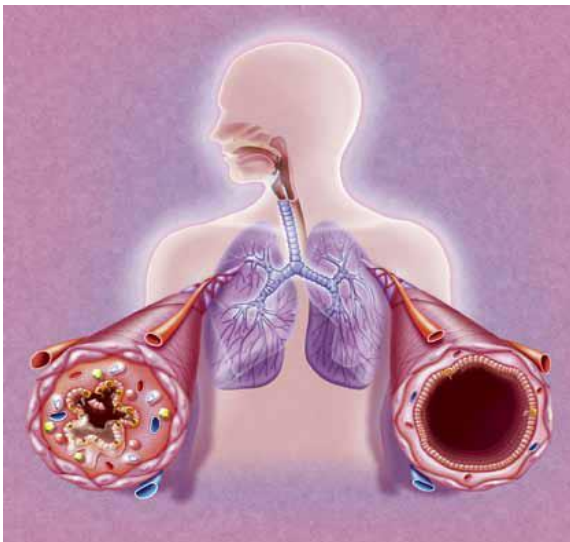


# Pharmacology of drugs used in bronchial asthma & COPD

*By*

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## **ILOs:** The students should be able to

- 1. Different types of drugs used for treatment of asthma**
- 2. Differentiate between treatment and prophylactic therapy for asthma**
- 3. Recognize the different types of bronchodilators regarding pharmacokinetics, pharmacodynamics, uses and side effects.**
- 4. Identify the different anti-inflammatory drugs for asthma in respect to kinetics, dynamics, uses and side effects.**

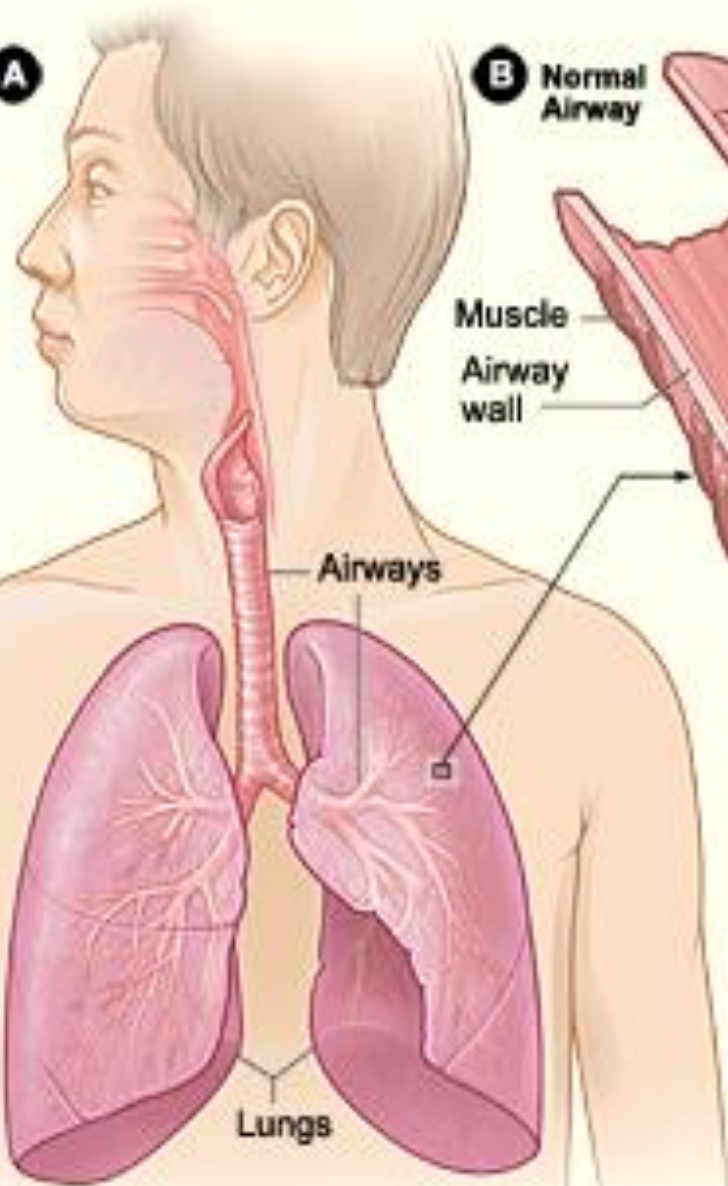
# Bronchial Asthma

Asthma is a chronic inflammatory disorder of bronchial airways that result in airway obstruction in response to external stimuli (as pollen grains, cold air and tobacco smoke).

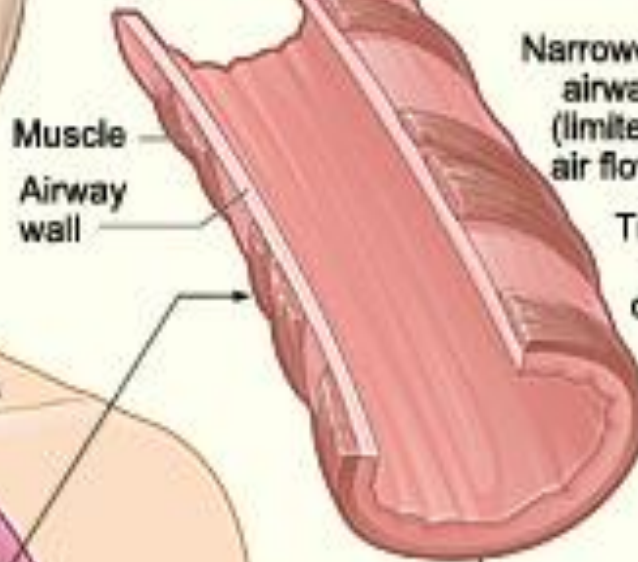
## Characters of airways in asthmatic patients :

- **Airway hyper-reactivity:** abnormal sensitivity of the airways to any external stimuli.
- **Inflammation**
  - ↑ edema, swelling
  - ↑ Thick mucus production.
- **Bronchospasm** (constriction of the bronchial smooth muscles).

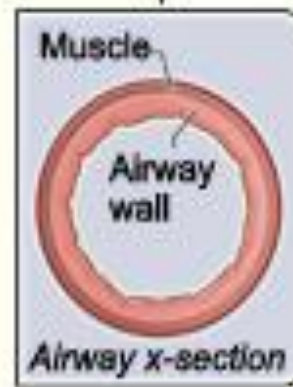
**A**



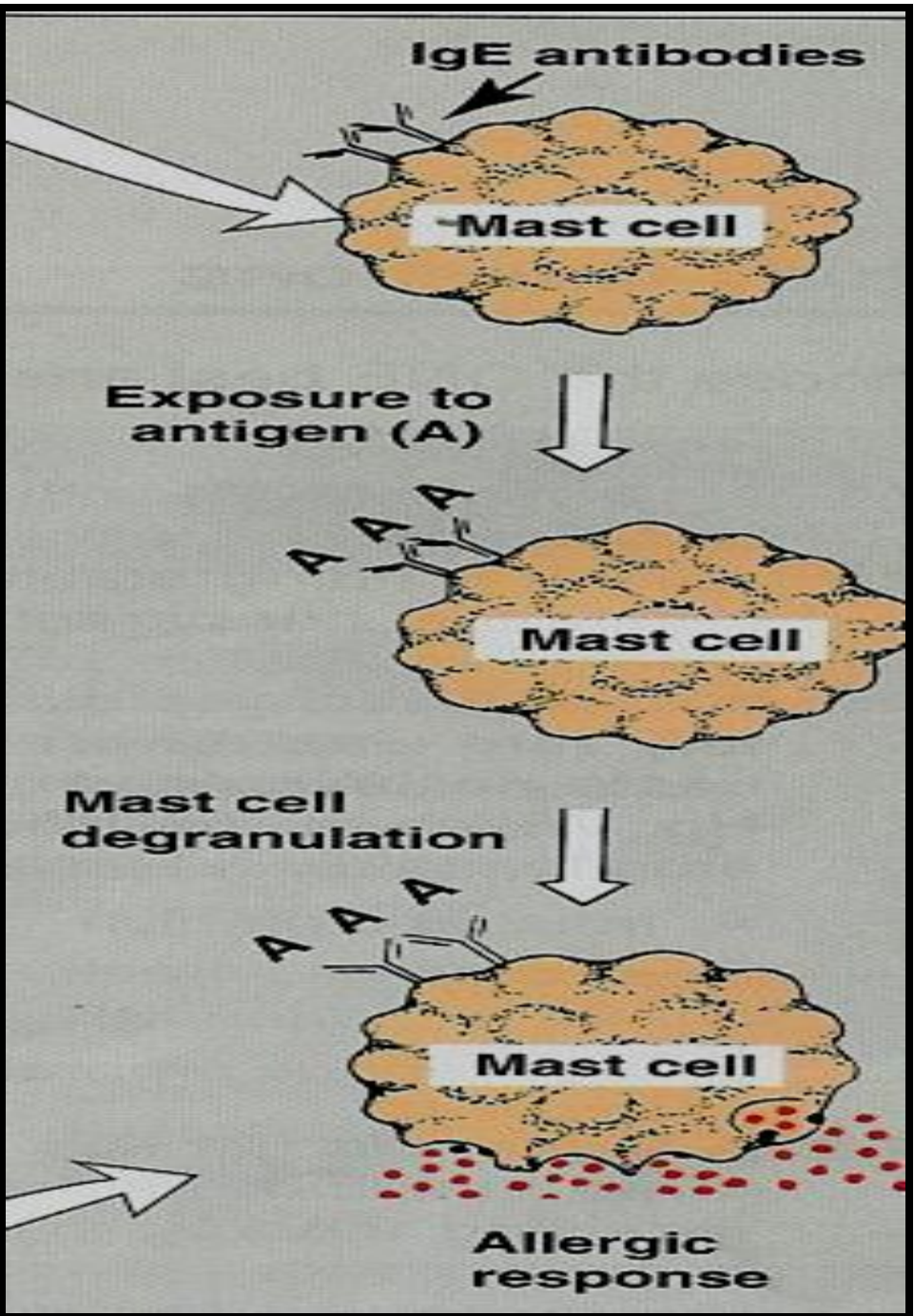
**B** Normal Airway



**C** During Asthma Symptoms



# Airway hyper-reactivity



# **Symptoms of asthma**

**Asthma produces recurrent episodic attack of**

- **Acute bronchoconstriction**
- **Shortness of breath**
- **Chest tightness**
- **Wheezing**
- **Rapid respiration**
- **Cough**

**Symptoms can happen each time the airways are irritated by inhaled irritants or allergens.**



# Causes

- **Infection**
- **Stress**
- **Exercise (cold air)**
- **Pets**
- **Seasonal changes**
- **Emotional conditions**
- **Some drugs as aspirin,  $\beta$ -bockers**



# Asthma drug targets

## ➤ **Parasympathetic supply**

**M3 receptors in smooth muscles and glands.**

➤ **Bronchoconstriction**

➤ **Increase mucus secretion**

## ➤ **No sympathetic supply** but **B<sub>2</sub> receptors** in smooth muscles and glands.

➤ **Bronchodilation**

➤ **Decrease mucus secretion**

# **Anti asthmatic drugs:**

## **1) Quick relief medications:**

**Bronchodilators used** to relieve acute episodic attacks of asthma.

## **2) Control therapy (prophylactic drugs):**

**Glucocorticoids; anti-inflammatory drugs**  
**used** to reduce the  
frequency of attacks, and nocturnal awakenings.

# Anti asthmatic drugs

## Bronchodilators

**(Quick relief medications)**

**treat acute attack of asthma**

- **Short acting  $\beta$ 2-agonists**
- **Antimuscarinics**
- **Xanthine preparations**

## Anti-inflammatory Agents

**(Prophylactic therapy)**

**reduce the frequency of attacks**

- **Corticosteroids**
- **Mast cell stabilizers**
- **Leukotrienes antagonists**
- **Anti-IgE monoclonal antibody**
- **Long acting  $\beta$ 2-agonists**

# Bronchodilators

**These drugs can produce rapid relief of bronchoconstriction.**

## **Bronchodilators:**

- **$\beta$ 2 - adrenoreceptor agonists**
- **Antimuscarinics**
- **Xanthine preparations**

# Sympathomimetics

## $\beta$ - adrenoceptor agonists

### Mechanism of Action

- direct  $\beta_2$  stimulation  $\longrightarrow$  stimulate adenylyl cyclase  $\longrightarrow$   $\uparrow$  cAMP  $\rightarrow$  bronchodilation.
- Increase mucus clearance by (increasing ciliary activity).
- Stabilization of mast cell membrane.

# Classification of $\beta$ agonists

## ➤ Non selective $\beta$ agonists:

**epinephrine - isoprenaline**

## ➤ Selective $\beta_2$ – agonists (Preferable).

**Salbutamol (albuterol)**

**Terbutaline**

**Salmeterol**

**Formeterol**

# Non selective $\beta$ -agonists.

## Epinephrine

- **Potent bronchodilator**
- **Given subcutaneously, S.C.**
- **rapid action (maximum effect within 15 min).**
- **Has short duration of action (60-90 min)**
- **Drug of choice** for acute anaphylaxis  
*(hypersensitivity reactions).*



## **Disadvantages**

- **Not effective orally.**
- **Hyperglycemia**
- **Skeletal muscle tremor**
- **CVS side effects:**  
tachycardia, arrhythmia, hypertension
- **Not suitable for asthmatic patients with hypertension or heart failure.**

## **Contraindications:**

**CVS patients, diabetic patients**

# Selective $\beta_2$ –agonists

- Are mainly given by **inhalation** by (metered dose inhaler or nebulizer).
- Can be given orally, parenterally.
- **Short acting  $\beta_2$  agonists**  
e.g. salbutamol, terbutaline
- **Long acting  $\beta_2$  agonists**  
e.g. salmeterol, formoterol

# Nebulizer



# Inhaler



## **Short acting $\beta_2$ agonists**

**Salbutamol**, inhalation, orally, i.v.

**Terbutaline**, inhalation, orally, s.c.

- **Have rapid onset of action (15-30 min).**
- **short duration of action (4-6 hr)**
- **used for acute attack of asthma (drugs of choice).**

# Long acting selective $\beta_2$ agonists

## Salmeterol & formoterol

- are given by inhalation
- Long acting bronchodilators (12 hours) due to high lipid solubility (creates depot effect).
- are not used to relieve acute episodes of asthma
- used for nocturnal asthma.
- combined with inhaled corticosteroids to control asthma (decreases the number and severity of asthma attacks).

## **Advantages of $\beta_2$ agonists**

- Minimal CVS side effects
- suitable for asthmatic patients with CV disorders as hypertension or heart failure.

## **Disadvantages of $\beta_2$ agonists**

- Skeletal muscle tremors.
- Nervousness
- Tolerance ( $\beta$ -receptors down regulation).
- Overdose may produce tachycardia due to  $\beta_1$  stimulation.

# Muscarinic antagonists

## Ipratropium – Tiotropium

- Act by blocking muscarinic receptors .
- given by aerosol inhalation
- Have delayed onset of action.
- Quaternary derivatives of atropine (polar).
- Does not diffuse into the blood
- Do not enter CNS.
- Have minimal systemic side effects
- **Ipratropium** has short duration of action 3-5 hr
- **Tiotropium** has longer duration of action (24 h).



# Pharmacodynamics

- Inhibit bronchoconstriction and mucus secretion
- Less effective than  $\beta_2$ -agonists.
- No anti-inflammatory action only bronchodilator

# Uses

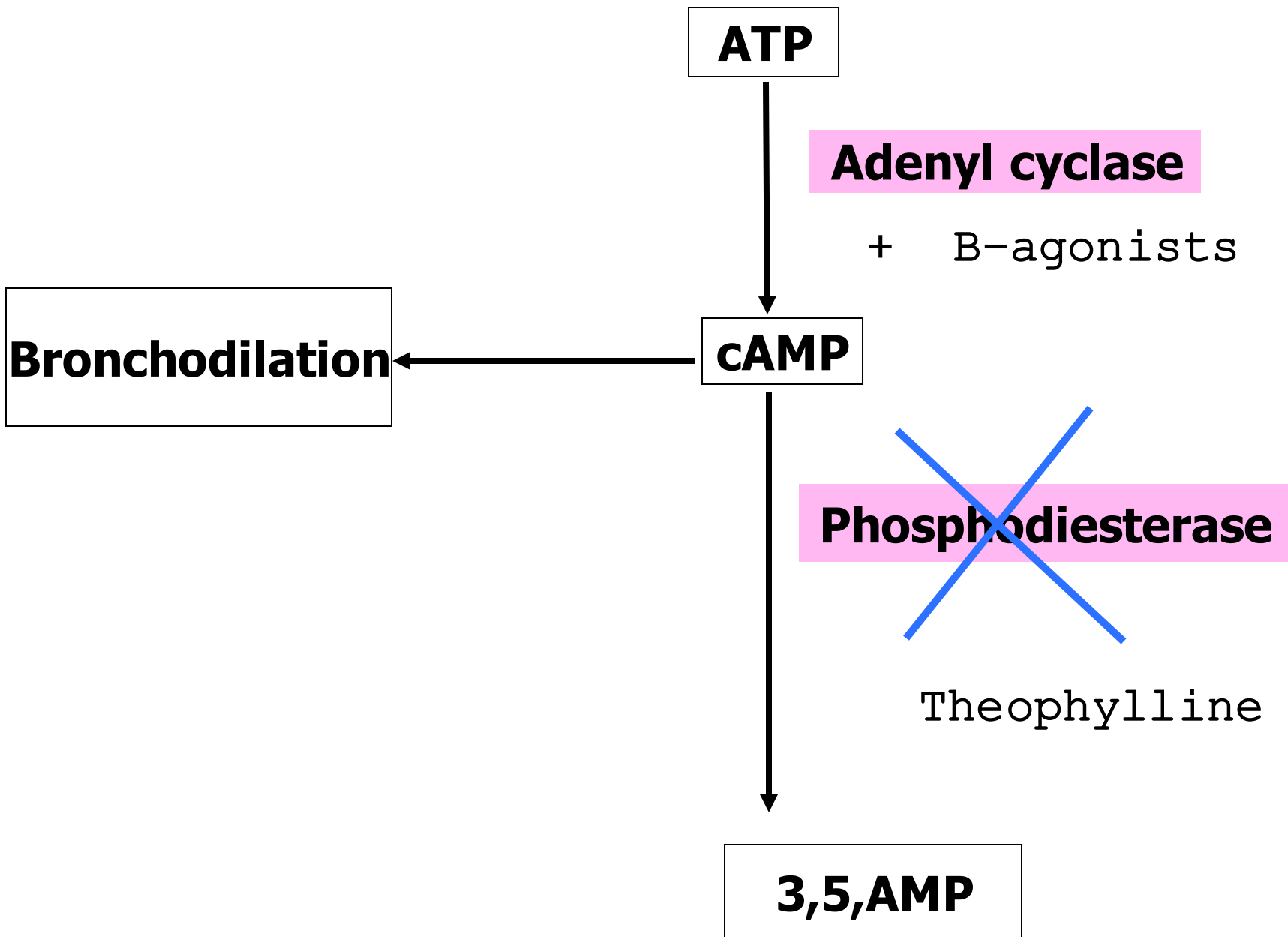
- Main choice in chronic obstructive pulmonary diseases (COPD).
- In acute severe asthma combined with  $\beta_2$  agonists & corticosteroids.

# Methylxanthines

- Theophylline - aminophylline

## Mechanism of Action

- are phosphodiesterase inhibitors
- $\uparrow$  cAMP  $\rightarrow$  bronchodilation
- Adenosine receptors antagonists (A1)
- Increase diaphragmatic contraction
- Stabilization of mast cell membrane



# Pharmacological effects :

- Bronchial muscle relaxation
- ↑ contraction of diaphragm → improve ventilation

**CVS:** ↑ heart rate, ↑ force of contraction

**GIT:** ↑ gastric acid secretions

**Kidney:** ↑ renal blood flow, weak diuretic action

## CNS stimulation

- \* stimulant effect on respiratory center.
- \* decrease fatigue & elevate mood.
- \* overdose (tremors, nervousness, insomnia, convulsion)

# Pharmacokinetics

- **Theophylline** is given orally
- **Aminophylline**, is given as slow infusion
- **metabolized by Cyt P450 enzymes in liver**
- $T_{1/2} = 8$  hours
- **has many drug interactions**
  - **Enzyme inducers:**
    - as phenobarbitone & rifampicin
    - $\uparrow$  metabolism of theophylline  $\rightarrow \downarrow T_{1/2}$ .
  - **Enzyme inhibitors:**
    - as erythromycin
    - $\downarrow$  metabolism of theophylline  $\rightarrow \uparrow T_{1/2}$ .

## Uses

- Second line drug in asthma (theophylline).
- For status asthmatics (aminophylline, is given as slow infusion).

## Side Effects

- **Low therapeutic index (narrow safety margin)**  
monitoring of theophylline blood level is necessary.
- **CVS effects:** hypotension, arrhythmia.
- **GIT effects:** nausea & vomiting
- **CNS side effects:** tremors, nervousness, insomnia, convulsion

# Prophylactic therapy

## Anti - inflammatory drugs include:

- **Glucocorticoids to be discussed in (COPD)**
- **Leukotrienes antagonists**
- **Mast cell stabilizers**
- **Anti-IgE monoclonal antibody**  
**e.g. omalizumab**



# **Anti - inflammatory drugs:**

**(control medications / prophylactic therapy)**

- ↓ bronchial hyper-reactivity.
- ↓ reduce inflammation of airways
- ↓ reduce the spasm of airways

# Glucocorticoids

## Mechanism of action

- **Anti-inflammatory action due to:**
  - Inhibition of **phospholipase A2**
  - ↓ prostaglandin and leukotrienes
  - ↓ Number of inflammatory cells in airways.
  - **Mast cell stabilization** → ↓ histamine release.
  - ↓ capillary permeability and mucosal edema.
  - Inhibition of antigen-antibody reaction.
- **Upregulate  $\beta_2$  receptors** (have additive effect to  $B_2$  agonists).

# Routes of administration

## ➤ **Inhalation:**

e.g. Budesonide & Fluticasone, beclometasone

- Given by inhalation (metered-dose inhaler).
- Have first pass metabolism
- Best choice in asthma, less side effects

➤ **Orally:** Prednisone, methyl prednisolone (for acute asthma attack)

➤ **Injection:** Hydrocortisone, dexamethasone

# Glucocorticoids in asthma

- Are not bronchodilators
- Reduce bronchial inflammation
- Reduce bronchial hyper-reactivity to stimuli
- Have delayed onset of action (effect usually attained after 2-4 weeks).
- Maximum action at 9-12 months.
- Given as prophylactic medications, used alone or combined with  $\beta_2$  agonists.
- Effective in allergic, exercise, antigen and irritant-induced asthma,

Systemic corticosteroids are reserved for:

- Status asthmaticus (i.v.).

## Inhalation has very less side effects:

- Oropharyngeal candidiasis (thrush).
- Dysphonia (voice hoarseness).

## Withdrawal

- Abrupt stop of corticosteroids should be avoided and dose should be tapered (*to avoid exacerbation of asthmatic attack and adrenal insufficiency*).

# Mast cell stabilizers

**e.g. Cromoglycate – Nedocromil (not commonly used)**

- act by stabilization of mast cell membrane.
- given by inhalation (aerosol, nebulizer).
- Have poor oral absorption (10%)

# Pharmacodynamics

- are Not bronchodilators
- Not effective in acute attack of asthma.
- **Prophylactic** anti-inflammatory drug
- Reduce bronchial hyper-reactivity.
- Effective in exercise, antigen and irritant-induced asthma.
- Children respond better than adults



## Uses

- Prophylactic therapy in asthma especially in children.
- Allergic rhinitis.
- Conjunctivitis.

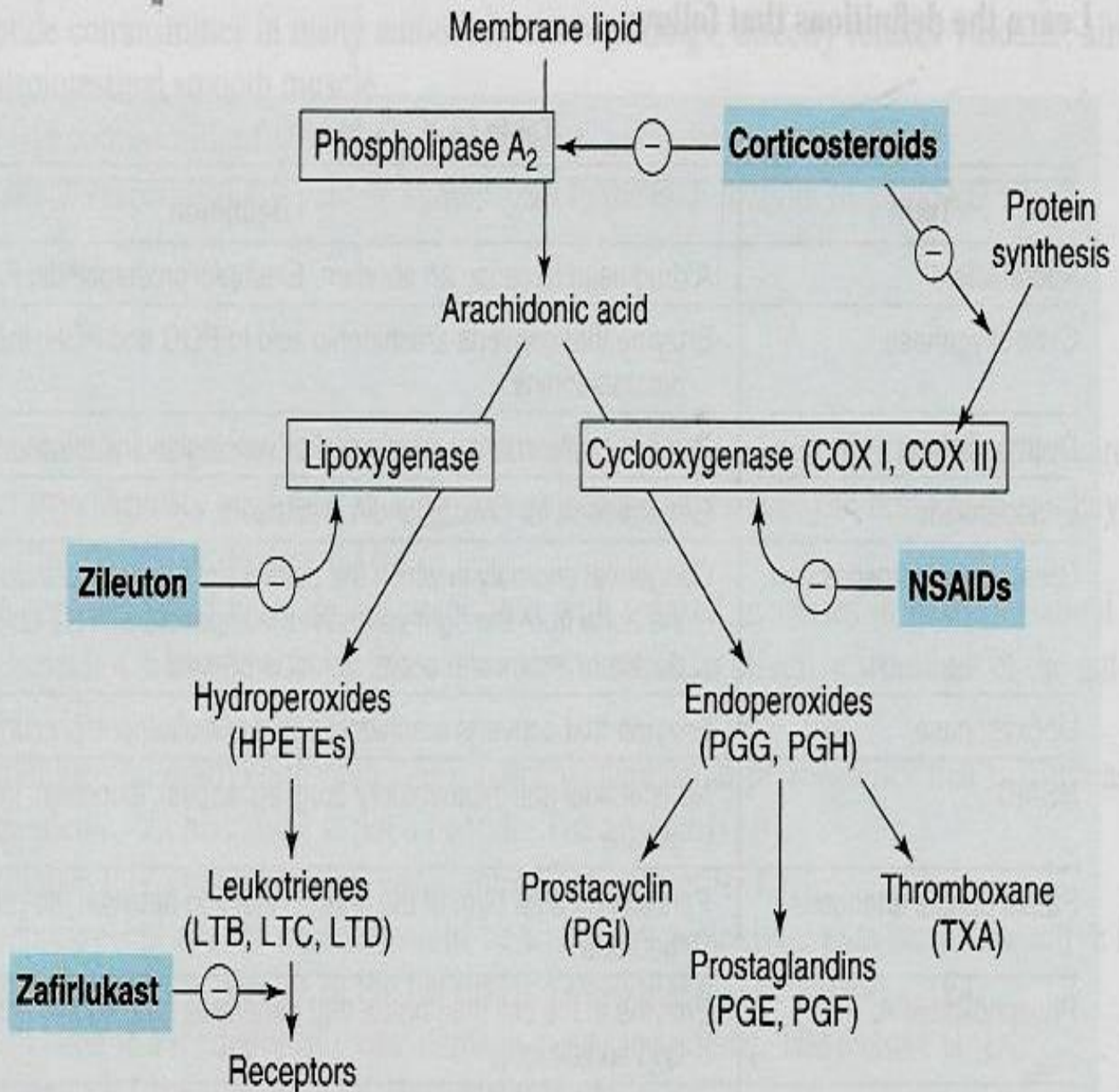
## Side effects

- Bitter taste
- minor upper respiratory tract irritation (burning sensation, nasal congestion)

# Leukotrienes antagonists

## Leukotrienes

- synthesized by inflammatory cells found in the airways (eosinophils, macrophages, mast cells).
- produced by the action of 5-lipoxygenase on arachidonic acid.
- **Leukotriene B4:** chemotaxis of neutrophils
- **Cysteinyl leukotrienes C4, D4 & E4:**
  - bronchoconstriction
  - increase bronchial hyper-reactivity
  - ↑ mucosal edema, ↑ mucus secretion



# Leukotriene receptor antagonists

e.g. **zafirlukast, montelukast, pranlukast**

- are selective, reversible antagonists of cysteinyl leukotriene receptors (**CysLT<sub>1</sub>receptors**).
- Taken orally.
- Are bronchodilators
- Have anti-inflammatory action
- Less effective than inhaled corticosteroids
- Have glucocorticoids **sparing effect** (potentiate corticosteroid actions).

# Uses of leukotriene receptor antagonists

- **Not** effective in acute attack of asthma.
- **Prophylaxis** of mild to moderate asthma.
- Aspirin-induced asthma
- Antigen and exercise-induced asthma
- Can be combined with glucocorticoids (additive effects, low dose of glucocorticoids can be used).

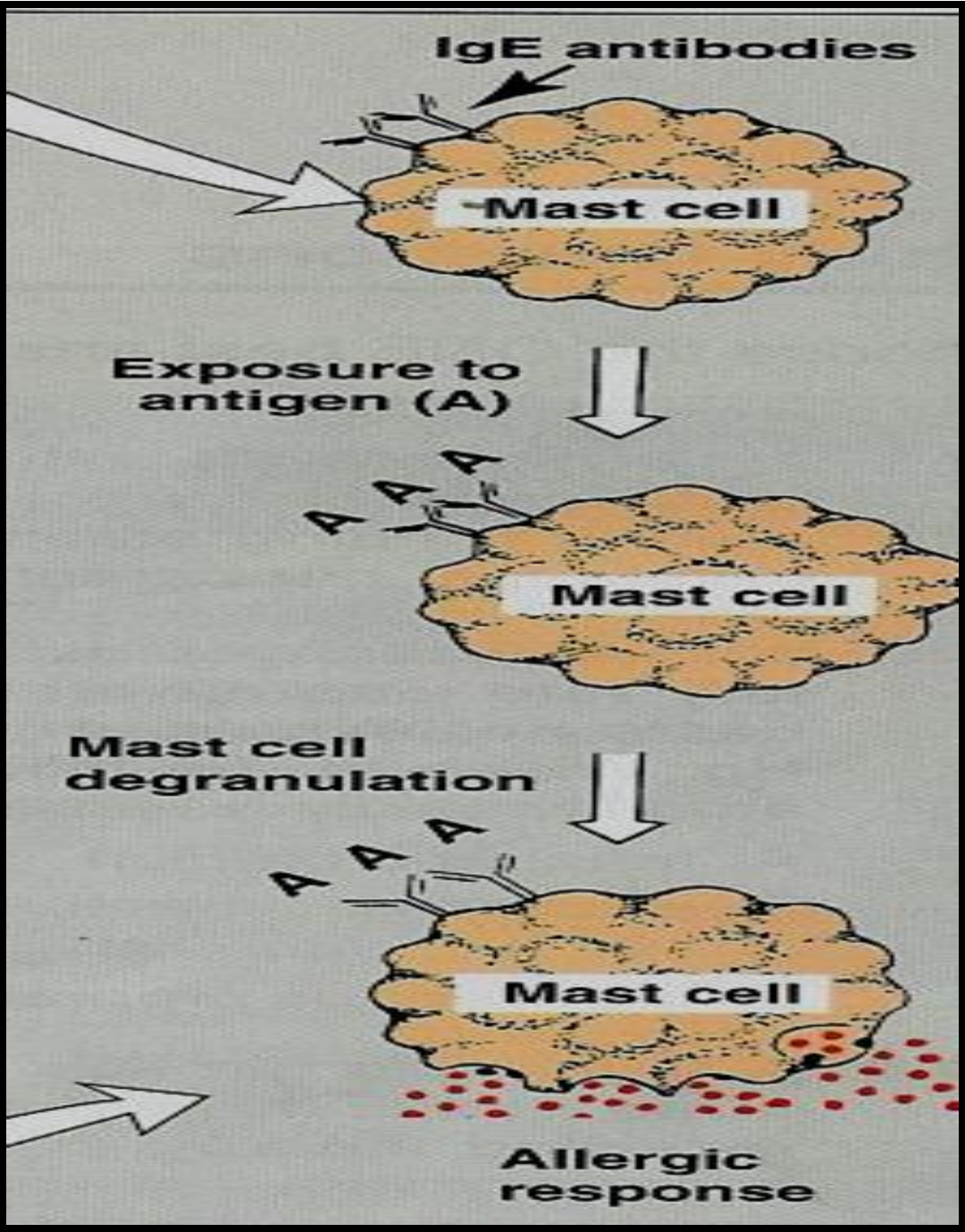
## Side effects:

Elevation of liver enzymes, headache, dyspepsia

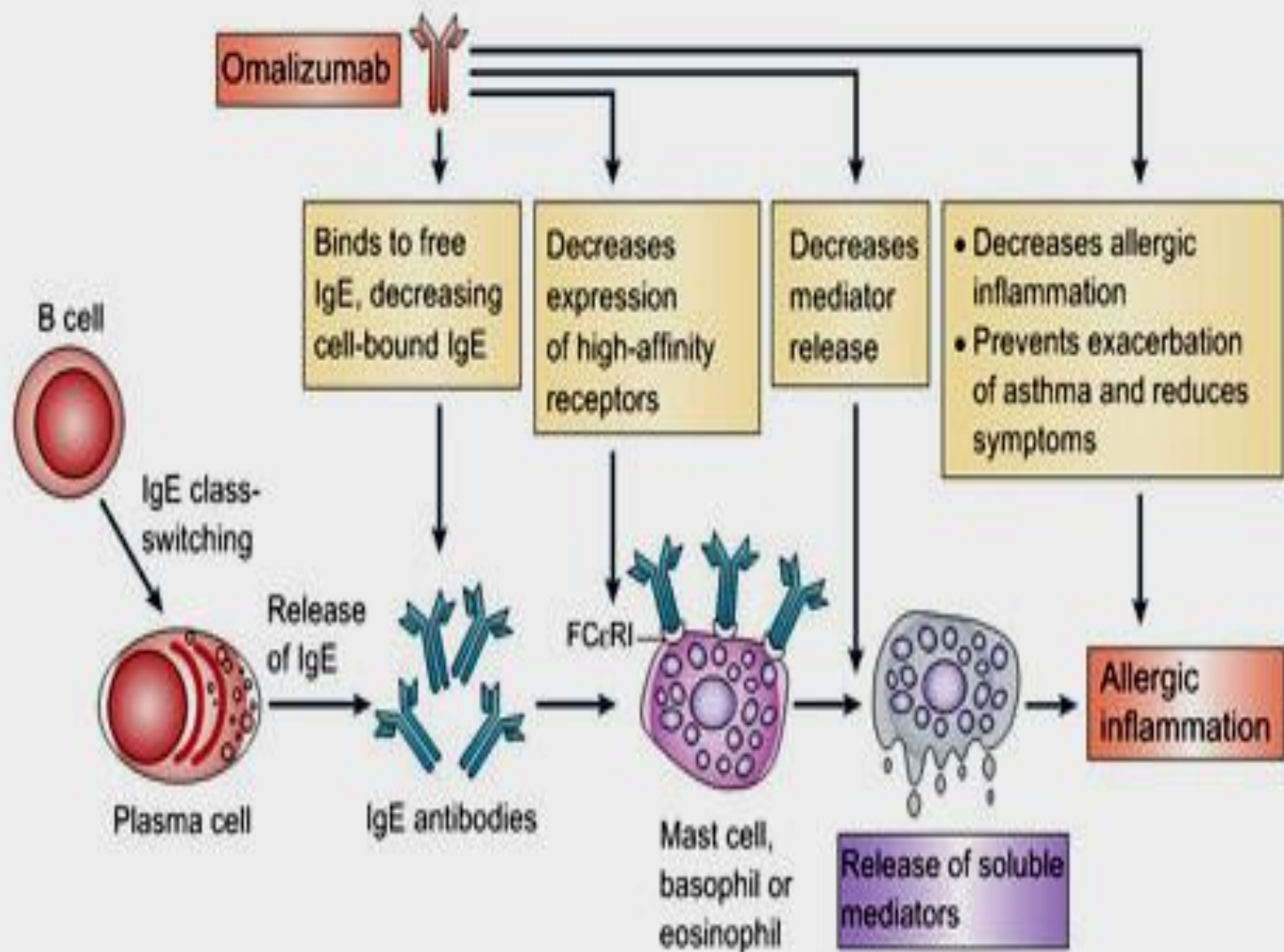
# Anti-IgE monoclonal antibody

## e.g. Omalizumab

- is a monoclonal antibody directed against **human IgE** – given by injection (s.c.)
- prevents IgE binding with its receptors on mast cells & basophiles.
- ↓ release of allergic mediators.
- Expensive-not first line therapy.
- used for treatment of moderate to severe allergic asthma which does not respond to high doses of corticosteroids.







**Figure 1.** Mechanisms of action of omalizumab in allergic asthma.

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**Abbreviation:** Fc RI, high-affinity IgE receptor.



- COPD NEXT

# Drugs used in chronic obstructive pulmonary disease (COPD)

- **COPD** is a chronic irreversible airflow obstruction, lung damage and inflammation of the air sacs (alveoli).
- **Smoking** is a high risk factor but air pollution and genetic factors can contribute.

## Treatment:

- Inhaled bronchodilators
- Inhaled glucocorticoids
- Oxygen therapy
- **Antibiotics** specifically macrolides such as **azithromycin** to reduce the number of exacerbations.

# Inhaled bronchodilators in COPD

## ➤ Inhaled antimuscarinics

➤ Ipratropium & tiotropium.

➤ are superior to  $\beta_2$  agonists in COPD

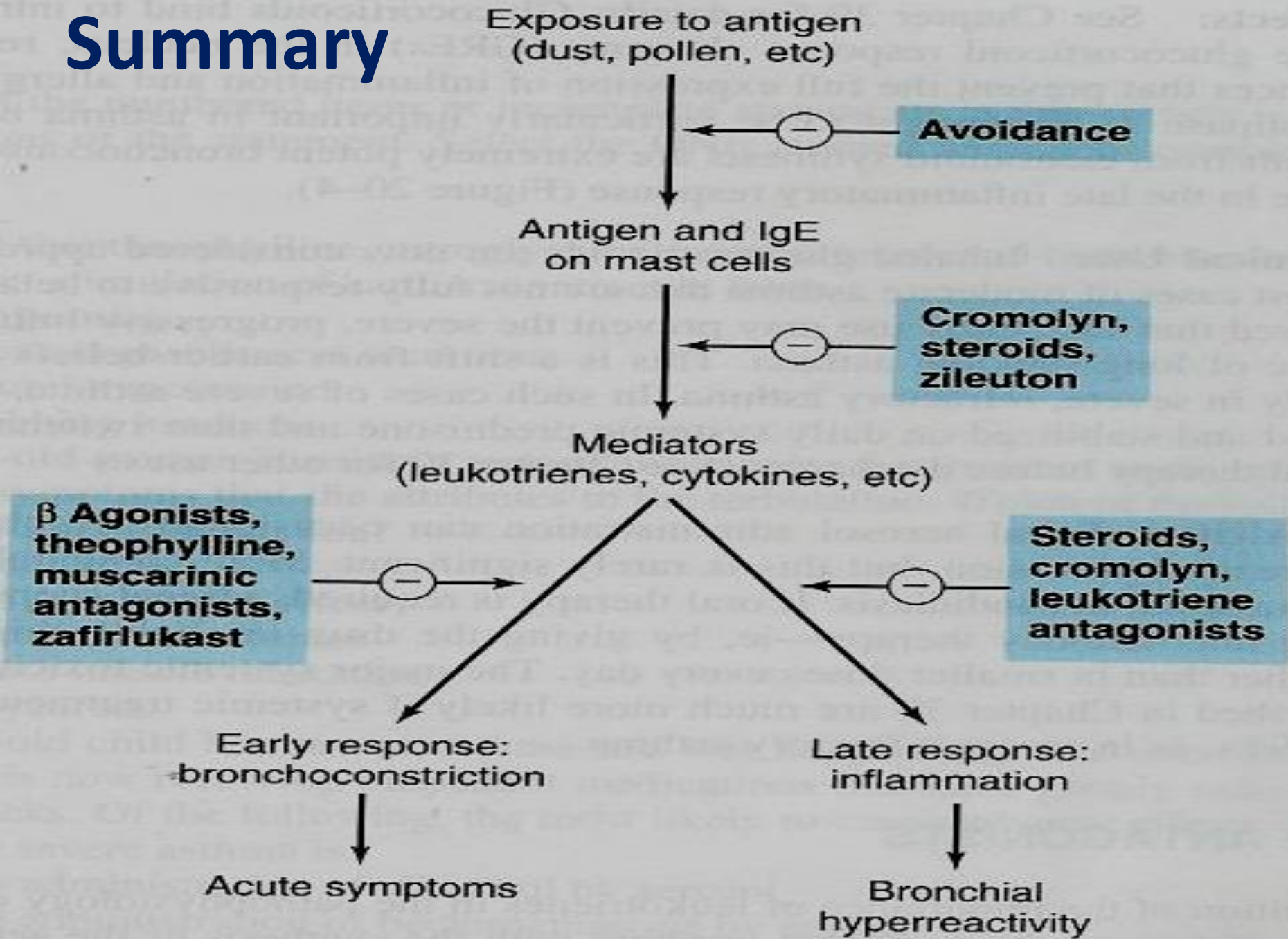
## ➤ $\beta_2$ agonists

➤ these drugs can be used either alone or combined

– salbutamol + ipratropium

– salmeterol + Tiotropium (long acting-less dose frequency).

# Summary



# Bronchodilators (relievers for bronchospasm)

<b>Drugs</b>		
<b>B2 agonists</b> Salbutamol, terbutaline	– Short acting – <b>main choice</b> in acute attack of asthma – Inhalation	↑ Adenyl cyclase  ↑ cAMP
Salmeterol, formoterol	Long acting, Prophylaxis Nocturnal asthma	
<b>Antimuscarinics</b> Ipratropium (Short) Tiotropium (long)	<b>Main drugs For COPD</b> Inhalation Inhalation	Blocks M receptors
<b>Xanthine derivatives</b> Theophylline Aminophylline	(orally) (parenterally)	Inhibits phosphodiesterase ↑ cAMP

# Anti-inflammatory drugs (prophylactic)

<b>Corticosteroids</b> (Inhibits phospholipase A2) Dexamethasone, Fluticasone, budesonide	<b>Inhalation</b>
prednisolone	<b>Orally</b>
Hydrocortisone	<b>parenterally</b>
<b>Mast stabilizers</b> Cromoglycate (Cromolyn), Nedocromil	<b>Inhalation, prophylaxis in children</b>
<b>Cysteinyl antagonists (CyLT1 antagoist)</b> Zafirlukast, montelukast	<b>orally</b>
<b>Omalizumab (Anti IgE antibody)</b>	<b>Injection, SC</b>