Pharmacology of drugs used in bronchial asthma & COPD

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ILOs: The students should be able to

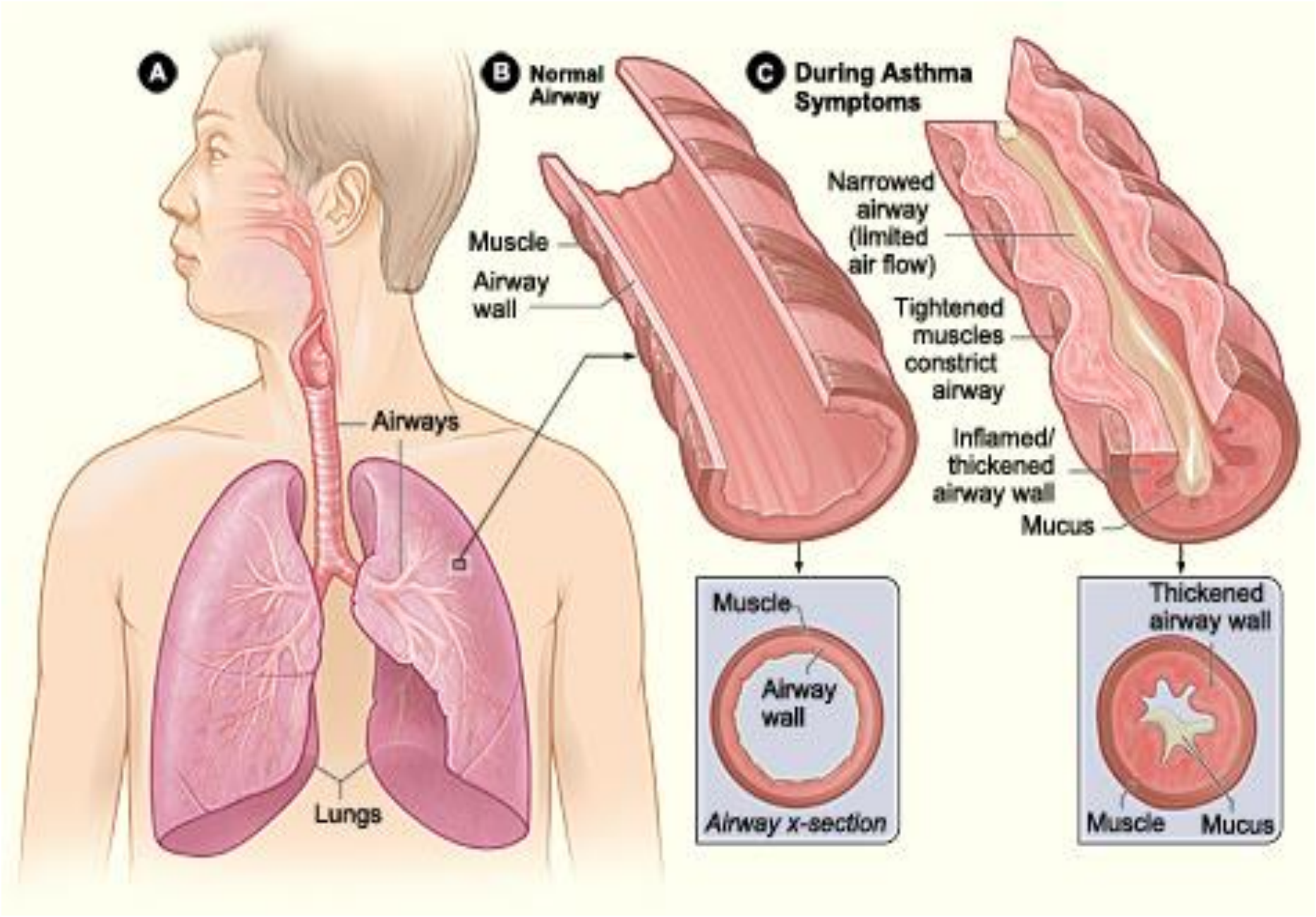
1. **Different types of drugs used for treatment of asthma**
2. **Differentiate between treatment and prophylactic therapy for asthma**
3. **Recognize the different types of bronchodilators regarding pharmacokinetics, pharmacodynamics, uses and side effects.**
4. **Identify the different anti-inflammatory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



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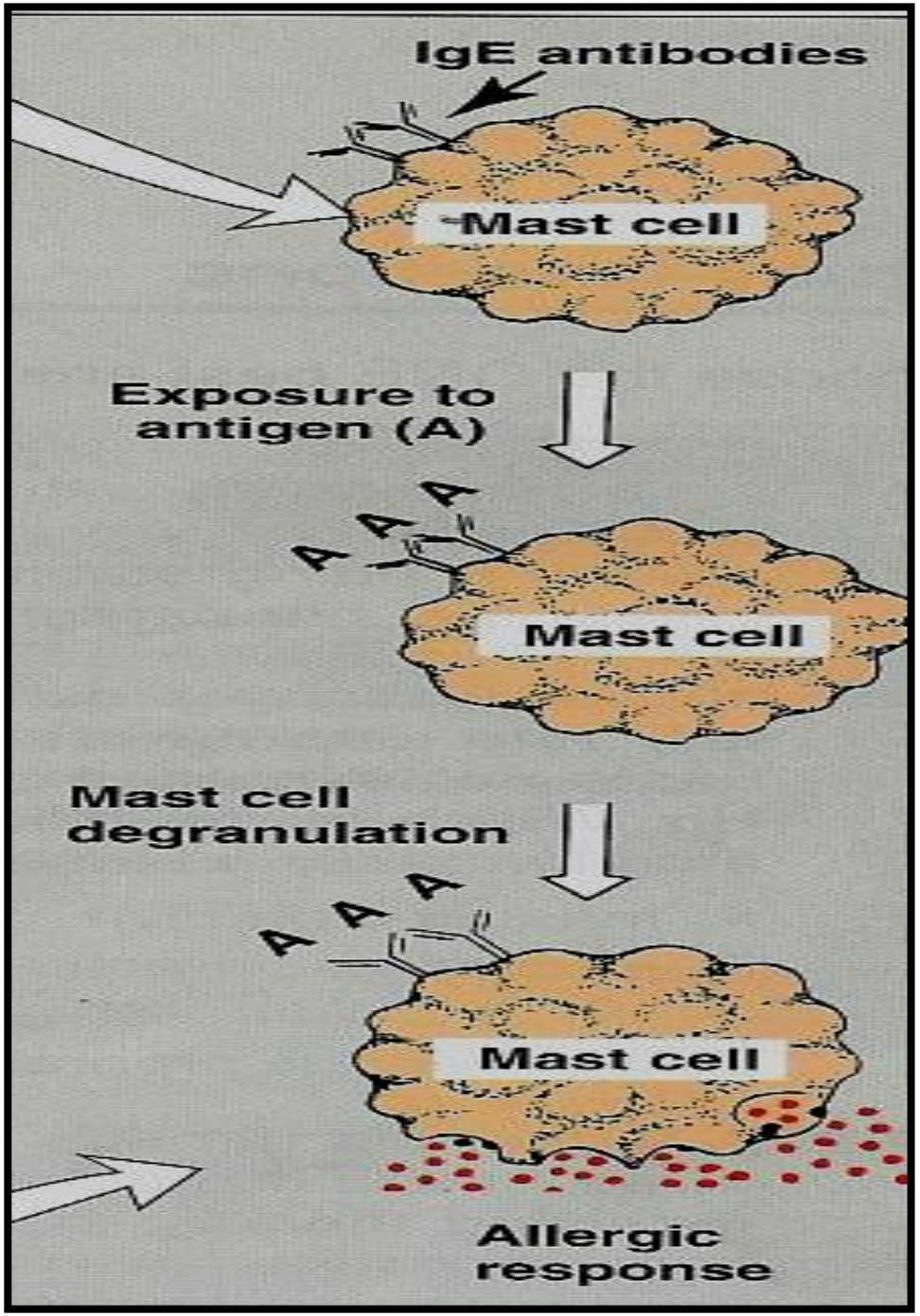
Airway hyper-reactivity



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, β-bockers**

Asthma drug targets

- **Parasympathetic supply**

  M3 receptors in smooth muscles and glands.

  - **Bronchoconstriction**
  - **Increase mucus secretion**

- **No sympathetic supply but B_2 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 β2-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 ß2-agonists**

Bronchodilators

These drugs can produce rapid relief of bronchoconstriction.

Bronchodilators:

- **β2 - adrenoreceptor agonists**
- **Antimuscarinics**
- **Xanthine preparations**

Sympathomimetics
β- adrenoceptor agonists

Mechanism of Action

- direct β_2 stimulation $\longrightarrow$ stimulate adenyl cyclase $\longrightarrow \uparrow$ cAMP $\rightarrow$ bronchodilation.
- Increase mucus clearance by (increasing ciliary activity).
- Stabilization of mast cell membrane.

Classification of β agonists

- **Non selective β agonists:**

  epinephrine - isoprenaline

- **Selective β2 – agonists (Preferable).**

  Salbutamol (albuterol)

  Terbutaline

  Salmeterol

  Formeterol

Non selective β-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 β2 –agonists

- Are mainly given by **inhalation** by (metered dose inhaler or nebulizer).
- Can be given orally, parenterally.
- Short acting ß2 agonists

  e.g. salbutamol, terbutaline
- Long acting ß2 agonists

  e.g. salmeterol, formoterol

Nebulizer

Inhaler

Short acting ß$_2$ 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 ß$_2$ 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 ß$_2$ agonists

- Minimal CVS side effects
- suitable for asthmatic patients with

CV disorders as hypertension or heart failure.

Disadvantages of ß$_2$ agonists

- Skeletal muscle tremors.
- Nervousness
- Tolerance (β-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 β_2-agonists.
- No anti-inflammatory action only bronchodilator

Uses

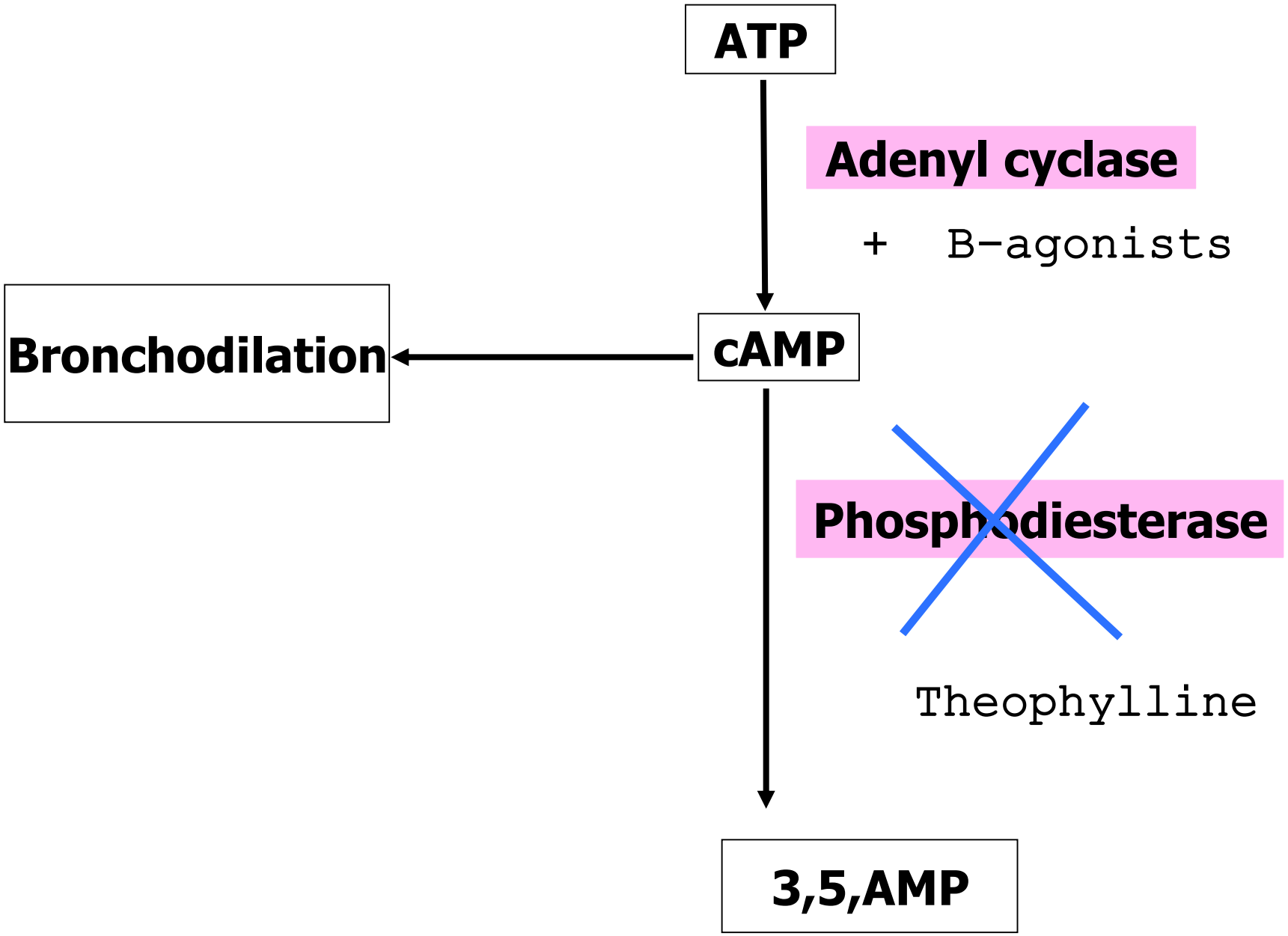
- Main choice in chronic obstructive pulmonary diseases (COPD).
- In acute severe asthma combined with β_2 agonists & corticosteroids.

Methylxanthines

- Theophylline - aminophylline

Mechanism of Action

- are phosphodiestrase inhibitors
- ↑ cAMP → bronchodilation
- Adenosine receptors antagonists (A1)
- Increase diaphragmatic contraction
- Stabilization of mast cell membrane


ATP
Adenyl cyclase
+ B-agonists
Bronchodilation
cAMP
Phosphodiesterase
Theophylline
3,5,AMP

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 ½= 8 hours
- **has many drug interactions**
  - **Enzyme inducers:**
    - as phenobarbitone & rifampicin
    - ↑ metabolism of theophylline → ↓ T ½.
  - **Enzyme inhibitors:**
  - as erythromycin

    ↓ metabolism of theophylline → ↑ T ½.

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 β_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 β_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 insufficency*).

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

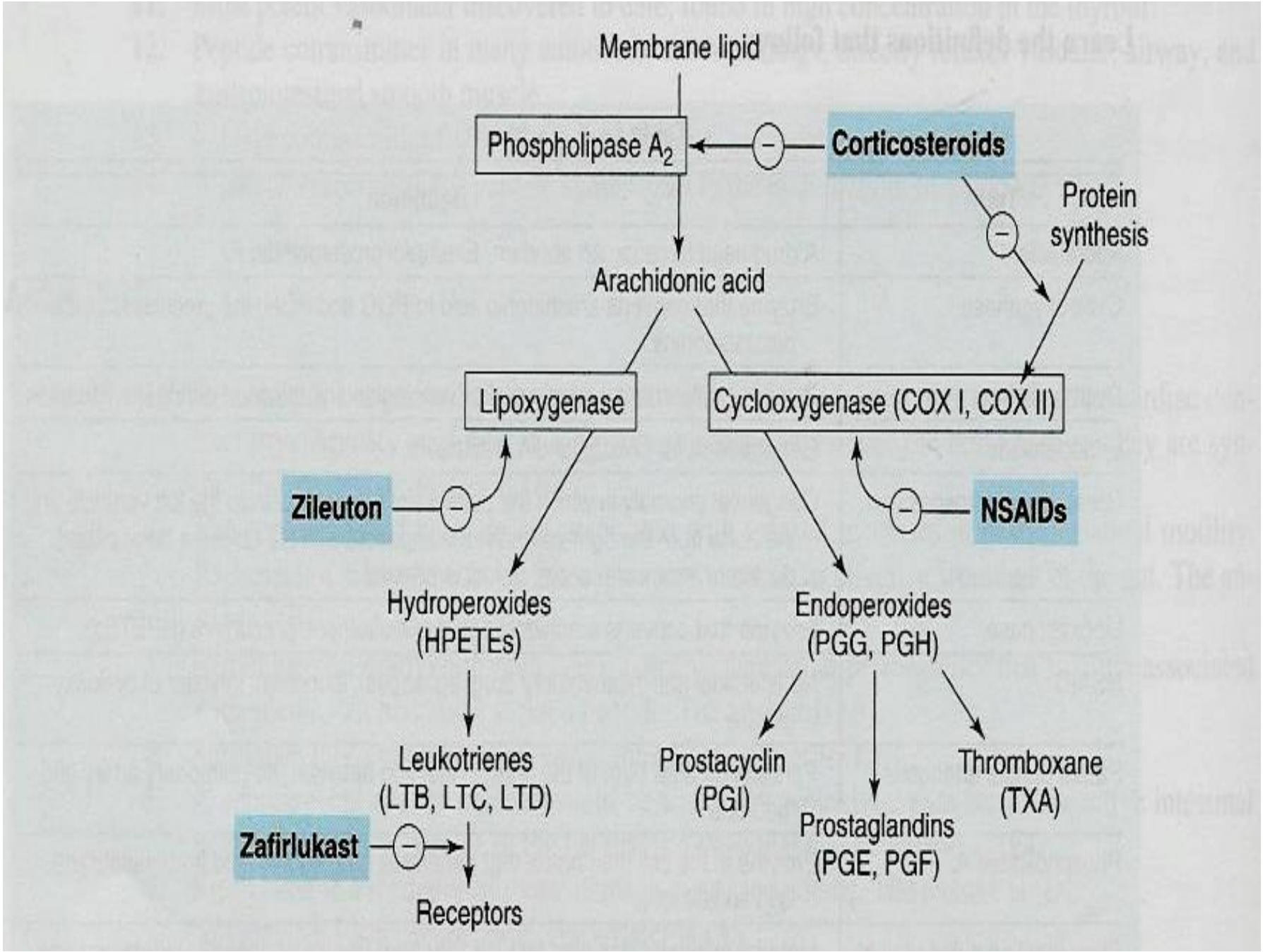
- Bitter taste
- minor upper respiratory tract irritation (burning sensation, nasal congestion)

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


Membrane lipid
Phospholipase A2
Corticosteroids
Protein synthesis
Arachidonic acid
Lipoxygenase
Cyclooxygenase (COX I, COX II)
Zileuton
NSAIDs
Hydroperoxides (HPETEs)
Endoperoxides (PGG, PGH)
Leukotrienes (LTB, LTC, LTD)
Prostacyclin (PGI)
Thromboxane (TXA)
Prostaglandins (PGE, PGF)
Zafirlukast
Receptors

Leukotriene receptor antagonists

e.g. zafirlukast, montelukast, pranlukast

- are selective, reversible antagonists of cysteinyl leukotriene receptors **(CysLT$_1$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).

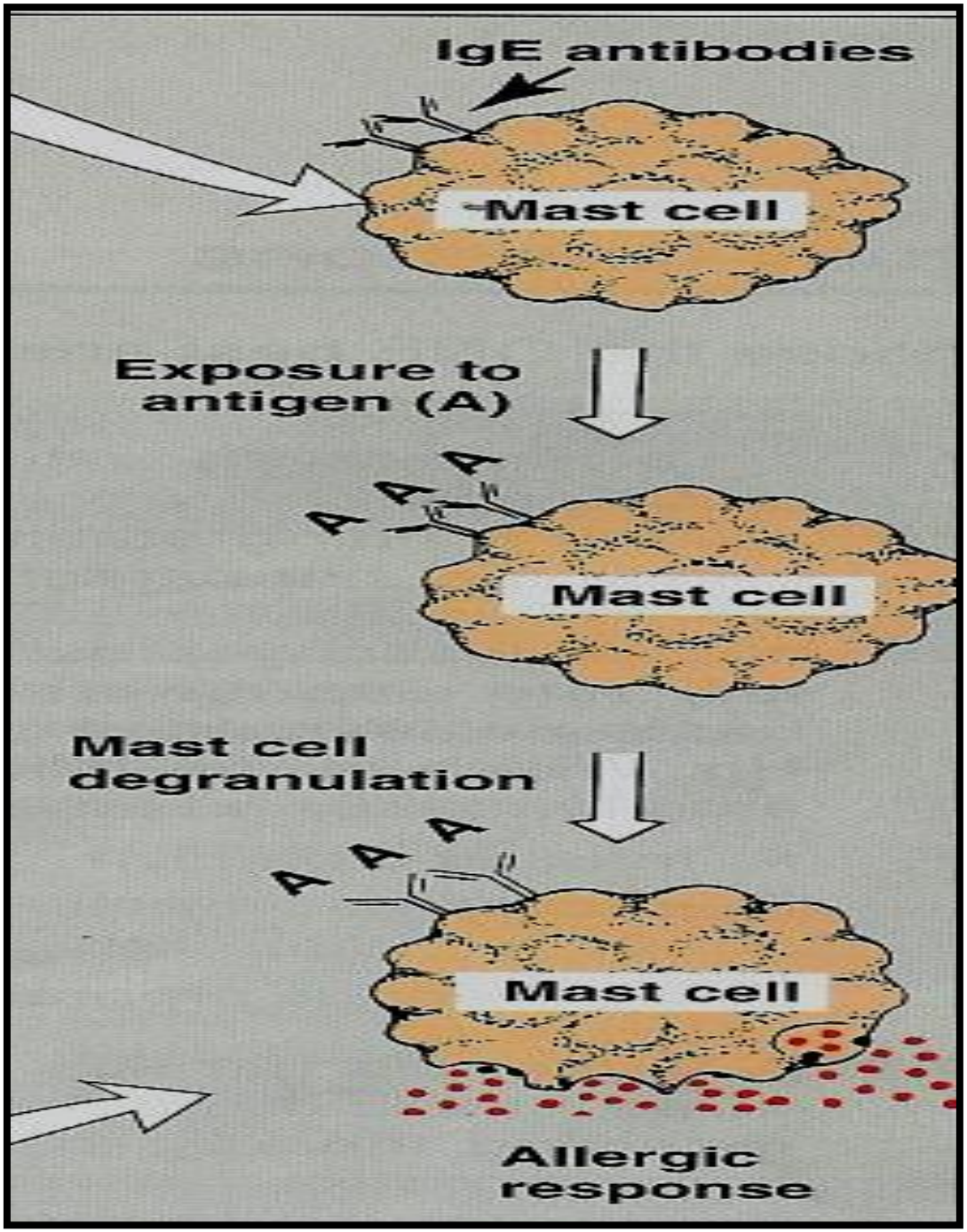
Side effects:

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.


IgE antibodies
Mast cell
Exposure to antigen (A)
A
A
A
Mast cell
Mast cell degranulation
A
A
A
Mast cell
Allergic response

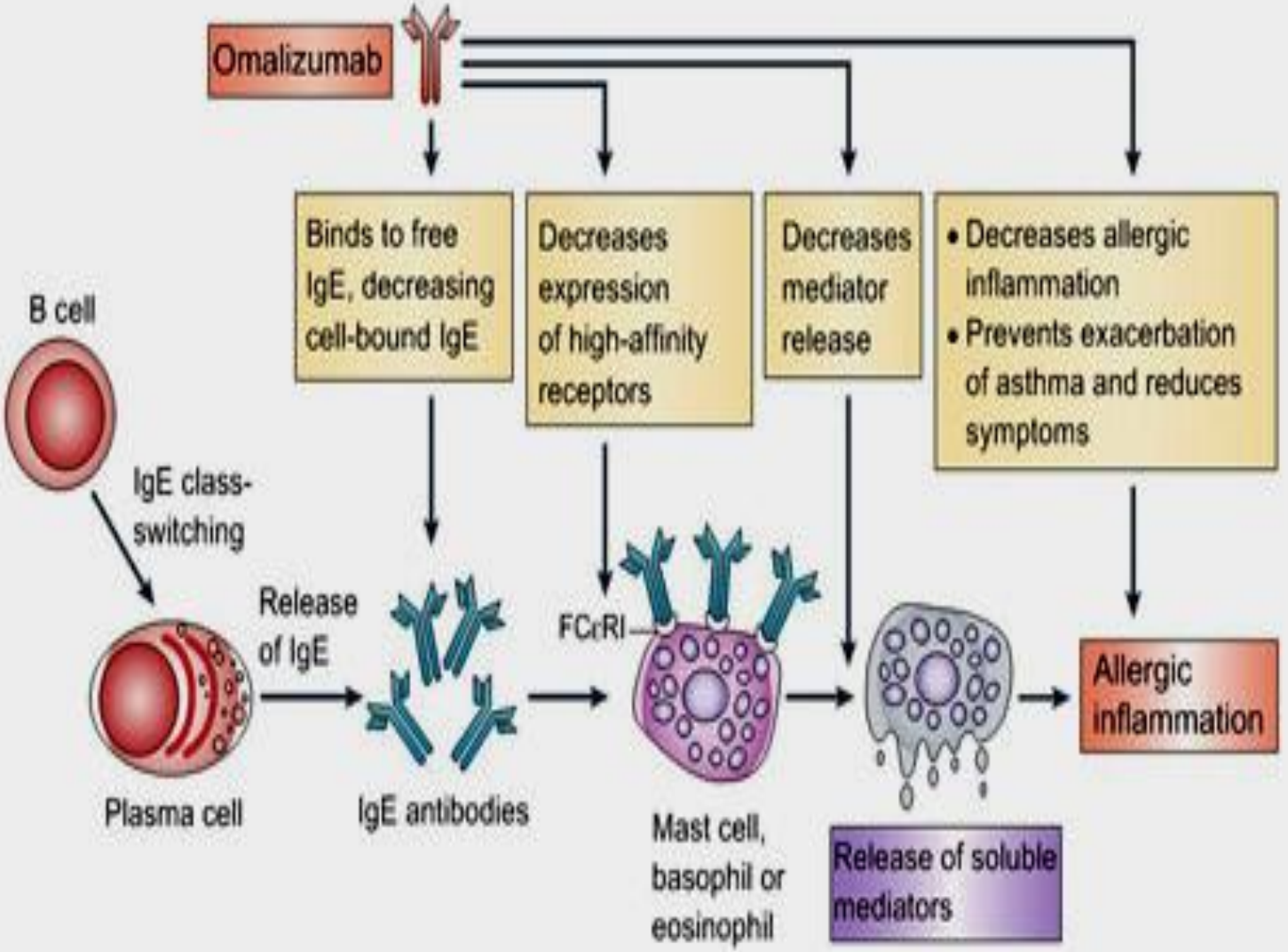


Figure 1. Mechanisms of action of omalizumab in allergic asthma.
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Abbreviation: Fc RI, high-affinity IgE receptor.

- 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.

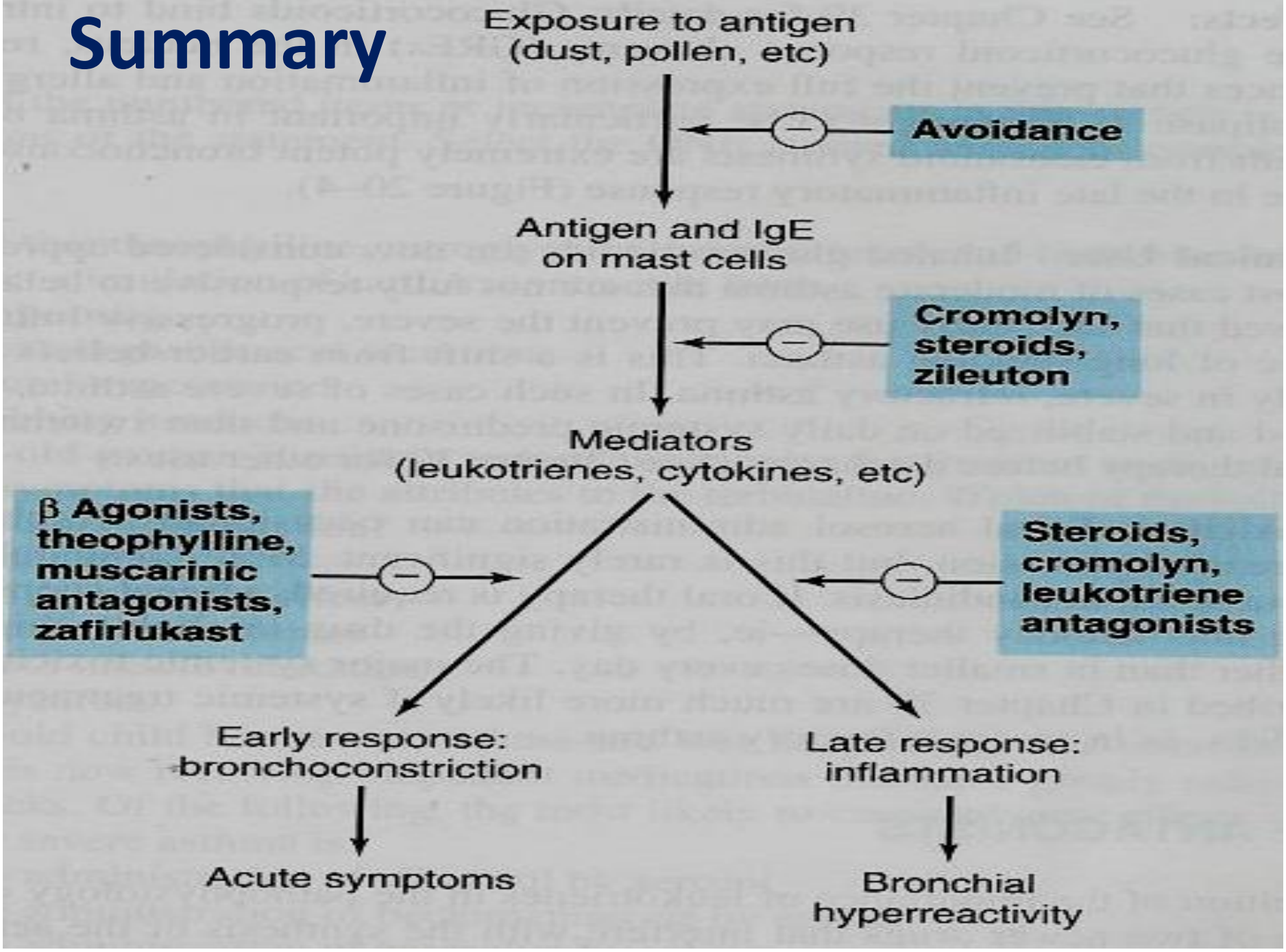
Treatment:

- 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 β2 agonists in COPD
- **β_2 agonists**
- these drugs can be used either alone or combined
  - salbutamol + ipratropium
  - salmeterol + Tiotropium (long acting-less dose frequency).

Summary


Exposure to antigen (dust, pollen, etc)
Avoidance
Antigen and IgE on mast cells
Cromolyn, steroids, zileuton
Mediators (leukotrienes, cytokines, etc)
β Agonists, theophylline, muscarinic antagonists, zafirlukast
Steroids, cromolyn, leukotriene antagonists
Early response: bronchoconstriction
Late response: inflammation
Acute symptoms
Bronchial hyperreactivity

Bronchodilators (relievers for bronchospasm)

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

Anti-inflammatory drugs (prophylactic)

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