

Drugs Acting on Respiratory System

EDY SUWARSO

I. Drug Therapy of Bronchial Asthma

The term ***asthma*** is derived from the Greek word meaning ***difficulty in breathing***. Asthma is a chronic inflammatory allergic disease: the patients suffer with reversible episodes of airways obstruction due to bronchial hyper-responsiveness.

In the **early (acute) phase** there are smooth muscle spasm and excessive bronchial secretion of mucus.

In the late **(chronic or delayed) phase**, inflammation continues, accompanied by fibrosis, oedema and necrosis of bronchial epithelial cells.

FACTORS THAT EXACERBATE ASTHMA

- 👂 Viral infections
- 👂 Cigarette smoke
- 👂 Exercise and hyperventilation
- 👂 Weather
- 👂 Foods, additives, drugs
- 👂 Stress
- 👂 Pollution
- 👂 Chemicals
- 👂 Occupational agents



The cardinal symptoms of asthma are breathlessness wheezing, cough and chest tightness with worsening of these symptoms at night. In the acute attack there are rapid respiratory rate and tachycardia. The majority of patients suffer with **atopic extrinsic asthma**, which is associated with exposure to specific allergen (pollen or house-dust mite) . In **non-atopic extrinsic asthma** the attack may be stimulated with some non-specific stimulus, e.g. chemical irritants. In such cases, IgG and Ig antibodies circulate in the blood but are not attached to the mast cells or basophils. Neutrophils destroy these antigen-antibody complexes. As a result, the liberated lysosomal enzymes

can digest the remaining mucoproteins. Drugs which stabilize the lysosomal membrane, e.g. GCS provide relief to these patients. In contrast, the many patients who acquire asthma after the age of 40 years have no identifiable external precipitating factor or immunological basis for asthmatic attack. This can be described as **intrinsic asthma**. Many patients suffer from both extrinsic and intrinsic forms of asthma. *In comparison with intrinsic asthma, extrinsic asthma is episodic and less prone to develop into status asthmaticus.* **Status asthmaticus** is a severe acute asthma, which is a life-threatening condition involving exhaustion, cyanosis, bradycardia, hypotension, dehydration and metabolic acidosis.

Cardiac asthma is a bronchospasm precipitated by uncompensated congestive heart failure.

Pathophysiology of Asthma

Antigens (pollen and house-dust mites) sensitize patients by eliciting the production of **IgE type of antibodies**, which remain either circulating in the blood or become attached to the mast cells of nasal or bronchial tissues and basophils. On re-exposure to the same antigen, the resulting antigen-antibody reaction in the **early phase** causes degranulation of the lung mast cells and releasing of the **powerful bronchoconstrictors**: histamine, 5-HT, PGD₂ and cysteinyl leucotriens (LTB₄, LTC₄ and LTD₄).

Lung mast cells also release ILs (IL-4, IL-5 and IL-13). In **the late (delayed) phase** of asthma, these mediators activate additional inflammatory cells (eosinophils, basophils, and alveolar macrophages) which also release LTs and ILs.

Other mediators of inflammation, in delayed phase, are: adenosine (causing bronchoconstriction), neuropeptides (SP, causing mucus secretion and increase in vascular permeability; neurokinin A, causing bronchoconstriction), PAF etc.

The normal tone of bronchial smooth muscle is influenced by a balance between parasympathetic, sympathetic and non-adrenergic–non-cholinergic (NANC) mediators activity.

Activation of M_3 -receptors by the release ACh results in increase in cGMP levels and leads to bronchoconstriction and increase in mucus secretion. β_2 -receptor stimulation leads to an increase of cAMP levels which results in bronchodilation.

The main NANC **inhibitory** neurotransmitter is NO.

The main NANC **excitatory** transmitters are neuropeptides (neurokinin A and SP), released from unmyelinated sensory C-fibres when stimulated by inflammatory mediators and irritant chemicals (SO_2 , cigarette smoke).

Why asthma makes it hard to breathe

Air enters the respiratory system from the nose and mouth and travels through the bronchial tubes.

In an asthmatic person, the muscles of the bronchial tubes tighten and thicken, and the air passages become inflamed and mucus-filled, making it difficult for air to move.

In a non-asthmatic person, the muscles around the bronchial tubes are relaxed and the tissue thin, allowing for easy airflow.



**Inflamed bronchial tube
of an asthmatic**

Normal bronchial tube

Classification of Antiasthmatic Drugs

1. Bronchodilators

- **Selective β_2 -agonists:** Clenbuterol, Salbutamol, Fenoterol, Indacaterol, Levosalbutamol, Salmeterol, Terbutaline
- **Nonselective β -agonists:** Epinephrine, Isoprenaline, Orciprenaline; Ephedrine
- **M-cholinolytics:** Ipratropium, Tiotropium, Oxitropium
- **Methyl Xanthines:** Theophylline, Aminophylline, Theotard

- ## 2. Mast Cell Stabilizers:
- Sodium Cromoglycate, Ketotifen, Nedocromil

3. Glucocorticosteroids (GCS)

- **Oral:** Prednisone, Methylprednisolone
- **Parenteral:** Methylprednisolone, Betamethasone
- **Inhalational:** Beclomethasone, Budesonide, Fluticasone, Triamcinolone

4. Inhalational β_2 -agonists/Glucocorticosteroids

Seretide[®] (fluticasone/salmeterol)

Symbicort[®] (budesonide/formoterol)

5. Leukotriene Modulators

- **5-Lipoxygenase Inhibitor:** Zileuton
- **LTD₄-antagonists:** Zafirlukast, Montelukast

6. Monoclonal Anti-IgE Antibody: Omalizumab

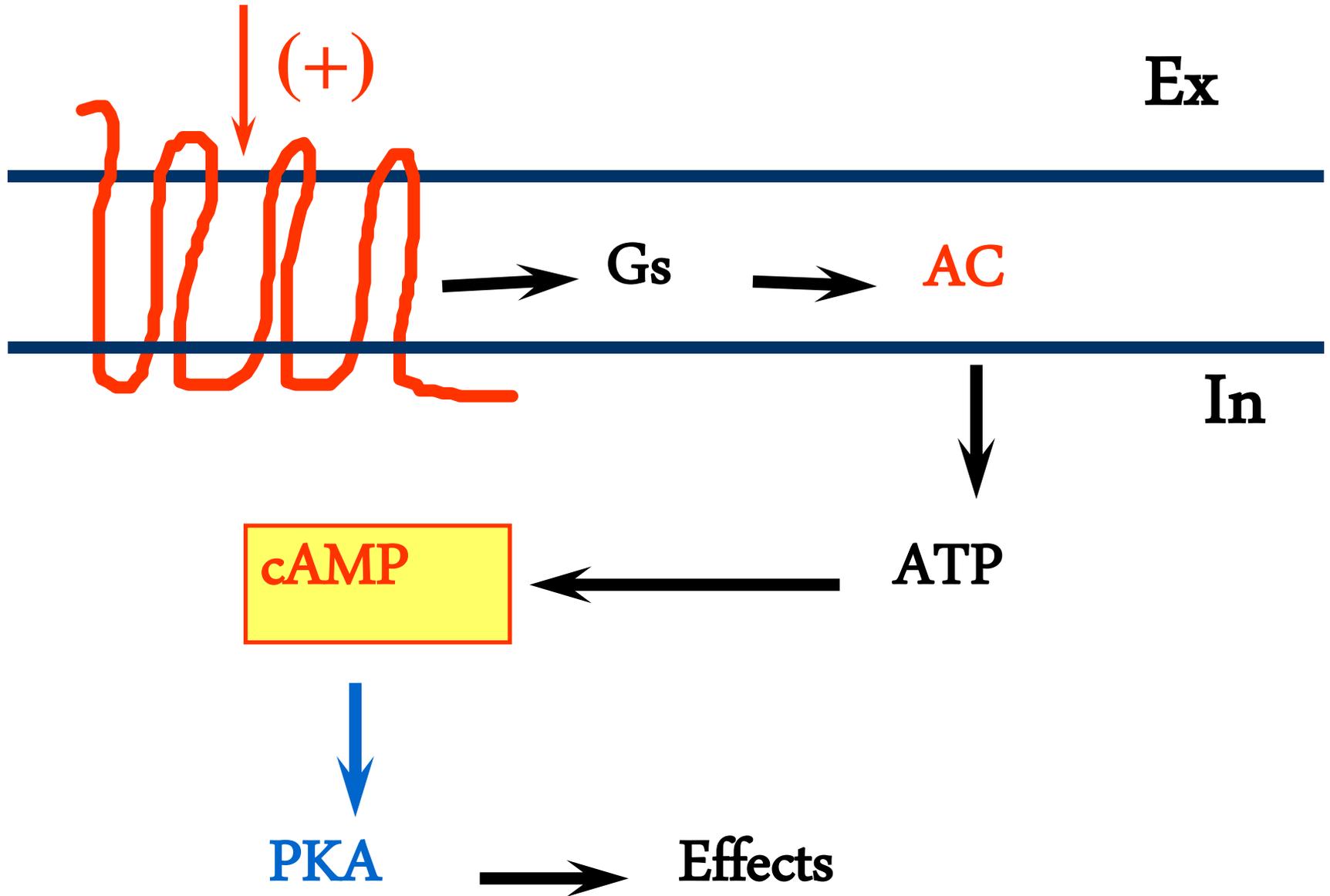
7. Miscellaneous: NO-donors, Calcium antagonists

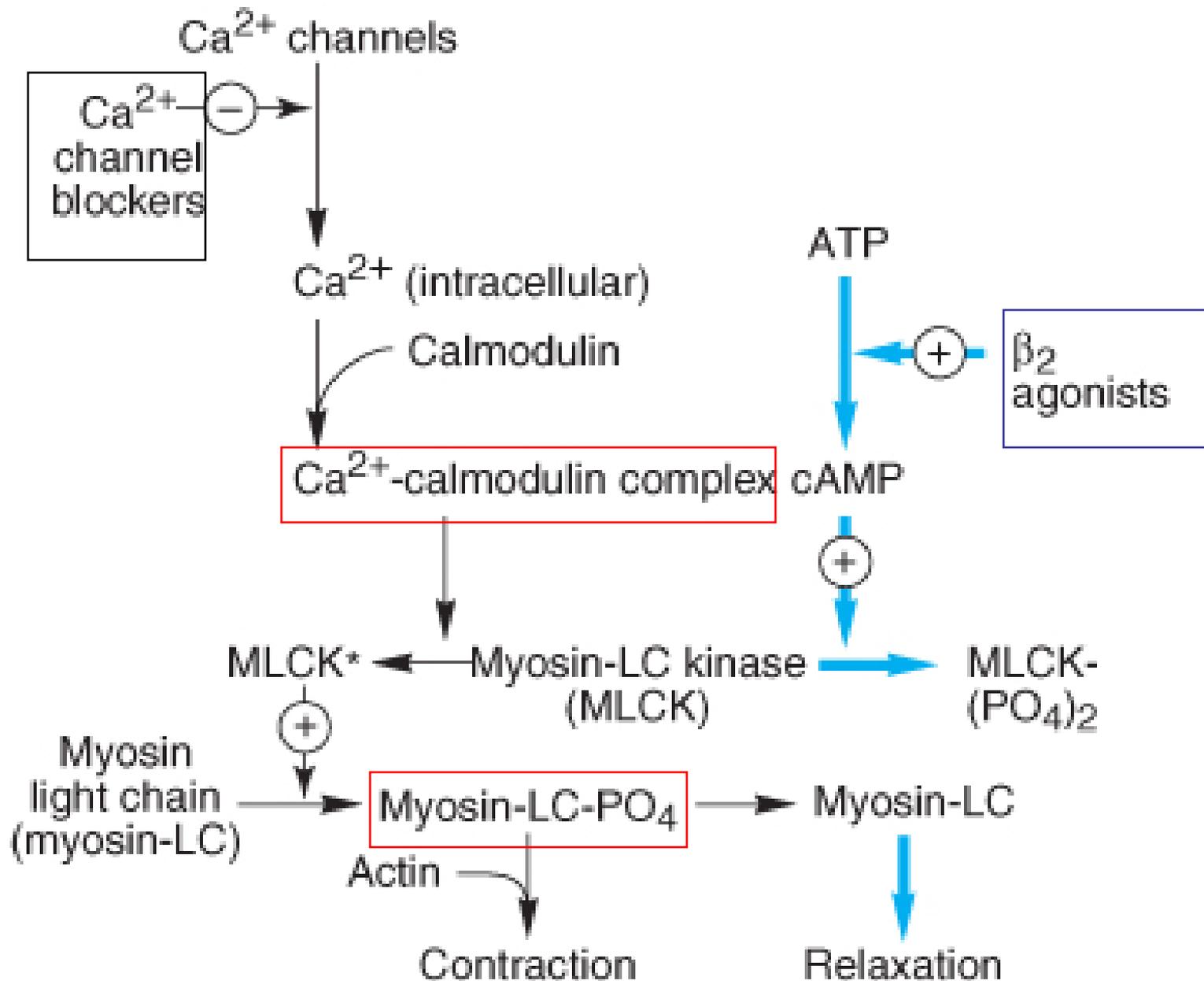
Bronchodilators – relievers (β -agonists, M-cholinolytics, Methyl Xanthins) **provide a rapid symptomatic relief** but they do not control the disease process.

Selective β_2 -agonists activate β_2 -receptors present on airway smooth muscle and mast cells too. These agents relax airway smooth muscle, inhibit the release of bronchoconstricting mediators from the adipocytes and increase the mucociliary transport by increasing the mucociliary activity.

ADRs: tremor, tachycardia, desensitization/down-regulation of β_2 -receptors that results in diminished responsiveness.

Adrenaline (β_1 & β_2)





Beta-2-agonists are available as metered-dose aerosol.



Short acting beta-2 agonists: *the onset of effect (per inhalation) begins after 3 to 5 min and continues 4–6 h:*

- Salbutamol (albuterol)
- Fenoterol, Terbutaline

Highly lipid, soluble long-acting agents

($t_{1/2}$ 12 h)

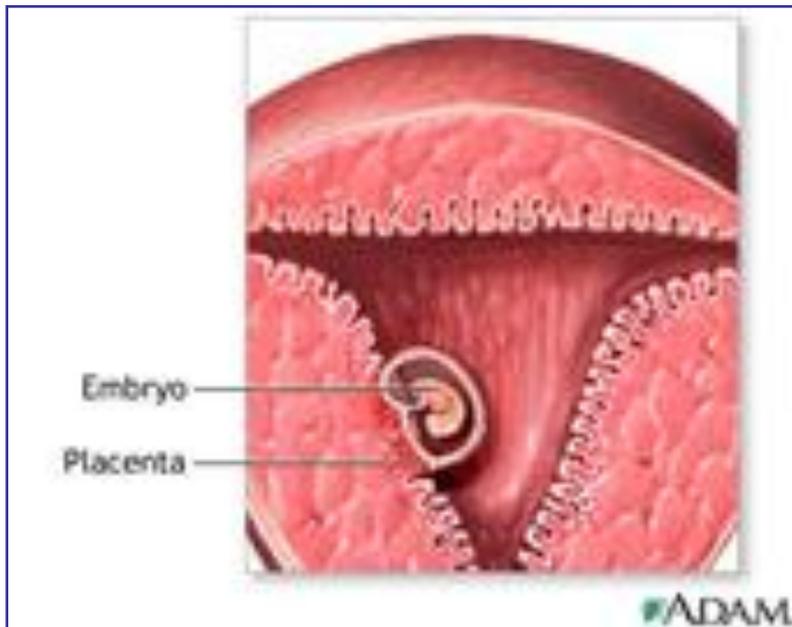
Effect: after 15–20 min, duration 12 h:

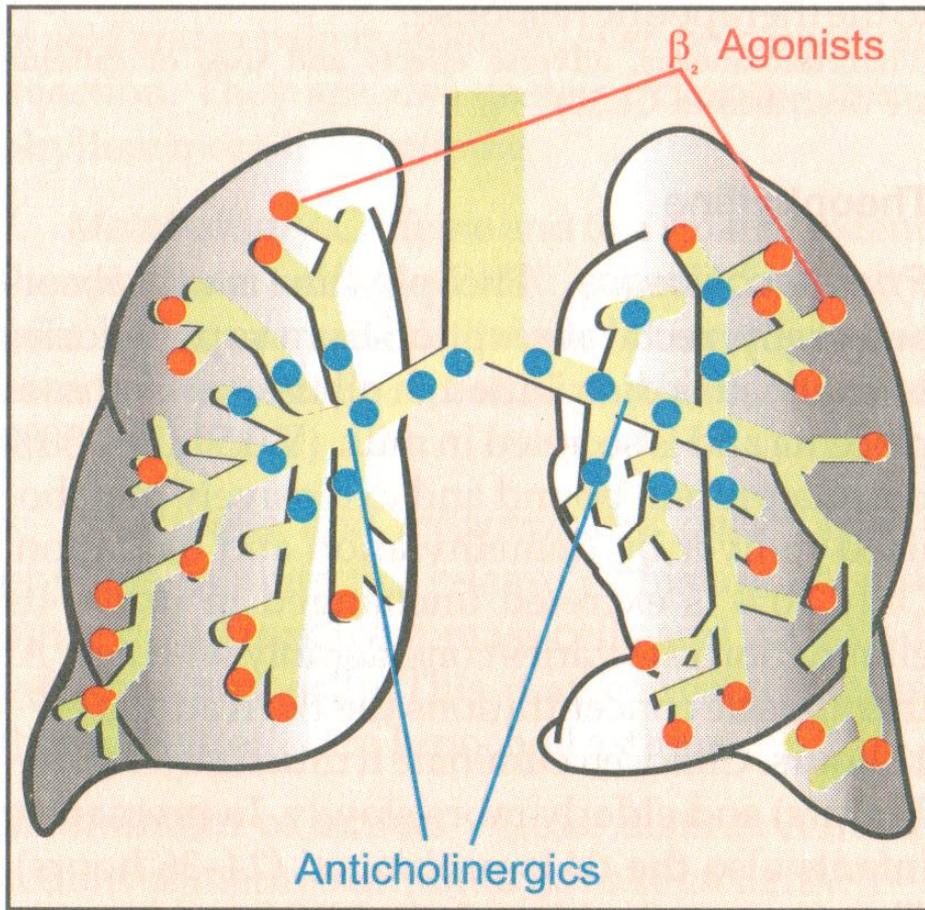
- Salmeterol, Formoterol



Selective β_2 -adrenomimetics with tocolytic effect

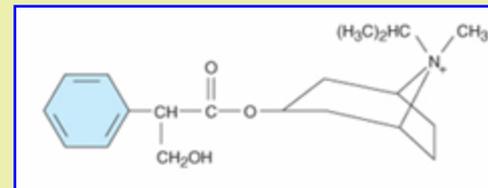
- Fenoterol (Partusisten[®]: tab. 5 mg)
- Hexoprenaline
- Salbutamol (Salbupart[®])
- Terbutaline





Anticholinergics in asthma

- Ipratropium



- Tiotropium

Primarily, the site of bronchodilation action of inhaled β_2 -adrenergic agonists is mainly the bronchiolar smooth muscle. Atropinic drugs cause bronchodilation by blocking cholinergic constrictor tone, act primarily in large airways.

Methyl Xanthines

(Theophylline, Aminophylline, Theotard):

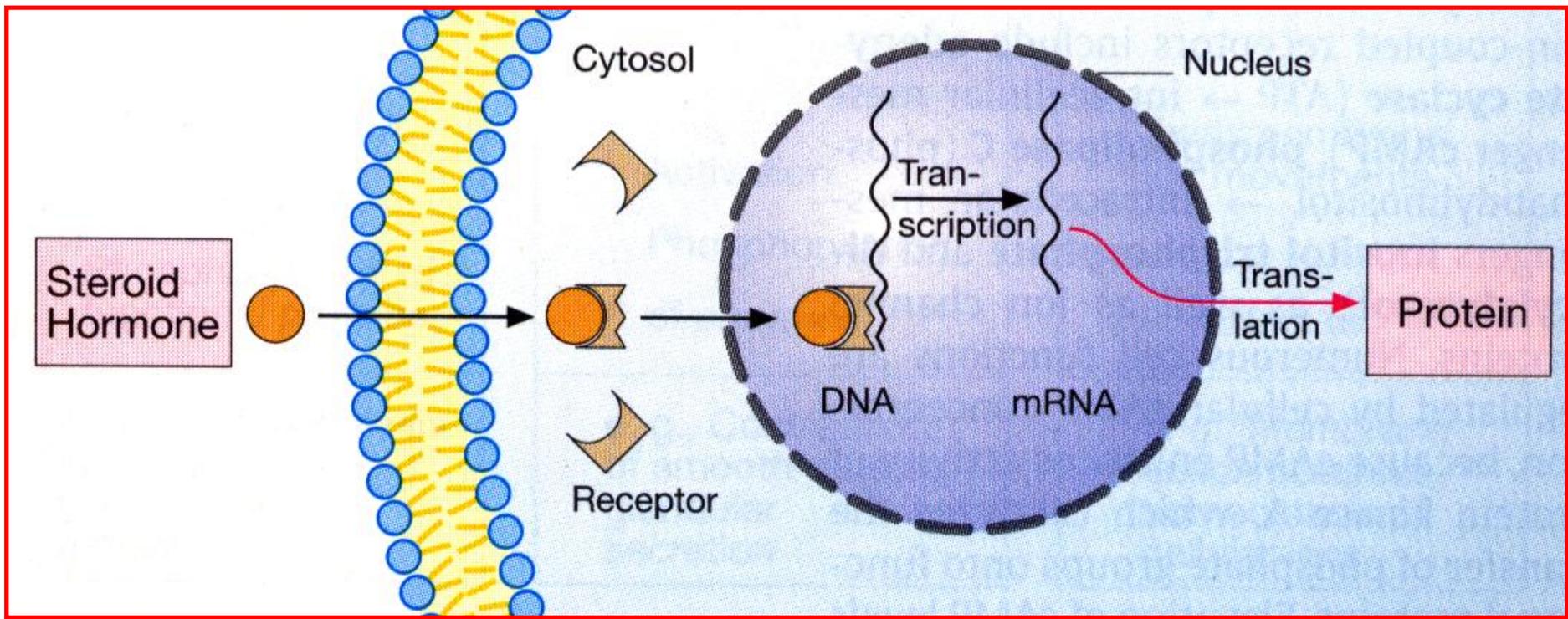
- a) **inhibit phosphodiesterase III** (present in airway muscle) **and IV** (present in eosinophil and mast cells), the two specific isoenzymes responsible for the degradation of cAMP;
 - b) **block the adenosine-1-receptors** on airway muscle and **adenosine-3-receptors**, present on mast cells.
- The main use of methyl xanthines is in the management of asthma and COPD (Chronic Obstructive Pulmonary Disease), usually as combination therapy with beta-2-agonists.

Glucocorticosteroids provide long-term stabilization of the symptoms due to their anti-inflammatory effects. Inhaled GCS, along with beta-2-agonists are the first choice drugs for chronic asthma.

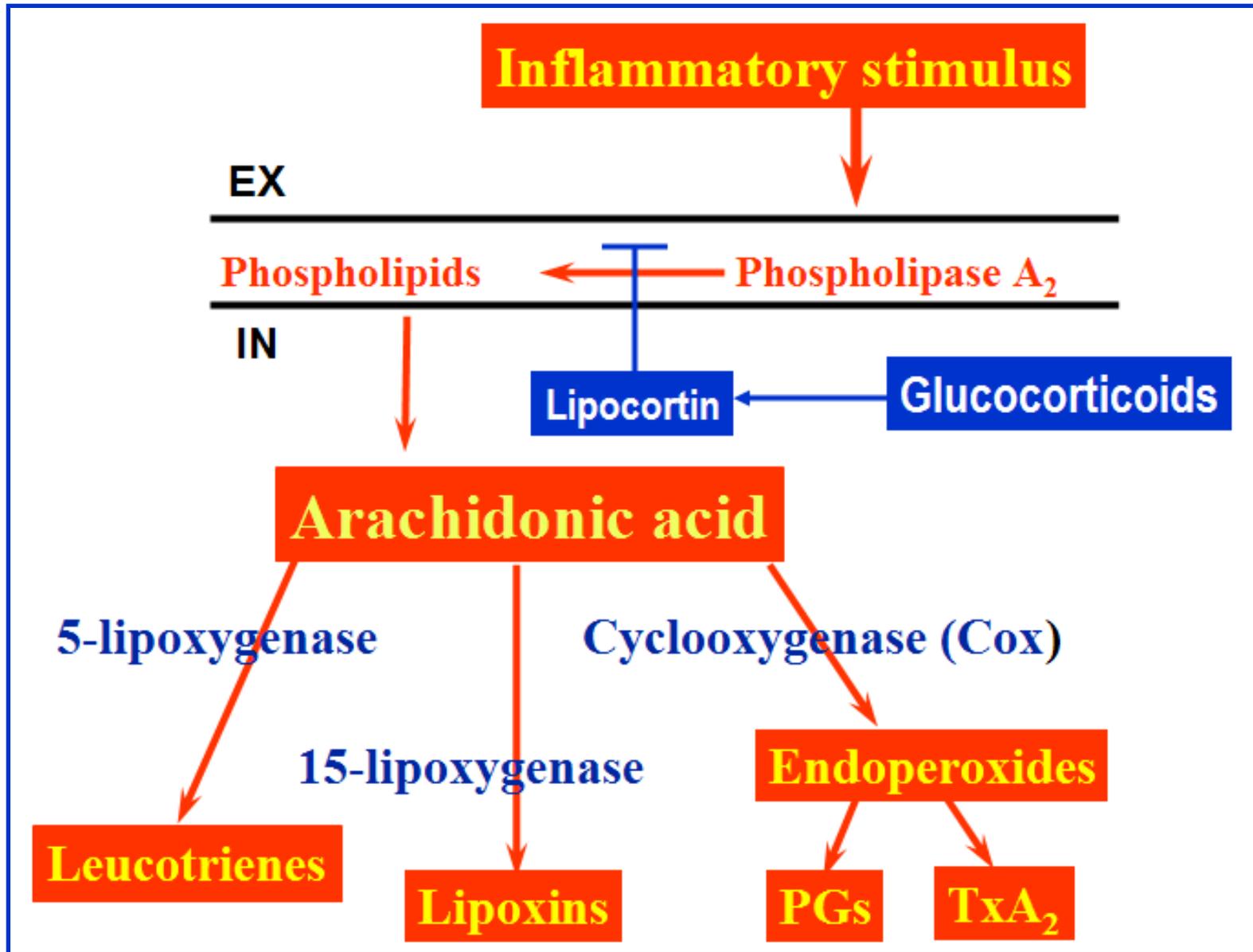
GCS inhibit the release of PGs and LTs and thus prevent smooth muscle contraction, vascular permeability and airway mucus secretion.

GCS produce eosinopenia which prevents cytotoxic effects of the mediators released from eosinophils.

GCS enhance beta-2-adrenergic response by up-regulating the beta-2-receptors in lung cells and leucocytes. Several hours are required for DNA transcription and RNA translation to occur after administering GCS.

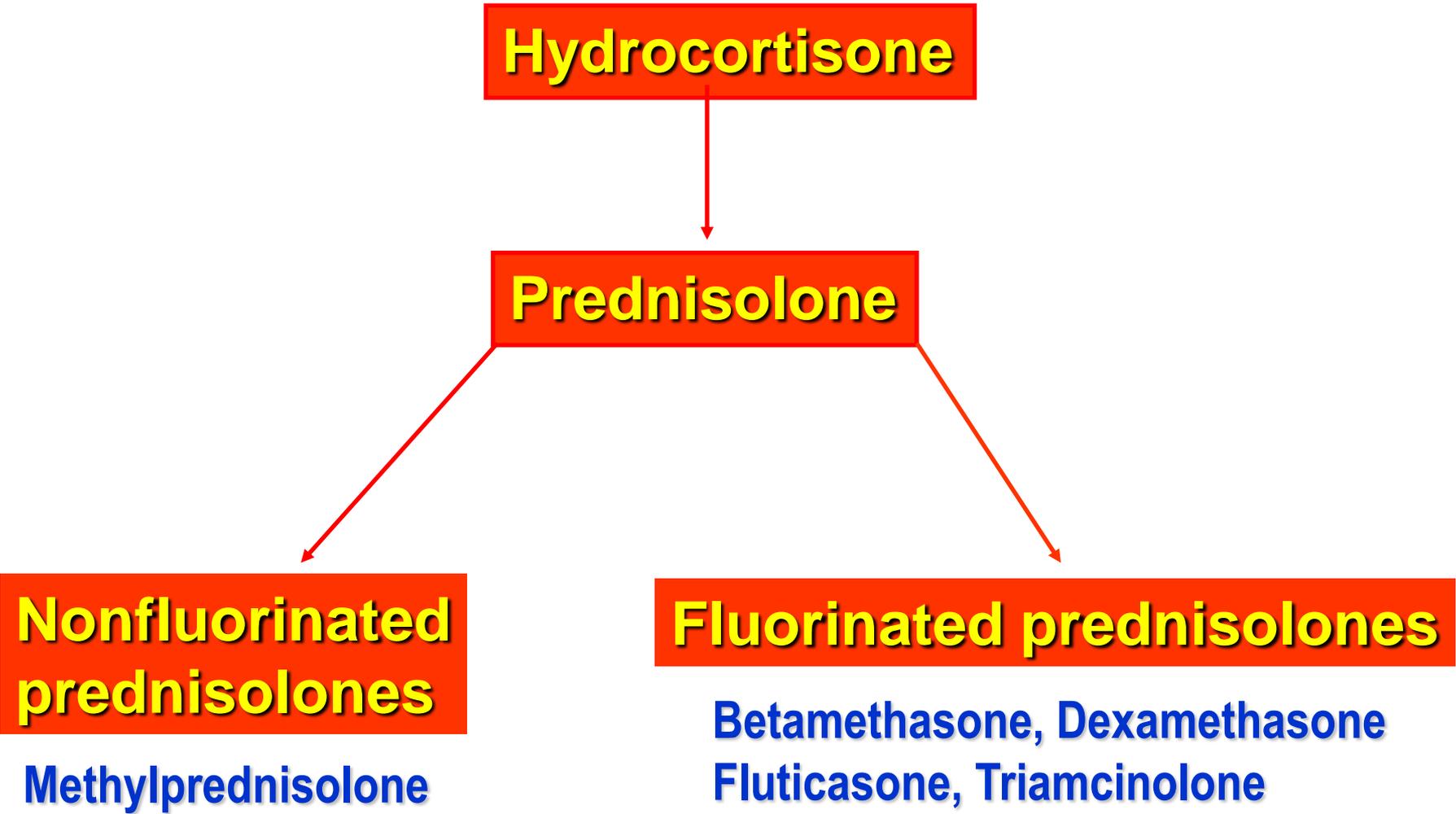


The ***anti-inflammatory actions*** of GCS are mediated by stimulation of synthesis of lipocortin, which inhibits pathways for production of PGs, LTs and PAF. These mediators would normally contribute to increased vascular permeability and subsequent changes including oedema, leucocyte migration, fibrin deposition.



The most used glucocorticoids

Hydrocortisone



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graph TD; A[Hydrocortisone] --> B[Prednisolone]; B --> C[Nonfluorinated prednisolones]; B --> D[Fluorinated prednisolones]; C --> E[Methylprednisolone]; D --> F[Betamethasone, Dexamethasone]; D --> G[Fluticasone, Triamcinolone];
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Prednisolone

**Nonfluorinated
prednisolones**

Methylprednisolone

Fluorinated prednisolones

**Betamethasone, Dexamethasone
Fluticasone, Triamcinolone**

Euphoria
(though sometimes
depression or psychotic
symptoms, and emotional
lability)

Buffalo hump

(Hypertension)

Thinning
of skin

Thin arms
and legs:
muscle wasting

(Benign intracranial
hypertension)

(Cataracts)

Moon face, with red
(plethoric) cheeks

Increased
abdominal fat

(Avascular necrosis
of femoral head)

Easy bruising

Poor wound
healing



**Cushing's
syndrome**

Adverse effects of GCS

- Cushing's syndrome
- Osteoporosis
- Tendency to hyperglycaemia
- Negative nitrogen balance
- Increased appetite
- Increased susceptibility to infections
- Obesity etc.

Leukotriene Modulators

Metabolism of arachidonic acid via 5-lipoxygenase pathway yields the cysteinyl LTs – C4, D4 and E4, which activate cysteinyl leukotriene receptors to cause bronchoconstriction, stimulate mucus secretion and increase capillary permeability, leading to pulmonary oedema.

Zileuton (p.o.) *inhibits the 5-lipoxygenase* and blocks synthesis of LTs.

Zafirlukast, Montelukast and Pranlukast (new agent) *block cysteinyl LT-receptors* and used with inhaled GCS in poorly respond asthmatic patients.

Arachidonic acid

5-Lipoxygenase

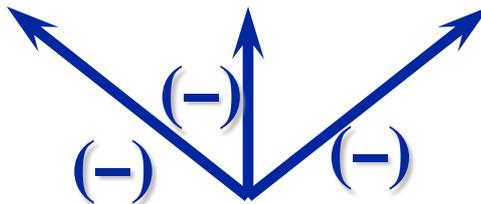
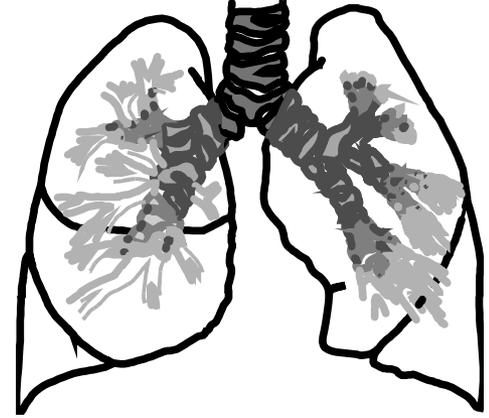
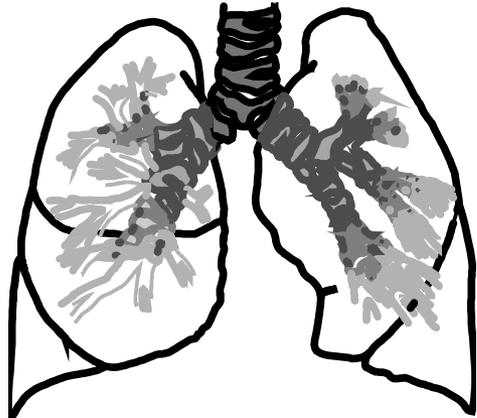
Leukotrienes (LTs)

**LTC₄-
receptor**

**LTD₄-
receptor**

**LTE₄-
receptor**

Montelukast, Zafirlukast



Mast cell stabilizers prevent transmembrane influx of calcium ions, provoked by antigen-IgE antibody reaction on the mast cell membrane. They prevent degranulation and release of histamine and other autacoids from mast cells. They also inhibit leukocyte activation and chemotaxis.

Indications: prophylactic treatment of asthma.

**Cromoglycate – per inh.
(Cromolyn – USAN)
Ketotifen (p.o.)
Nedocromil – per inh.**



Monoclonal Anti-IgE Antibody

Omalizumab is a recombinant humanized monoclonal antibody. (1) It inhibits the binding of IgE to mast cells and basophils; (2) it inhibits the activation of IgE already bound to mast cells and prevents their degranulations; (3) it down-regulates Fc epsilon receptor-1, present on mast cells and basophils.

Omalizumab is indicated for asthmatic patients who are not adequately controlled by inhaled GCS and who demonstrate sensitivity to aero-allergens.

Treatment of Status Asthmaticus

It is a potentially life-threatening acute attack of severe asthma needing immediate treatment. Most often hospitalization is necessary.

- (1) A high concentration (40–60%) of O₂ is administered.
- (2) High doses of inhaled short acting beta-2-agonist.
- (3) High doses of systemic GCS (p.o./i.v.)
- (4) Ipratropium through inhalation.

MATUR NUWUN