Drug Therapy For Bronchial Asthma

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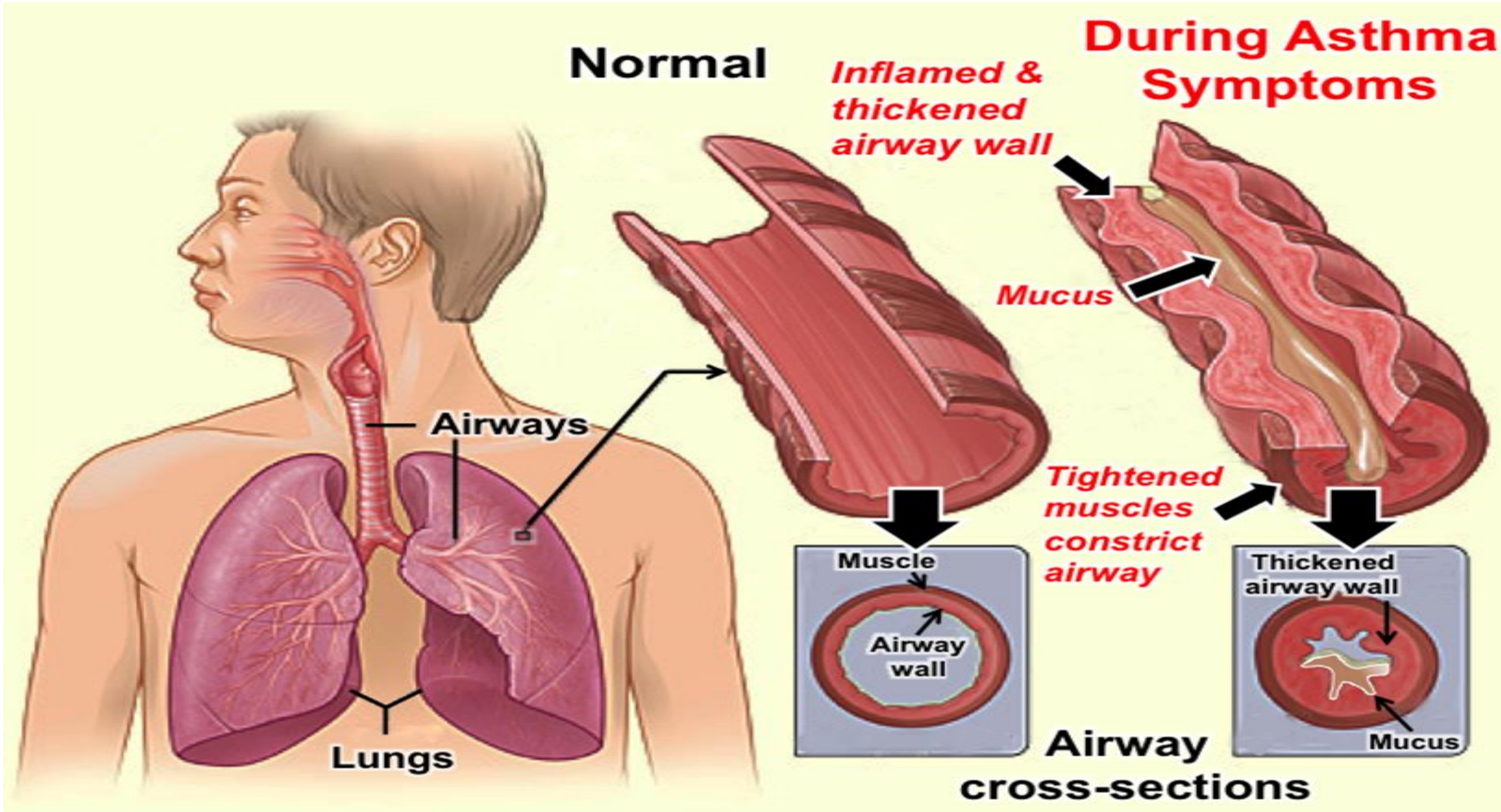
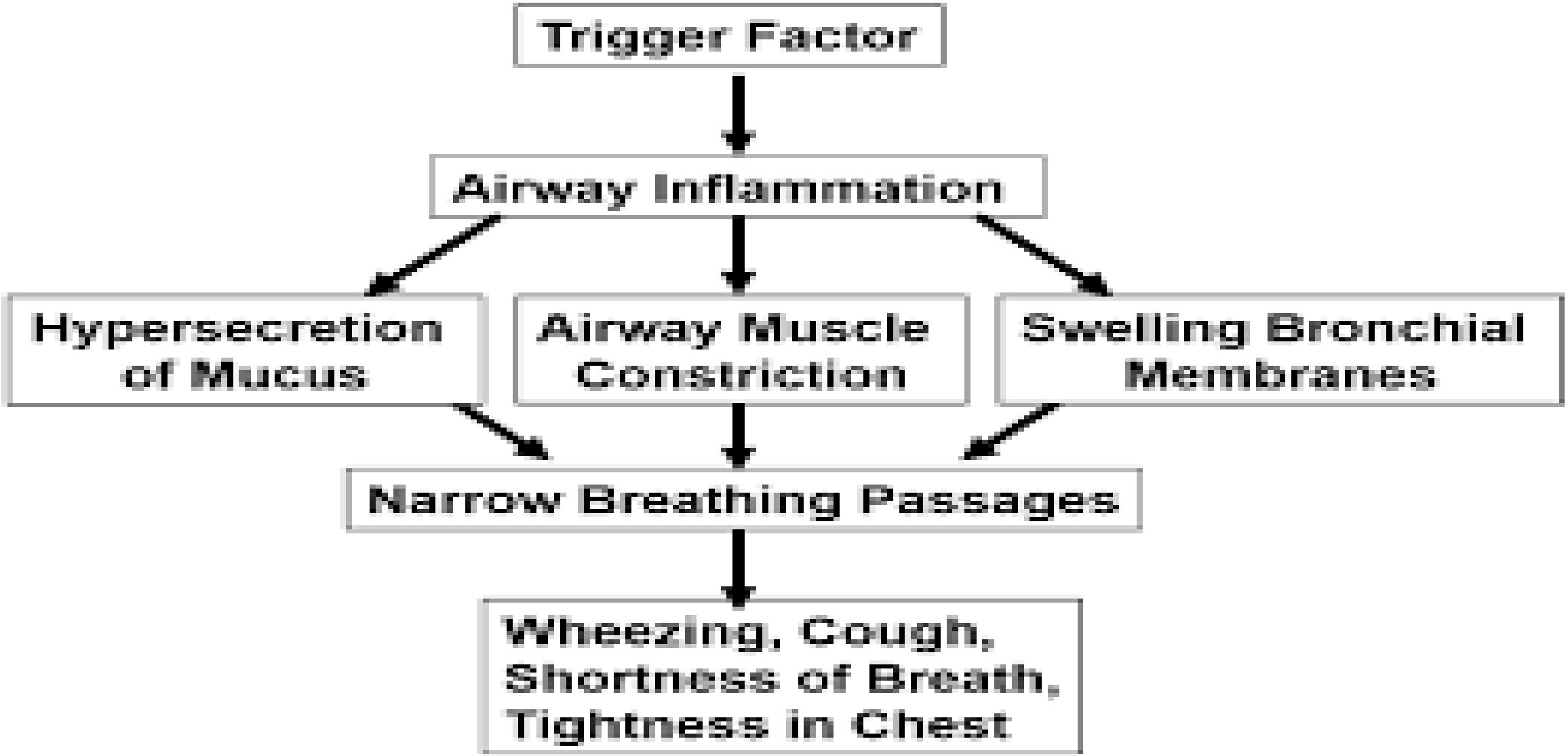
Bronchial Asthma

- **Inflammatory disease** characterized by **reversible airway obstruction** due to **bronchoconstriction, mucosal edema, cellular infiltration, and viscid secretions**
- Manifested clinically by **paroxysms** of dyspnea, cough and wheezes


Normal
During Asthma Symptoms
Inflamed & thickened airway wall
Mucus
Tightened muscles constrict airway
Airways
Lungs
Muscle
Airway wall
Thickened airway wall
Mucus
Airway cross-sections


Trigger Factor
Airway Inflammation
Hypersecretion of Mucus
Airway Muscle Constriction
Swelling Bronchial Membranes
Narrow Breathing Passages
Wheezing, Cough, Shortness of Breath, Tightness in Chest

Drug therapy for bronchial asthma

1- Bronchodilators

- B2 agonist
- Methylxanthines
- Anticholinergics

2- Anti-inflammatory drugs

- Corticosteroids
- Mast cell stabilizers
- Omalizumab
- Leukotriene antagonists

3- Supportive treatment

- Mucolytics & expectorants
- Antimicrobials
- Oxygen inhalation

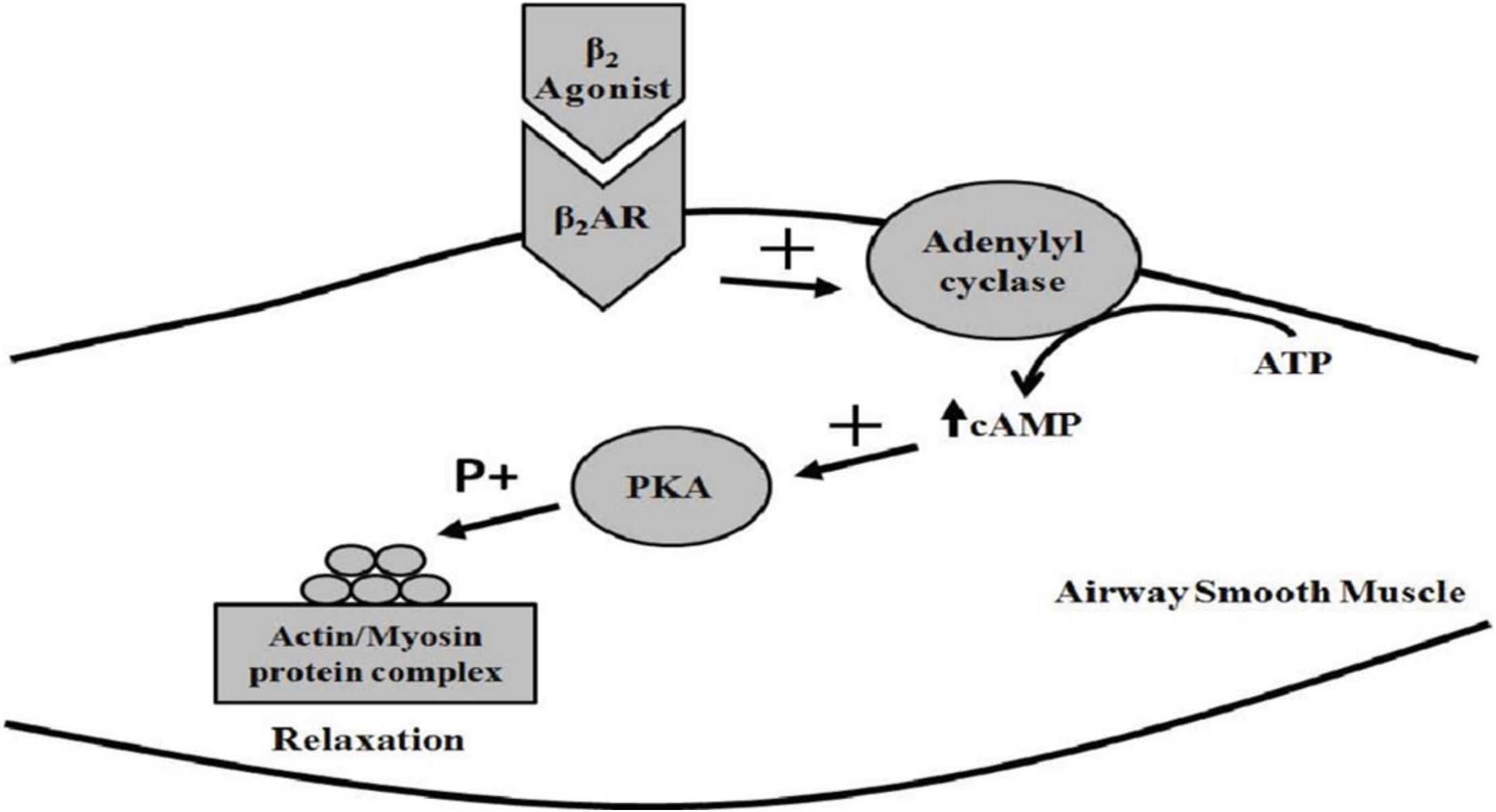
Bronchodilators

1- β_2 agonists

A. **Non-selective β-agonists (β_1, β_2):** Adrenaline **(used only in bronchial asthma due to anaphylactic shock)**

Selective β_2 agonists:

- **Short-acting:** salbutomal, terbutaline (4-6 H)
- **Long acting:** salmeterol and formeterol (12 H)


β2 Agonist
β2AR
Adenylyl cyclase
ATP
cAMP
PKA
P+
Actin/Myosin protein complex
Relaxation
Airway Smooth Muscle

- Selective β_2 agonists replaced non-selective β agonists as they **lack their side effects** e.g. palpitation, tachycardia and arrhythmias

1) Salbutamol: Short acting beta2 agonist (SABA)

- Selective stimulant of β_2 adrenergic receptors
- Selective action on the bronchi
- Given orally & by inhalation

1) Terbutaline: Short acting beta2 agonist (SABA)

- Like salbutamol but has a delayed onset of action

3) Salmeterol & Formoterol: long acting beta2 agonist (LABA)

- Selective long-acting β_2 agonists
- Given by inhalation for long-term prevention of bronchial asthma
- Should be **combined with inhaled corticosteroids** to avoid tolerance

Adverse effects:

- Tremors
- Tachycardia: Arrhythmia may occur in patients with underlying cardiac diseases eg, ischemic heart disease
- Tolerance
- Hypokalemia

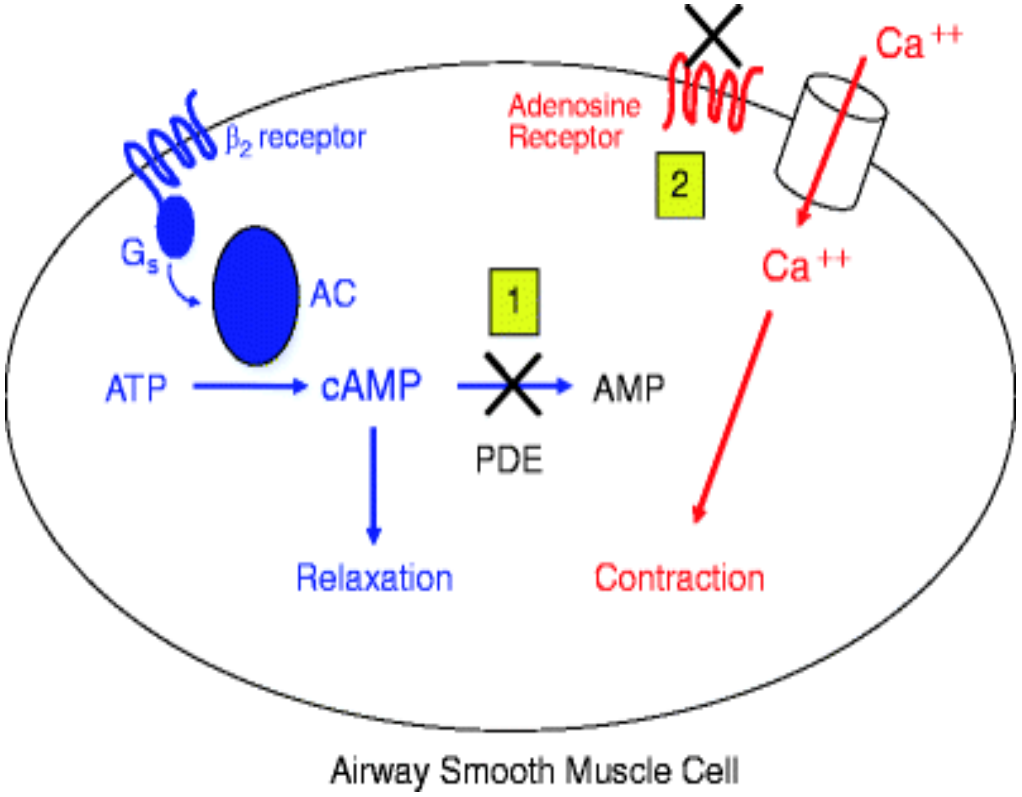
Note: Adverse effects occur **more frequently with oral preparations** than with inhalation

Note: Nebulizers provide more quantity of the drug than MDIs, so nebulized β_2 agonists can cause more adverse effects

2- Methylxanthines (Aminophylline & Theophylline)

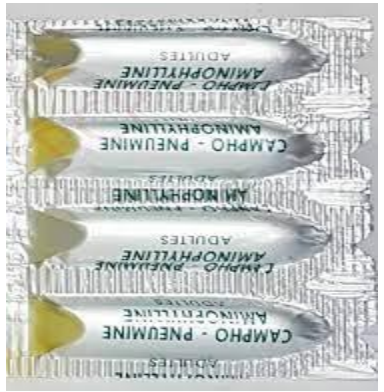
Mechanism of action:

- **PDE inhibitors** → ↑ cAMP which causes redistribution of intracellular Ca^{+2} → bronchodilatation
- **Block adenosine receptors** → bronchodilatation
- **Improve diaphragmatic contraction & ventilatory response** to hypoxia
- ↓ mediators release from mast cell.



Pharmacokinetics:

- Theophylline is absorbed by all routes
- Distributed all over the body & **passes BBB** and placental barrier
- **Metabolized in liver** (by xanthine oxidase) into soluble methyluric acid (not precipitated in the joints ➔ **not contraindicated in gout**)
- **Narrow therapeutic window** with low safety



Pharmacological actions:

- **Relaxation of the smooth muscle** (bronchial, intestinal, biliary, ureteric and vascular smooth muscles "except cerebral blood vessels" → vasodilatation and hypotension)
- **CVS: Direct:** positive inotropic & chronotropic effects - VD (hypotension)

  Central: stimulation of CIC (bradycardia) & VMC (hypertension)
- Large & rapid IV injection → **hypotension & arrhythmia.**

Precautions:

- **Monitoring** of plasma level (to avoid toxicity)
- **Slow IV administration** to avoid hypotension & arrhythmia.

Note: Roflumilast:

- **Selective PDE-4 inhibitor** → selective action on airways & inflammatory cells → **fewer adverse effects** than methylxanthines
- Approved for treatment of **COPD (chronic obstructive disease)**

3- Muscurinic (M) Antagonists

- **Atropine (tertiary amine)** blocks bronchial M receptors, but it is **not effective in bronchial asthma** because:

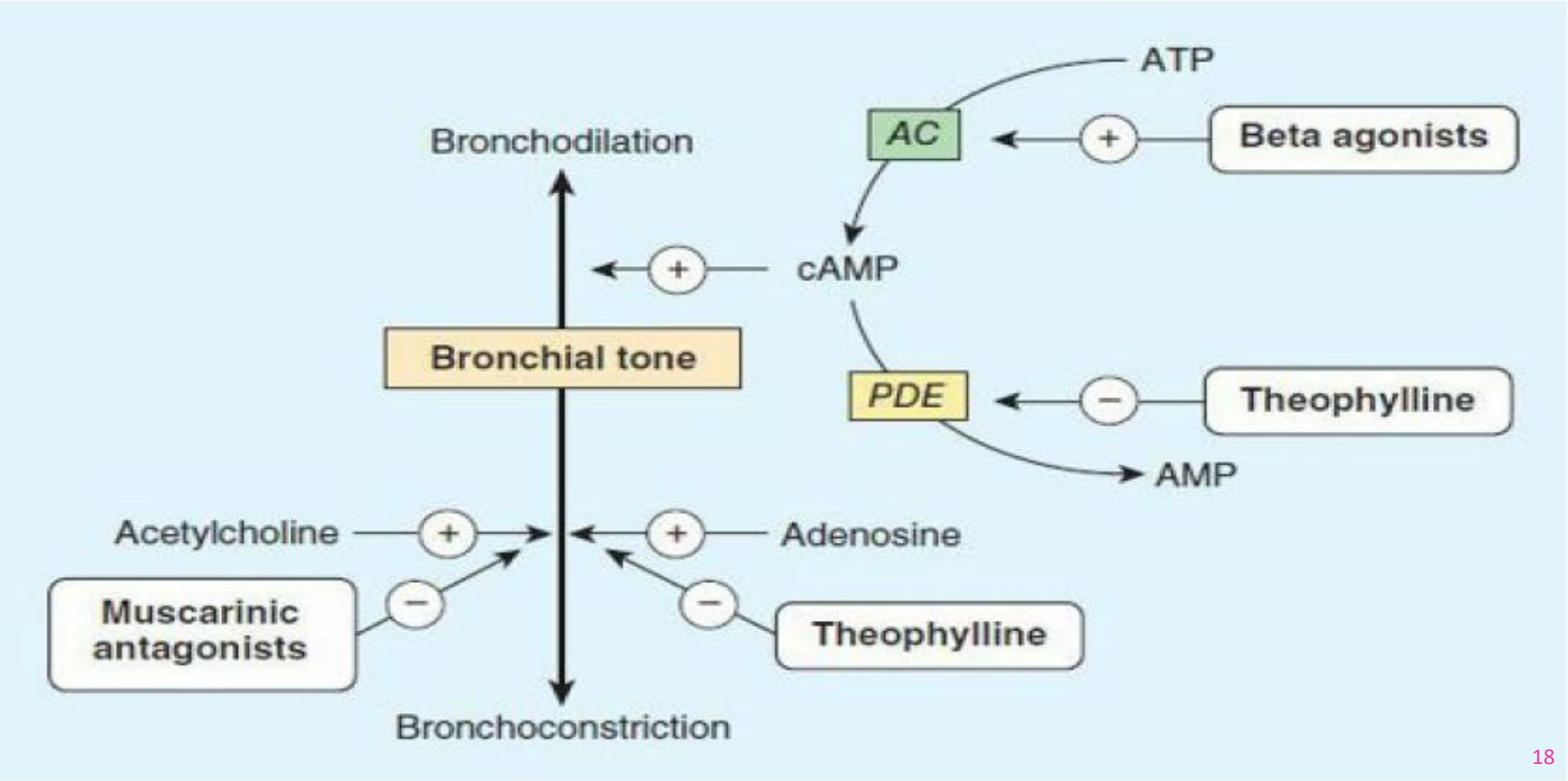
1. Cholinergic pathways play a minor role in pathogenesis of bronchial asthma
2. Non-selective effects:
   - Dryness of bronchial secretions
   - ↓ Muco-ciliary function

Ipratropium bromide:

- ✓ Quaternary ammonium derivative of atropine
- ✓ Minimal amounts are absorbed ➔ no systemic adverse effects
- ✓ More selective (causes bronchodilation without effects on sputum viscosity or ciliary function)
- ✓ No central effects
- ✓ Given by inhalation & can be combined with β_2 agonists
- ✓ Short-acting ➔ used 3-4 times daily

- **Tiotropium:** differs from ipratropium in the following:
  - ✓ **Long-acting** (given once/day)
  - ✓ Given by inhalation
  - ✓ Approved for treatment of **COPD with no cardiac adverse effects.**

Bronchodilators



Anti-Inflammatory Drugs

1- Corticosteroids

Mechanism of action:

- ✓ ↑ Synthesis of **lipocortin** → ↓ PLA_2 activity → ↓ arachidonic acid, PGs and LTs synthesis
- ✓ Immunosuppressive action (↓ antibody synthesis) & inhibition of Ag/Ab reaction & mast cell stabilization
- ✓ ↓ Capillary permeability & reduce mucosal edema
- ✓ ↑ Catecholamines effect through:
  - Block neuronal reuptake
  - ↑ Methylation of noradrenaline to adrenaline

Uses in bronchial asthma:

- ✓ Prophylaxis (in between attacks)
- ✓ Repeated nocturnal asthma
- ✓ Acute severe asthma

Preparations:

A. **Inhalation:** beclomethasone, **budesonide**, fluticasone (long-acting)

B. **Parentral: methyl prednisolone**, **hydrocortisone**, dexamethsone, ACTH

C. **Oral:** prednisolone

Adverse effects:

A. **Inhalation:**
   - ✓ Oral moniliasis (treated by nystatin)
   - ✓ Dysphonia due to weakness (myopathy) of adductor muscle of the cord

B. **Suppressive effects:** adrenocortical suppression

C. **Cushing's syndrome** (with the use of large doses of corticosteroids)

D. **Metabolic:** hypokalemia, hyperglycemia, salt & water retention, weight gain and hypertension

E. **Cataract**

2- Leukotriene Antagonists

- **They include:**

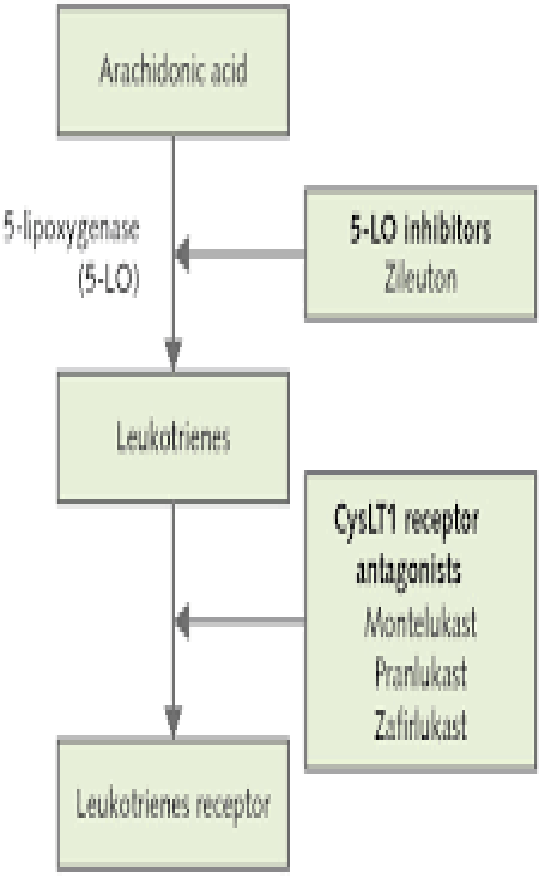
1. **LT receptor antagonists** (Montelukast & zafirlukast)
2. **5-LOX inhibitors** (zileuton): ↓ LTs synthesis

- **Pharmacokinetics:**

✓ All members are given orally

✓ Zafirlukast absorption is affected by food

✓ They are metabolized by liver



- **Uses:**
  - ✓ prophylaxis of bronchial asthma **especially** **aspirin-induced asthma**
- **Adverse effects:**
  - ✓ **Liver toxicity:**
    - ❖ Regular monitoring of liver transaminases is required if their levels exceeded 3-5 times the normal level, these drugs should be discontinued
    - ❖ More reported with **zileuton**
  - ✓ **Systemic vasculitis (Churg-Strauss syndrome):** rare

3- Mast cell stabilizers

Members:

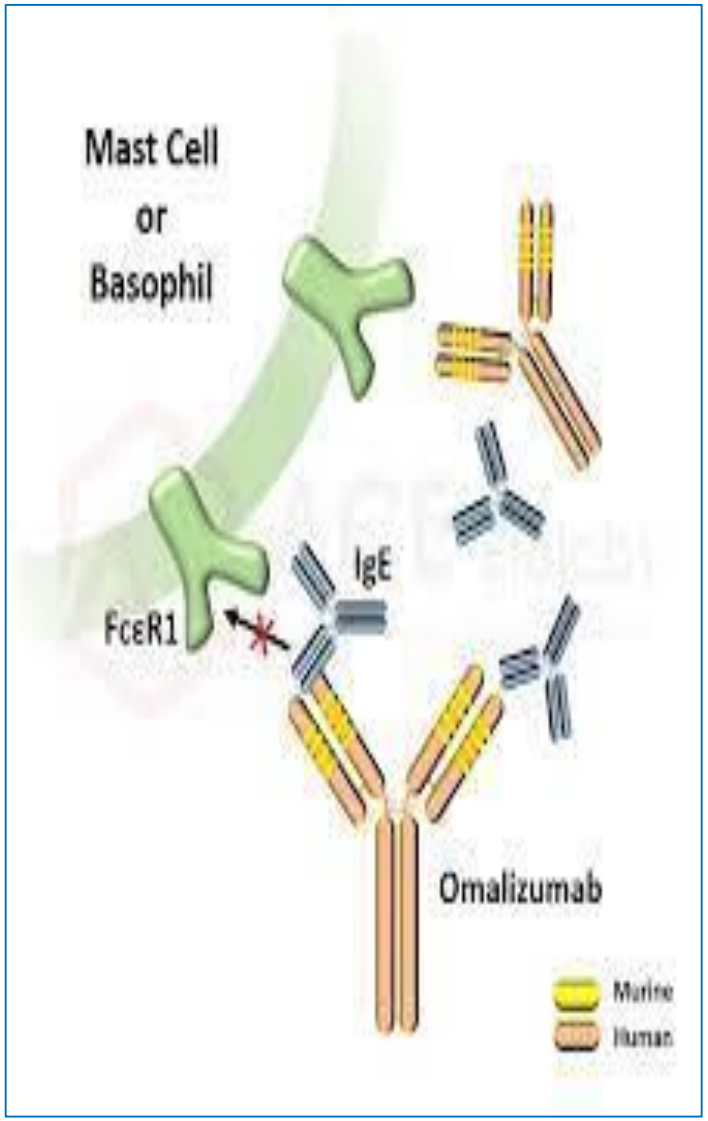
1. Disodium cromoglycate (Cromolyn sodium)
2. Ketotifen

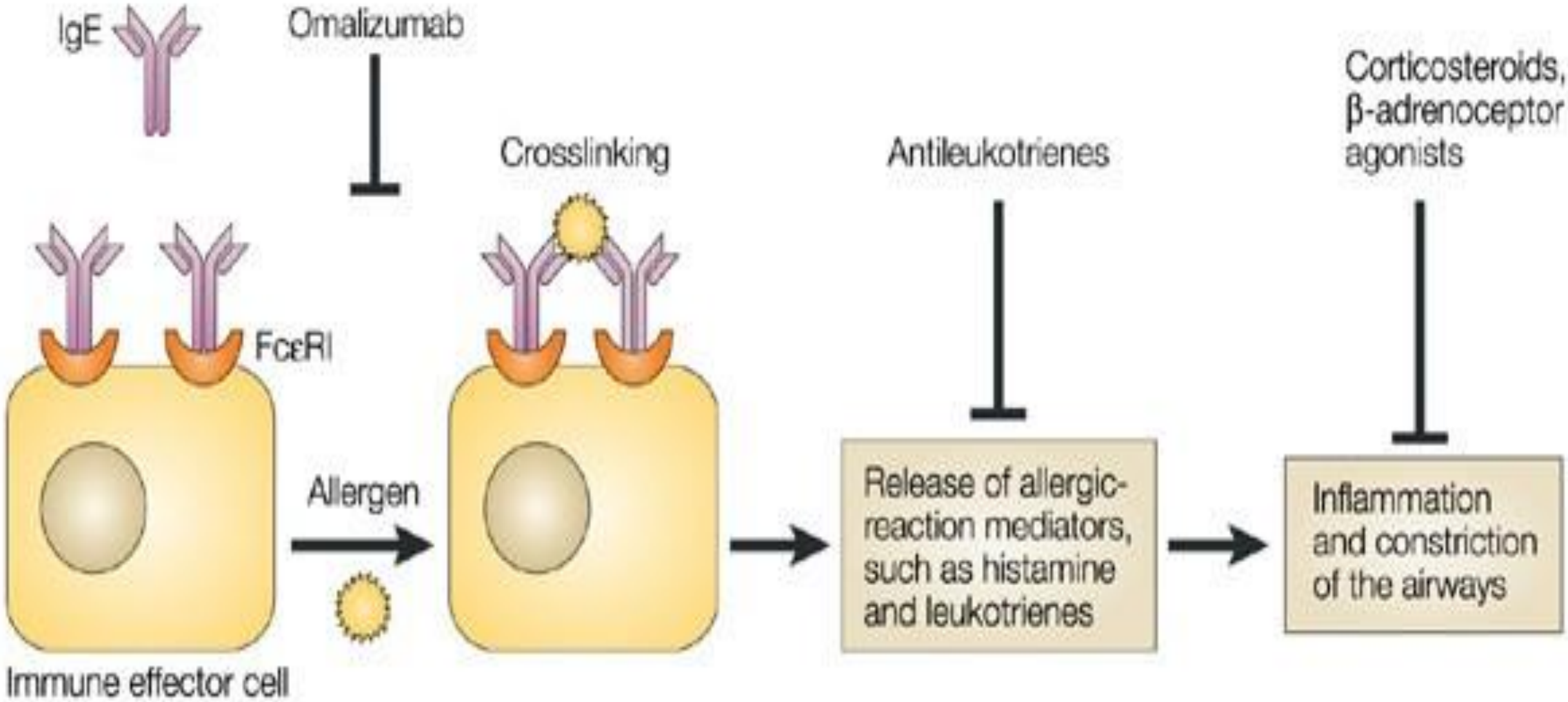
- ✓ They are **not bronchodilators**
- ✓ So, they cannot relieve acute attacks of asthma
- ✓ They can be effective only if given before the exposure the antigen
- ✓ **Mechanism:** stabilization of mast cell membrane (possibly by blocking calcium influx) ➔ ⬇ release of allergic mediators eg, histamine & LTs.

- ✓ They are useful chiefly for asthma prophylaxis, particularly children & young adults
- ✓ Ketotifen has additional antihistamine effect
- ✓ **Route:**
  - **Disodium cromoglycate:** inhalation
    - ❖ It is also available as nasal spray for **allergic rhinitis & as eye drops for allergic conjunctivitis**
  - **Ketotifen:** oral administration
- ✓ **Adverse effects:**
  - **Disodium cromoglycate:**
    - ❖ Local irritation: **bronchospasm & cough**
  - **Ketotifen:**
    - ❖ Drowsiness

4-Omalizumab

- ✓ Selectively **binds to human IGE** ➔ inhibits IGE binding to its receptor on mast cells & basophils surface ➔ ⬇ release of inflammatory mediators
- ✓ It decreases severity and frequency of asthma exacerbations
- ✓ Used in patients resistant to conventional therapy (β2 agonists & inhaled corticosteroids)
- ✓ Its use is limited by its high cost





Nature Reviews | Drug Discovery

Bronchial Asthma Prophylaxis

- ✓ **Control of predisposing factors**
- ✓ **Desensitization**
- ✓ **Drugs that prevent or diminish the frequency of the attacks:**

1. Bronchodilators (long duration)
2. Corticosteroids (oral or inhalation)
3. LT antagonists
4. Mast cell stabilizers
5. Omalizumab

Acute attack

Inhaled short-acting β2 agonist e.g. salbutamol or terbutaline

Long-term prophylaxis (Between attacks):

Severity	Long-term control	Quick relief of acute symptoms
Intermittent Less than 2/ week	No daily medication.	Short-acting β2 agonist
Mild persistent more than 2/ week	Low-dose inhaled corticosteroids (ICS).	Short-acting β2 agonist
Moderate persistent daily	Low- to medium-dose ICS + long-acting β2 agonist (LABA).	Short-acting β2 agonist
Severe persistent continual	High-dose ICS + LABA	Short-acting β2 agonist

Acute severe asthma (Status asthmaticus)

✓ **Treatment:**

1. Hospitalization & O_2 therapy
2. **Inhaled short-acting β_2 agonist** (frequent or continuous administration) is the **1st line of choice**. **Ipratropium bromide** should be added.
3. **Systemic corticosteroids:**
   - Oral prednisolone (or)
   - IV hydrocortisone or methylprednisolone (if the patient has vomiting or unable to swallow)
4. **IV fluids** (some patients are dehydrated). **K+ supplements** are considered (repeated administration of β_2 agonists ➔ hypokalemia)
5. If failed to improve, **aminophylline slow IV infusion** can be administered
6. **Mechanical ventilation** is considered if the patient still deteriorating
7. On discharge, oral prednisolone should be continued for short courses

References

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THANK YOU