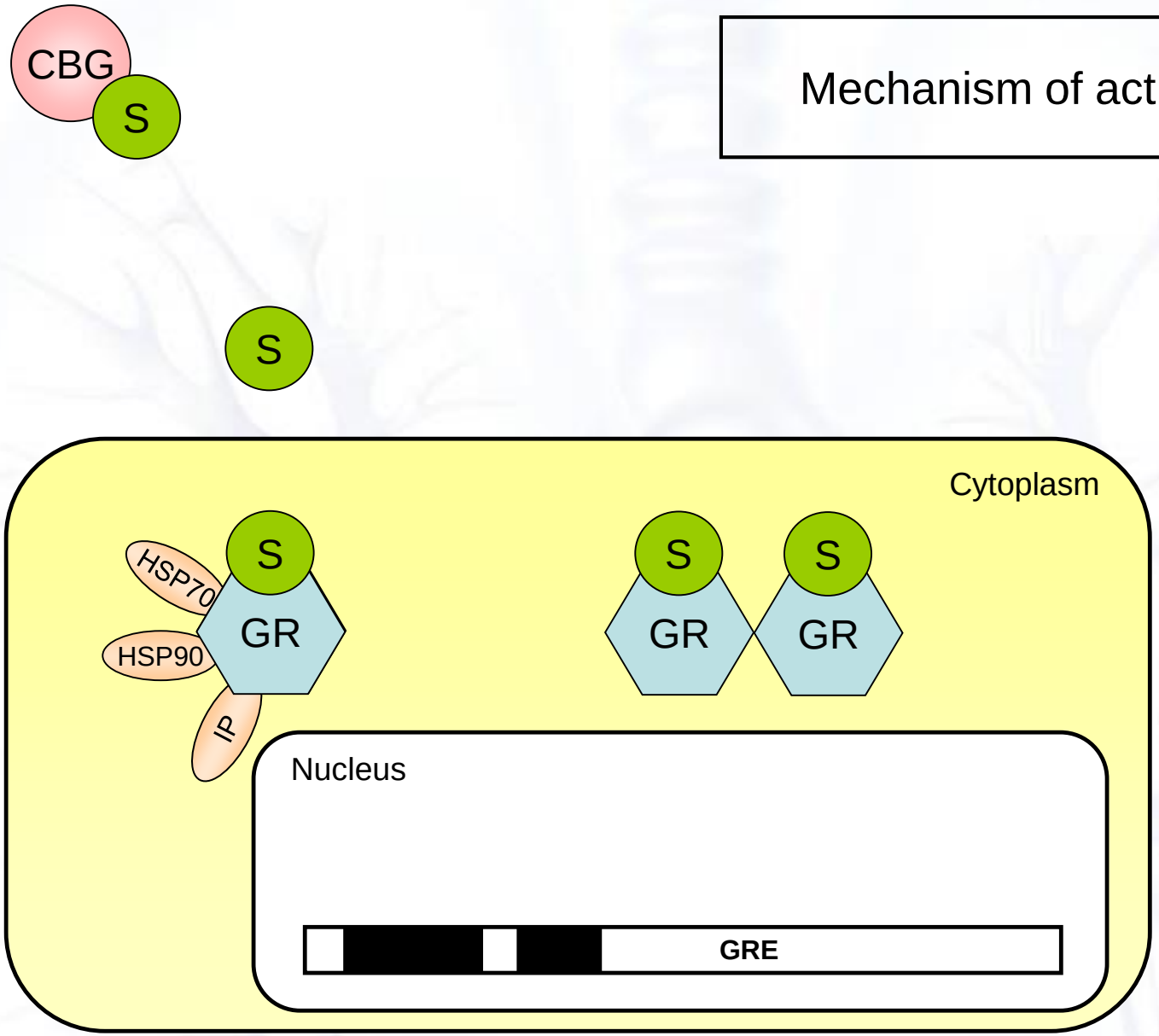






	M	G
Cortisol	1	1
Fludrocortisone	125	10
Prednisone	0,8	4
Prednisolone	0,8	4
Methylprednisolone	0,5	5
Triamcinolone	0	5
Dexamethasone	0	25
Betamethasone	0	25

Mechanism of action



Therapeutic effects of ICSs

- anti-inflammatory / immunosuppressive effect

  vasodilation ↓, extravasation and edema ↓

  neutrophil migration ↓, activity of leukocytes and macrophages ↓

  annexin-1 ↑ → COX-2 expression ↓, PLA_2 ↓ (PG, LT ↓)

  pro-inflammatory cytokines ↓ (IL-1 - IL-6, IL-8, TNF-α, GM-CSF)

  iNOS expression ↓

  histamine release ↓

  IgG production ↓

  complement cascade ↓

- bronchial hyperreactivity ↓

- β_2-adrenoceptor expression ↑

Problems

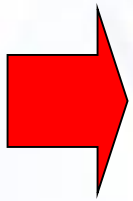
Ø bronchodilation, slow onset (> 4 h) → used only to prevent asthmatic attacks

relatively flat dose-response curve

„non-responder” patients (steroid resistance)

Adverse effects of glucocorticoids (systemic administration)

- infections - oropharyngeal candidiasis
- hyperglycemia, diabetes
- peptic ulcer (PG ↓, defense against H. pylori ↓)
- Cushing's syndrome
- osteoporosis, avascular necrosis of the femoral head
- reduced growth
- muscle weakness, decreased muscle mass
- CNS (seizures, depression, intracranial pressure ↑)
- GH, LH, TSH secretion ↓
- glaucoma, hypokalemia, delayed wound healing, thinning of the skin
- acute adrenal insufficiency (if chronic treatment is stopped suddenly)



Relative contraind.:

- cardiovasc. diseases
- peptic ulcer
- glaucoma
- diabetes
- osteoporosis
- psychosis
- infections (HSV, TBC)

❖ Inhaled corticosteroids (ICSs)

Drug	Route of adm.	Daily dosage		
		Low dose	Medium dose	High dose
Beclomethasone dipropionate (prodrug)	inhalation	200 – 500 µg	500 – 1000 µg	1000 – 2000 µg
Budesonide		200 – 400 µg	400 – 800 µg	800 – 1600 µg
Fluticasone		100 – 250 µg	250 – 500 µg	500 – 1000 µg
Ciclesonide (prodrug)		80 – 160 µg	160 – 320 µg	320 – 1280 µg

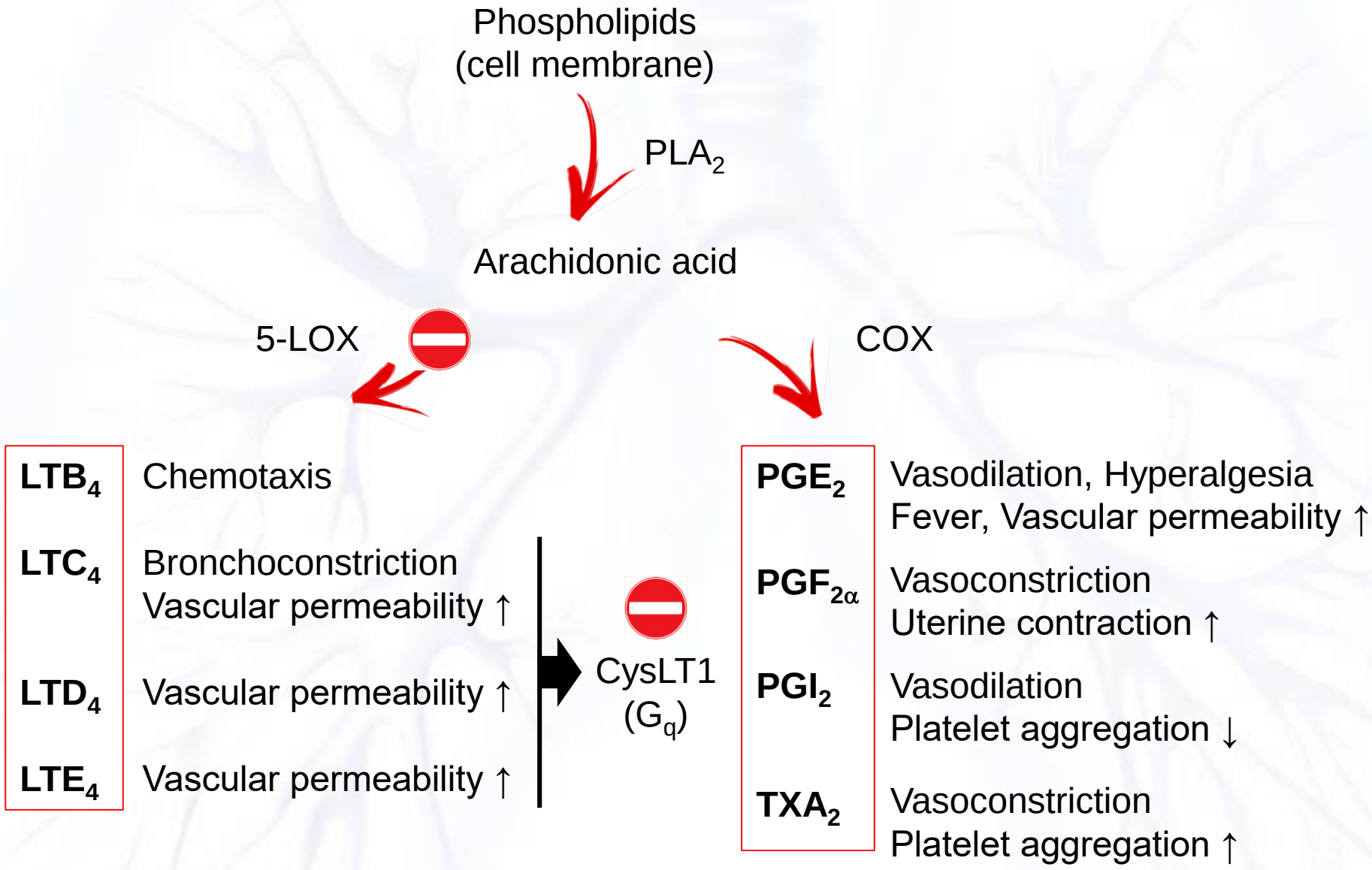
Adverse effects of ICSs

- at low doses mild
    - oropharyngeal candidiasis
    - hoarseness (vocal cord changes)
- at medium / high doses risk of systemic adverse effects

Clinical use

- prevention of attacks in patients with mild - severe asthma or COPD
- systemic steroid treatment - in case of severe acute attacks or severe persistent asthma (prednisolone p.os or methylprednisolone i.v.) - more side effects

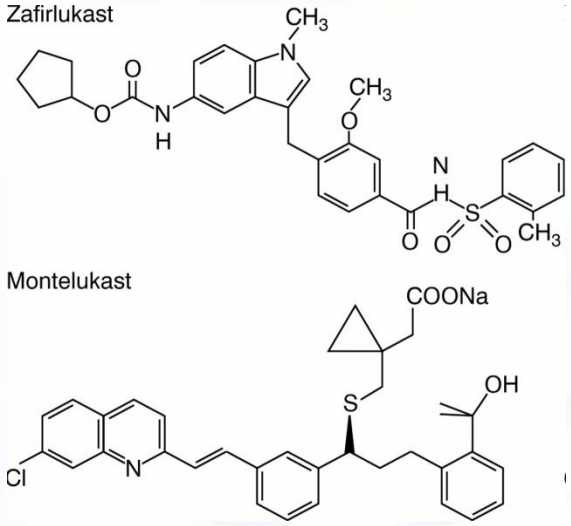
Anti-inflammatory drugs 2.
Leukotriene antagonists



❖ $CysLT_1$ receptor antagonists

Zafirlukast

Montelukast



Therapeutic effects

- inflammation ↓ (LTC_4, LTD_4, LTE_4 ↓ → vasc. permeability ↓, edema ↓)
- bronchodilation (mild → only prophylactic use)
- disadvantage: some patients are „non-responders”

Clinical use

- prevention of attacks (oral use, 1-2 x daily)

Adverse effects

- mild (headache, diarrhea), Churg-Strauss syndrome ?

❖ 5-lipoxygenase inhibitors

Zileuton

Therapeutic effects

- inflammation ↓ (LTC_4, LTD_4, LTE_4 ↓ → vasc. permeability ↓, edema ↓)

  + chemotaxis ↓ (LTB_4)

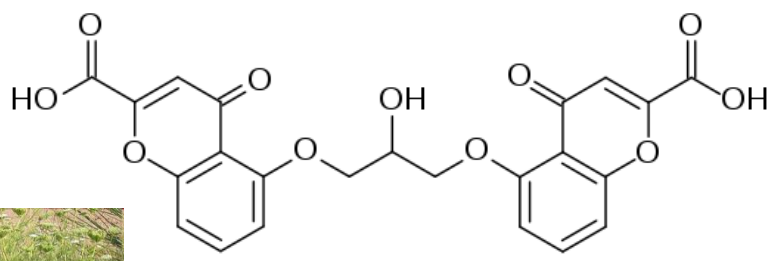
  + $CysLT_2$ receptor-mediated effects ↓

- bronchodilation (mild → only prophylactic use)

Disadvantages

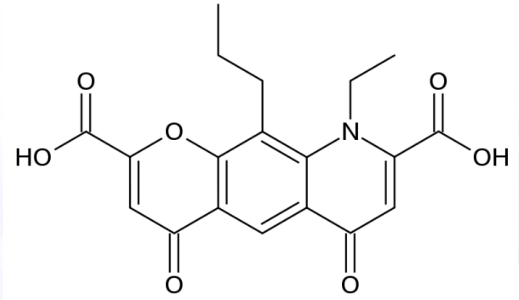
- 2,5 h $T_{1/2}$ → 4x daily administration (oral)
- risk of liver damage (4-5 %)
- metabolism via CYP1A2 (possible interaction with theophylline)

Anti-inflammatory drugs 3. Degranulation inhibitors



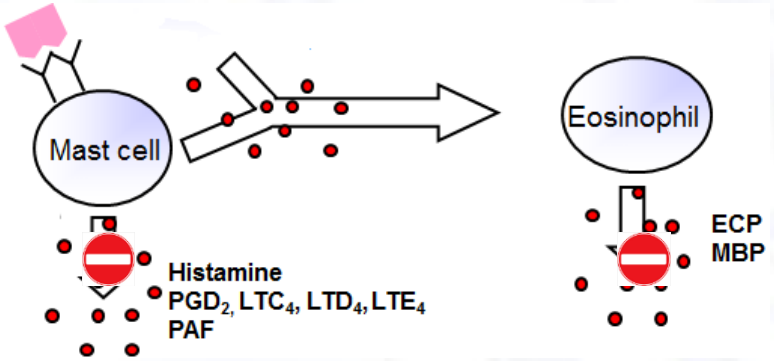
Cromolyn

A. visnaga → Khellin



Nedocromil

Effects



- inflammation ↓ (mechanism of action ?)
  - degranulation of mast cells ↓
  - release of mediators from eosinophils ↓
- bronchial hyperreactivity ↓ (inhibition of irritant receptors)

Adverse effects

- mild: local irritation, cough

Clinical use

- allergic rhinitis, conjunctivitis
- prevention of attacks in mild asthma (mild effect, inhalation 4x daily, maximum effect develops in 3-4 weeks)

Anti-inflammatory drugs 4. Monoclonal antibodies

Omalizumab

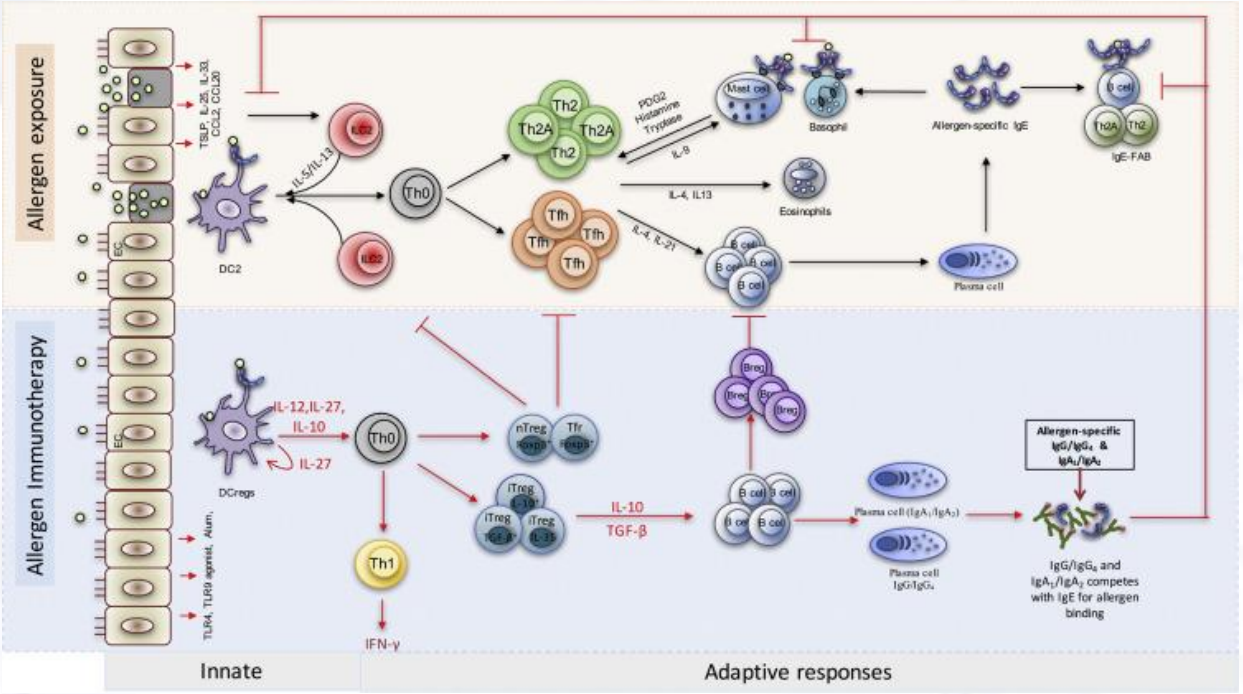
- humanized anti-IgE mAB
- prevents IgE-binding to and activation of mast cells, monocytes, granulocytes
- used to prevent attacks in severe persistent allergic asthma (if ICSs combined with LABA fail to control disease symptoms)
- also used to treat chronic spontaneous urticaria
- $T_{1/2}$ - 26 days, administration in every 2-4 weeks (s.c.)
- Adverse effects: allergy (local erythema → anaphylactic reactions)

Reslizumab (i.v.), Mepolizumab, Benralizumab (s.c.)

- humanized anti-IL5 mABs
- prevention of attacks in severe eosinophilic asthma (once every 4 weeks)
- Adverse effects: allergy, headache, muscle pain

Further options in the treatment of asthma

- H_1 receptor antagonists (weak effect, sedation)
- PDE_4 inhibitors (Roflumilast, *Ibudilast*)
- Desensitization immunotherapy
- Antibiotics, oxygen



Journal of Allergy and Clinical Immunology, 140:6, 1485-1498, 2017

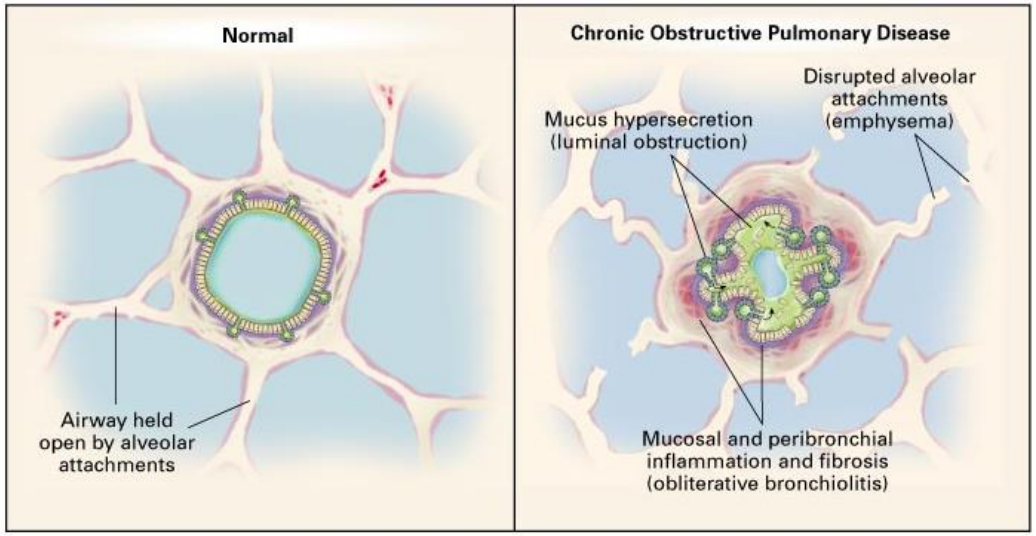
COPD : pathogenesis and definition

- components of COPD (their proportion varies individually):
  - chronic bronchitis
  - obstruction of small airways, formation of mucous plugs
  - emphysema, enlargement of airspaces, destruction of pulmonary parenchyma, decrease of pulmonar elasticity

- frequent exacerbations, symptoms significantly decrease the quality of life

- progression of disease
in spite of medical treatment

- major cause (80-90%): chronic smoking (smoking cessation → progression ↓)



	Asthma	COPD
Atopy	✓	-
Time of diagnosis	at any age (often during childhood)	usually above 40
History of smoking	-	✓
Symptoms	episodic	continuous
Airway obstruction	reversible	irreversible
Hyperreactivity	✓	-
Typical inflammatory cells	eosinophils	neutrophils
Steroids and β_2-agonists	effective	less effective
Antimuscarinic drugs	less effective	effective

Stages of asthma

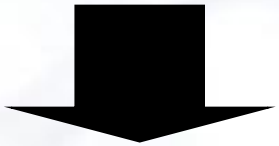
	Frequency of symptoms	Nighttime symptoms	Pulmonary functions (spirometry results)
1. stage Mild intermittent	symptoms max. 1x / week	≤ 2x / month	FEV_1 or PEF ≥ 80% PEF variability < 20%
2. stage Mild persistent	symptoms min. 2x / week, but not every day	> 2x / month	FEV_1 or PEF ≥ 80% PEF variability 20-30%
3. stage Moderate persistent	daily symptoms, can impair physical activity	> 1x / week	FEV_1 or PEF 60-80%, PEF variability > 30%
4. stage Severe persistent	daily symptoms, reduced activity, frequent exacerbations	frequent	FEV_1 or PEF ≤ 60%, PEF variability > 30%

FEV_1: Forced expiratory volume at 1 sec
PEF: Peak expiratory flow

Stepwise treatment strategy of asthma

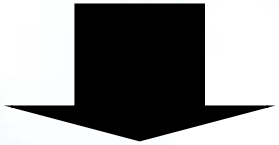
1. Assess the severity of asthma and start the treatment according to the guidelines

Step-up if necessary



2. Increase the intensity of treatment stepwise, until the asthma is controlled

Step-down if possible



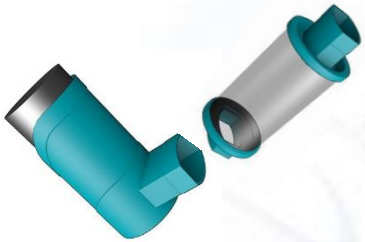
3. Reduce the dose of anti-inflammatory agents gradually (if possible), to minimize the side effects

Levels of asthma control

	Controlled	Partially controlled (one of the parameters)	Not controlled (min. 3 of the parameters)
Daytime symptoms	< 2 days / week	> 2 days / week	> 2 days / week
Reduced physical activity	Ø	✓	✓
Nighttime awakenings	Ø	✓	✓
Requirement of short-term relievers	< 2 / week	> 2 / week	> 2 / week
PEF / FEV_1	normal	< 80 %	< 80 %
Exacerbation	Ø	≥ 1 / year	≥ 1 / year

- assess the level of control regularly, step up/down if necessary

Inhalators, nebulizer



Metered Dose Inhaler (MDI)

Dry Powder Inhaler (DPI)

Nebulizer

Portable	Portable	Not portable
Solution / Suspension – aerosol	Solid particle	Solution – aerosol
Propellant (chlorofluorocarbons, CFCs – ozone damage)	No propellant	No propellant
Suspensions must be shaken before inhalation	No shaking	No shaking
Slow, deep inhalation – coordinated inhalation is required (except with spacer)	Quick, forceful, deep inhalation – patient controls inhalation	Slow, deep inhalation
More cost-effective	More expensive	For patients with poor inspiratory flow rate, or cognitive impairment

	Frequency of symptoms	Nighttime symptoms	Pulmonary functions
1. stage Mild intermittent	symptoms max. 1x / week	≤ 2x / month	FEV_1 or PEF ≥ 80% PEF variability < 20%
Drug of choice		Alternatives	
inhaled short-acting β2-agonists		- inhaled antimuscarinic agents - oral short-acting β2-agonists	

❖ Use of antimuscarinic agents

- as adjuncts to β_2-agonists (e.g. ipratropium + fenoterol)
- instead of β_2-agonists, if those are contraindicated or not tolerated
- if cholinergic tone is elevated (e.g. nocturnal asthma)
- **COPD**

Less effective than β_2-agonists (except COPD)

	Frequency of symptoms	Nighttime symptoms	Pulmonary functions
2. stage Mild persistent	symptoms min. 2x / week, but not every day	> 2x / month	FEV_1 or PEF ≥ 80% PEF variability 20-30%

Drug of choice	Alternatives
Reliever + low dose inhaled steroid	Reliever + leukotriene inhibitors

❖ Inhaled corticosteroids (ICSs)

- controllers from the 2nd stage of asthma
(more frequent episodes and/or airway obstruction persists despite the use of relievers)

- low dose
(Bec.: 200-500 µg, Bud.: 200-400 µg, Flu.: 100-250 µg, Cic.: 80-160 µg)

- mild side effects, mainly locally (oropharyngeal candidiasis, hoarseness)

- usually administered in the morning (less influence on HPA-axis)

- if the control is adequate → dose reduction (to the minimum necessary dose)

- discontinuation of the therapy usually leads to loss of control within a few weeks

- intermittent vs continuous administration

- non-responders (different disease phyenotypes?)

❖ Leukotriene inhibitors

- alternatives to inhaled steroids
(less effective, changing the treatment → may result in loss of control)

- indication:

  - if the patient rejects the use of steroids („steroid phobia”)

  - if steroids are not well tolerated (e.g. hoarseness)

- oral use (children)

  - montelukast 1x daily, zafirlukast 2x daily

  - some patients are „non-responders”

  - Zileuton – liver function monitoring

	Frequency of symptoms	Nighttime symptoms	Pulmonary functions
3. stage Moderate persistent	daily symptoms, can impair physical activity	> 1x / week	FEV_1 or PEF 60-80%, PEF variability > 30%

Drug of choice	Alternatives
Reliever + low dose inhaled steroid + LABA	Reliever + - low dose inhaled steroid + LT-antagonist - low dose inhaled steroid + retard theophylline - medium dose steroid

❖ Long-acting β_2-AR-agonists /LABA/

- once (evening) or twice daily (morning and evening, half dose)

- slower onset of action (fastest: formoterol), duration > 12 h

- in combination with anti-inflammatory agents (Ø monotherapy)

- oral agents (Clenbuterol, Bambuterol, Procaterol) → more side effects

- synergistic effect: low dose steroid + LABA > high dose steroid

- disadvantage: increased risk of death from an asthma attack („black box" warning) – probably in case of monotherapy

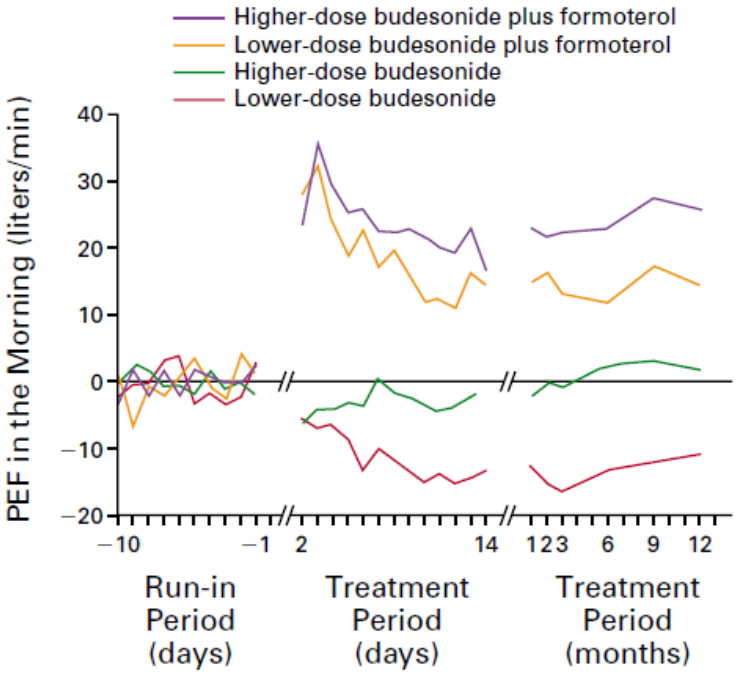
The New England
Journal of Medicine

VOLUME 337 NOVEMBER 13, 1997 NUMBER 20

EFFECT OF INHALED FORMOTEROL AND BUDESONIDE ON EXACERBATIONS OF ASTHMA

ROMAIN A. PAUWELS, M.D., CLAES-GÖRAN LÖFDAHL, M.D., DIRKJE S. POSTMA, M.D., ANNE E. TATTERSFIELD, M.D., PAUL O'BYRNE, M.B., PETER J. BARNES, D.M., AND ANDERS ULLMAN, M.D., FOR THE FORMOTEROL AND CORTICOSTEROIDS ESTABLISHING THERAPY (FACET) INTERNATIONAL STUDY GROUP*

- 852 patients treated with steroid
- 4 weeks run-in period with 2x800 µg budesonide, then randomized to 1 year treatment with:
  - 2x 100 µg budesonide + placebo
  - 2x 100 µg budesonide + 12 µg formoterol
  - 2x 400 µg budesonide + placebo
  - 2x 400 µg budesonide + 12 µg formoterol
- + terbutaline as needed



	Frequency of symptoms	Nighttime symptoms	Pulmonary functions
4. stage Severe persistent	daily symptoms, reduced activity, frequent exacerbations	frequent	FEV_1 or PEF ≤ 60%, PEF variability > 30%

Drug of choice	Alternatives
Reliever + med/high dose inhaled steroid + LABA	Reliever + - med/high dose inhaled steroid + LT-antagonist - med/high dose inhaled steroid + theophylline + other anti-inflammatory agents or oral steroid, if necessary (5. stage)

	Low dose	Medium dose	High dose
Beclomethasone	200 – 500 µg	500 – 1000 µg	1000 – 2000 µg
Budesonide	200 – 400 µg	400 – 800 µg	800 – 1600 µg
Fluticasone	100 – 250 µg	250 – 500 µg	500 – 1000 µg
Ciclesonide	80 – 160 µg	160 – 320 µg	320 – 1280 µg

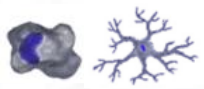
❖ Systemic steroids

Prednisolone, Methylprednisolone

- in severe persistent asthma
  - 4-6 mg MP p. os daily or every 2nd day
  - 1 mg/kg MP for 5-10 days p. os in the case of acute exacerbation (then gradual dose reduction)
- in severe acute attack 3 x 40 mg MP i.v.
- short use to gain prompt control, when initiating long-term therapy
- more side effects
- mechanism of acute action ?
  - number of β_2-receptors (in vitro) ↑ and activity of mast cells (in vivo) ↓ within 2 h
  - inhaled steroids reduce the blood flow of airways within 30 min (edema ↓ ?)

Different asthma phenotypes

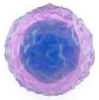
Allergens, viruses, air pollution



Alveolar macrophages / DCs

Lower airways epithelial cells

Th2 Asthma



Th2

IL-4
IL-5
IL-13
high eosinophils
high serum periostin

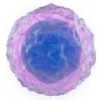
Good clinical response to:

- ICS
- anti-IL-5 mABs (mepolizumab, reslizumab, benralizumab)
- anti-IL-13 mABs (lebrikizumab, tralokinumab)

No response to:

- anti-IL-1β, anti-IL-4, anti-IL-17, anti-TNF-α

Non-Th2 Asthma



Th1
Th17

TNF-α
IFN-γ
IL-17
high neutrophils

Good clinical response to:

- anti-CXCL2

No response to:

- anti-IL-1β, anti-IL-8, anti-TNF-α

Treatment strategy of COPD I. Assessment of patient category

Patient category	Characteristics	Pulmonary function	Exacerb. / year	CAT score	MMRC score
A	low risk, less symptoms	$FEV_1 \geq 50$ %	≤1	< 10	0-1
B	low risk, more symptoms	$FEV_1 \geq 50$ %	≤ 1	≥ 10	≥ 2
C	high risk, less symptoms	$FEV_1 < 50$ %	≥ 2	< 10	0-1
D	high risk, more symptoms	$FEV_1 < 50$ %	≥ 2	≥ 10	≥ 2

CAT: COPD Assessment Test
MMRC: Modified Medical Research Council Dyspnea Scale

Treatment strategy of COPD II. Pharmacologic management

Patient category	First choice	Alternative choice	Other possibilities
A	SAMA / SABA	LAMA / LABA / SABA and SAMA	Theophylline
B	LAMA / LABA	LAMA and LABA	SABA and/or SAMA / Theophylline
C	ICS + LABA / ICS + LAMA	LAMA and LABA / LAMA and PDE_4 inhibitor / LABA and PDE_4 inhibitor	SABA and/or SAMA / Theophylline
D	ICS + LABA and/or LAMA	ICS + LABA and LAMA / ICS + LABA + PDE_4 inhibitor / LAMA and LABA / LAMA and PDE_4 inhibitor	Carbocysteine SABA and/or SAMA Theophylline