Pharmacology of drugs used in bronchial asthma & COPD

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ILOs: The students should be able to

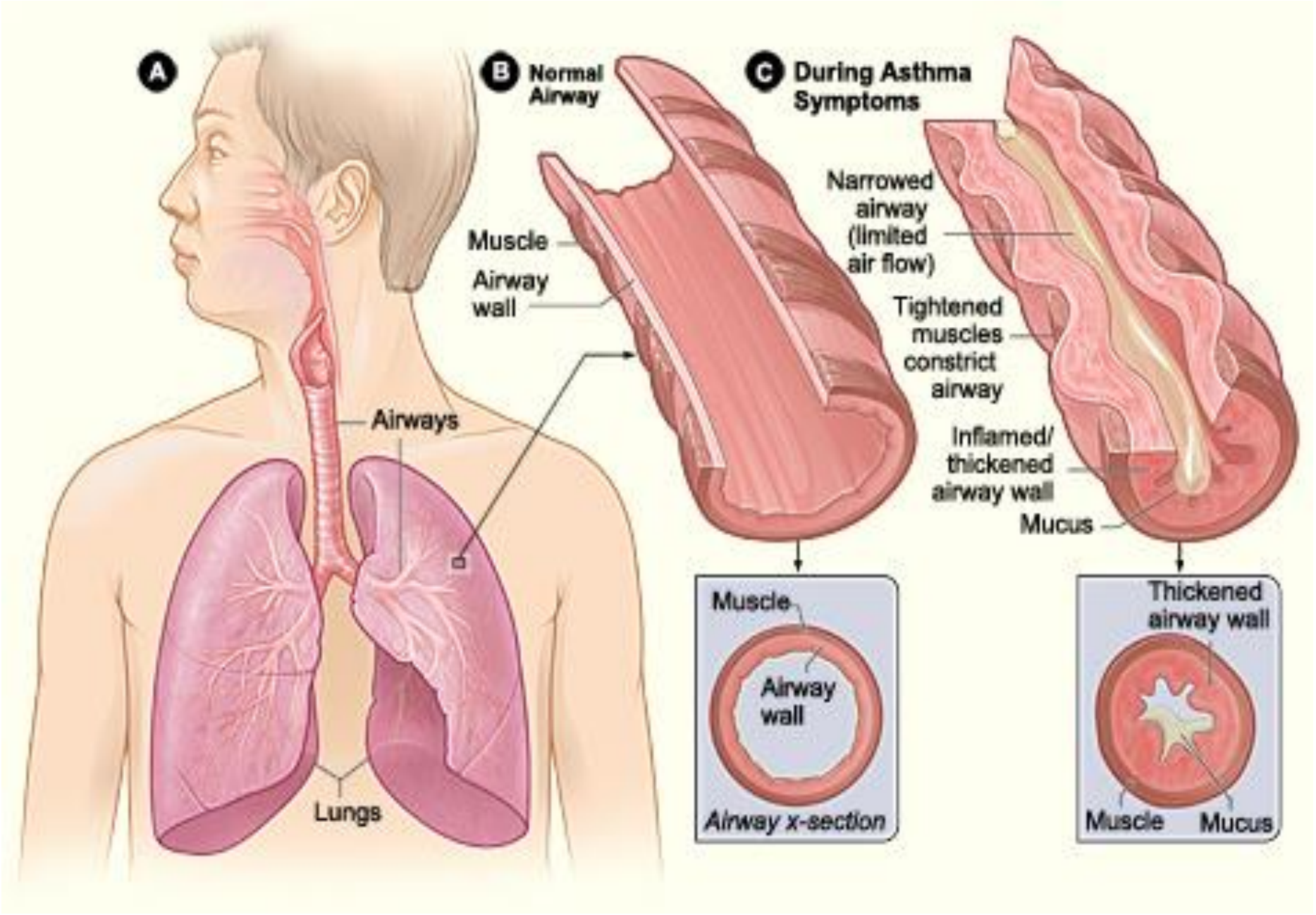
1. **Different types of drugs used for treatment of asthma**
2. **Differentiate between treatment and prophylactic therapy for asthma**
3. **Recognize the different types of bronchodilators regarding pharmacokinetics, pharmacodynamics, uses and side effects.**
4. **Identify the different anti-inflammatory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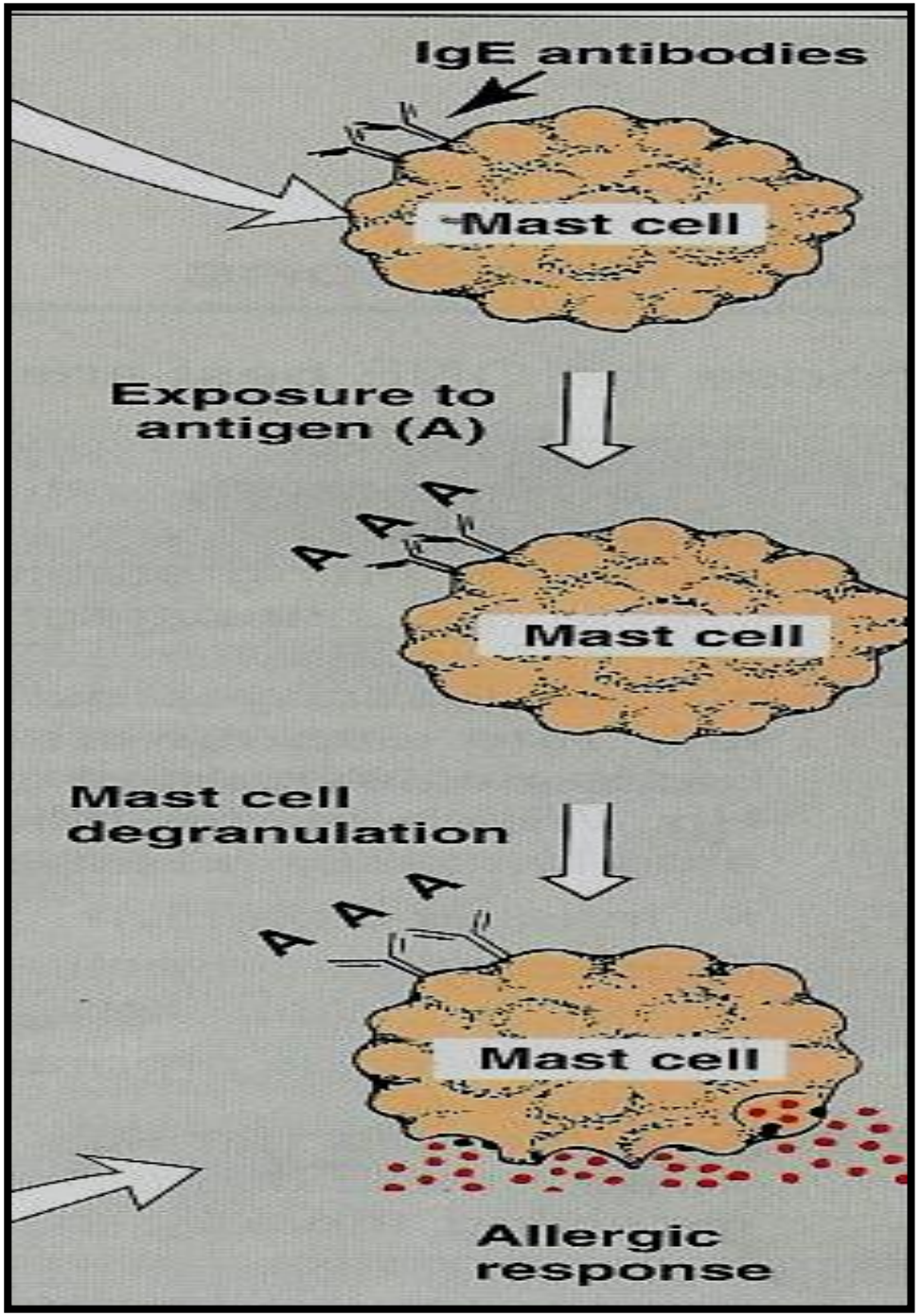
Airway hyper-reactivity



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 such as symbicort (formeterol+budesonide) (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

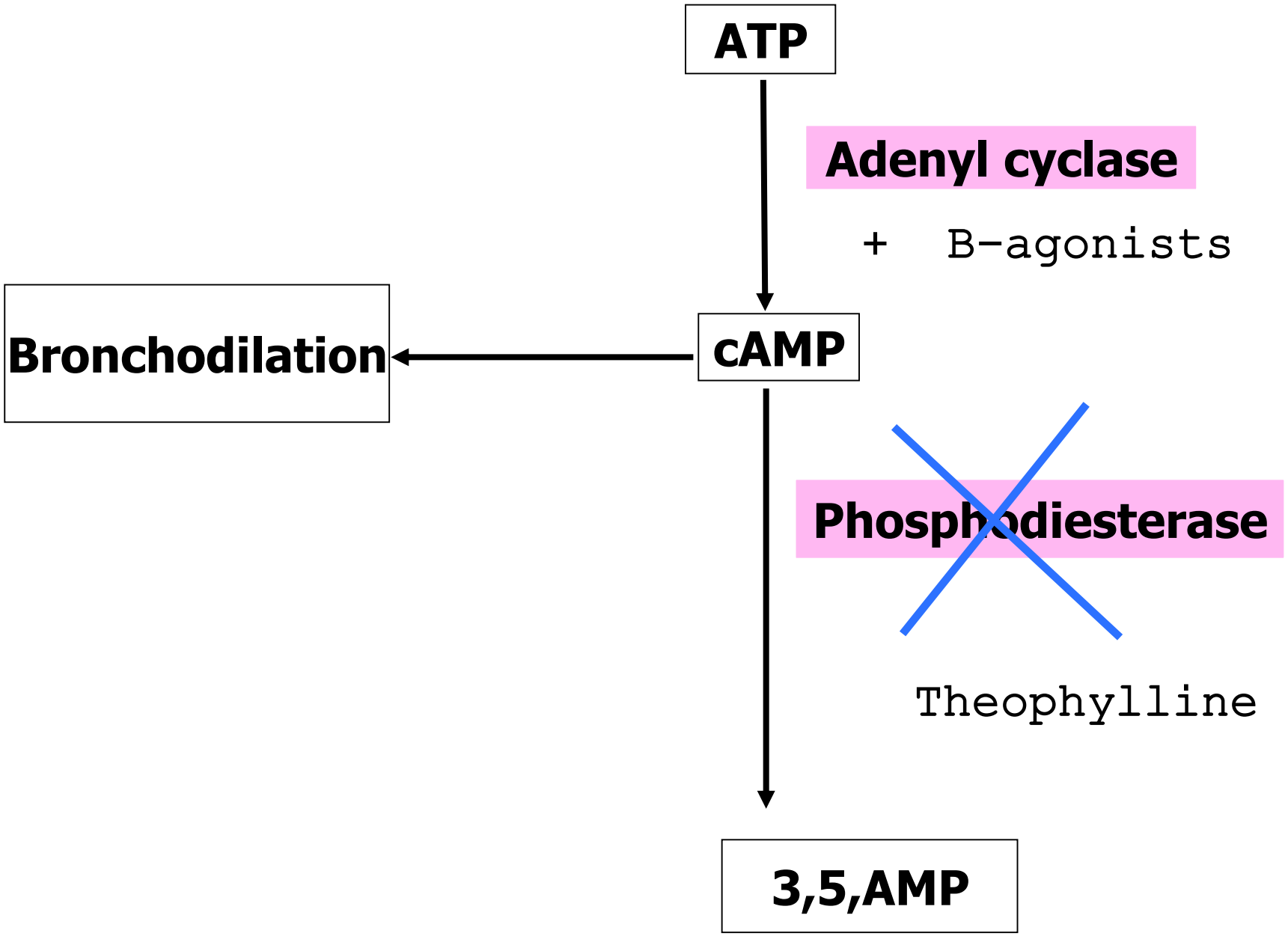
- Main choice in chronic obstructive pulmonary diseases (COPD).
- In acute severe asthma combined with β_2 agonists & corticosteroids.

Methylxanthines

- Theophylline - aminophylline

Mechanism of Action

- are phosphodiestrase inhibitors
- ↑ cAMP → bronchodilation
- Adenosine receptors antagonists (A1) (not very significant in asthma)
- 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).

(to reduce these effects, Instruct patient to rinse mouth properly after inhalation).

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

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).

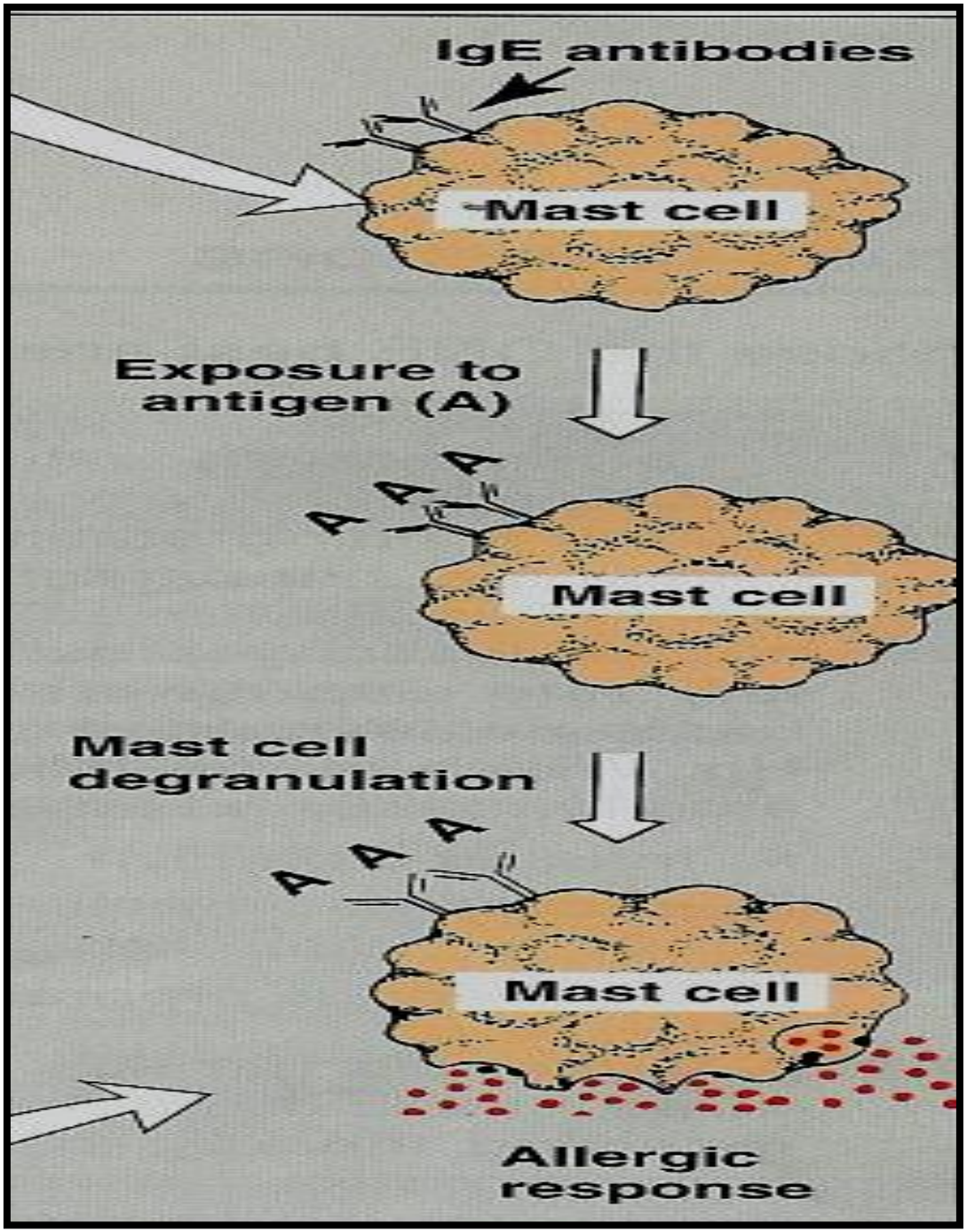
Side effects:

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

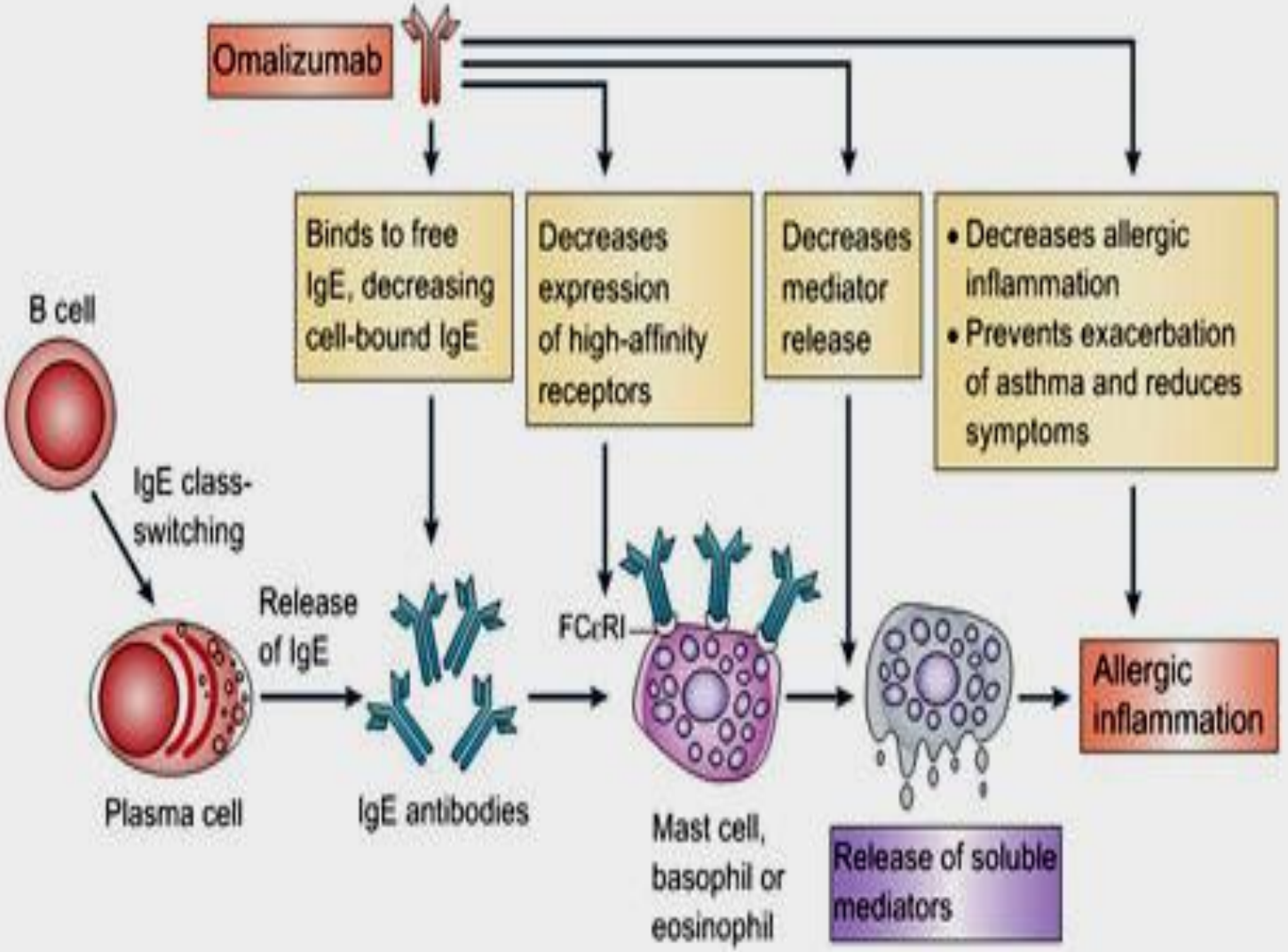


Figure 1. Mechanisms of action of omalizumab in allergic asthma.
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Abbreviation: Fc RI, high-affinity IgE receptor.

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