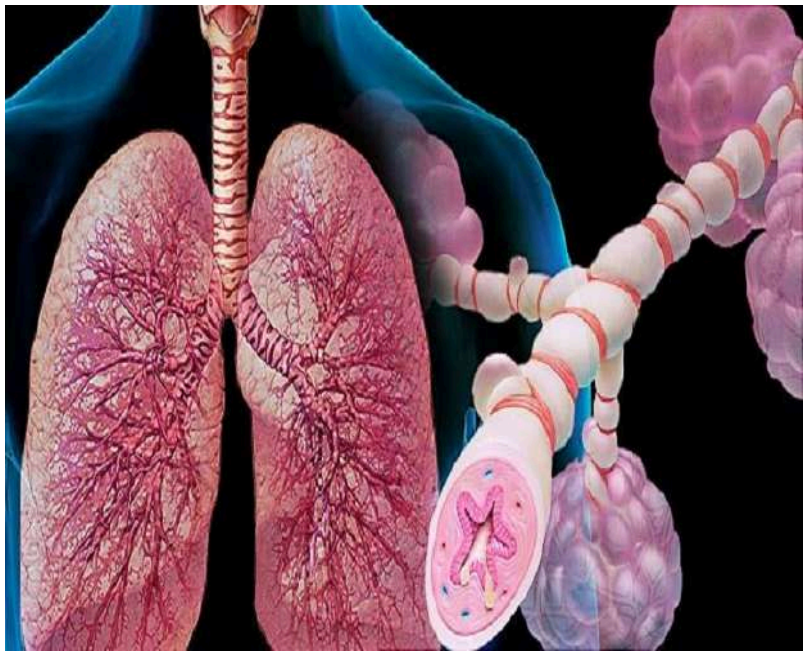
Drug Therapy For Bronchial Asthma



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Drug therapy for bronchial asthma

Bronchodilators

1- β2 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)

1) Salbutamol: Short acting beta2 agonist (SABA)
- Selective stimulant of β_2 adrenergic receptors
- Selective action on the bronchi
- Given orally & by inhalation

2) 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 β2 agonists can cause more adverse effect

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

3- Muscarinic (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 the pathogenesis of bronchial asthma
2. Non-selective effects:
- Dryness of bronchial secretions
- ? Muco-ciliary function15

- 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

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. Parenteral: methylprednisolone, hydrocortisone, dexamethasone, 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

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

Supportive treatment

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

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

Bronchial Asthma (الربو الشعبي)

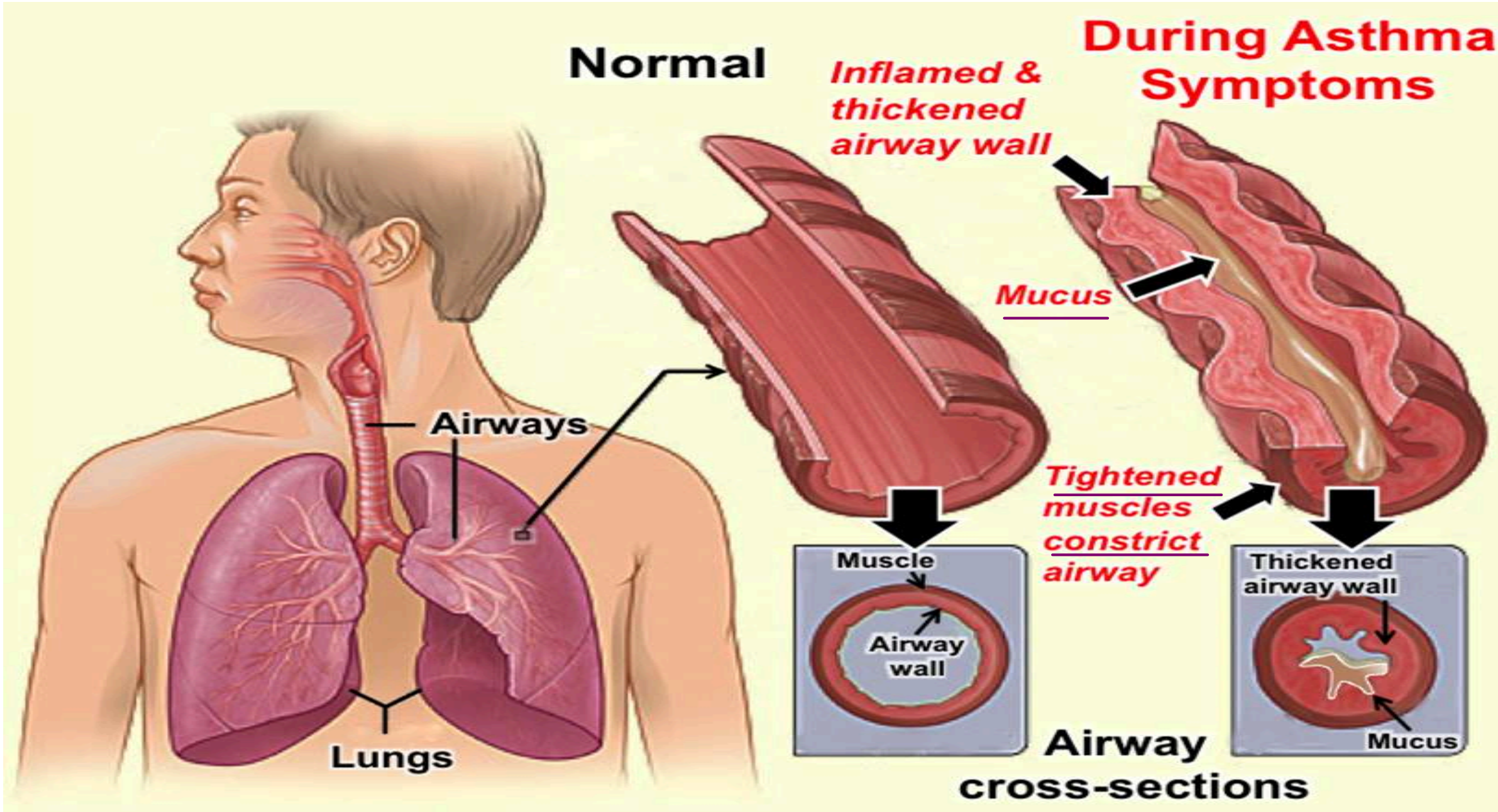
Breathe Calmly, Stay Alive

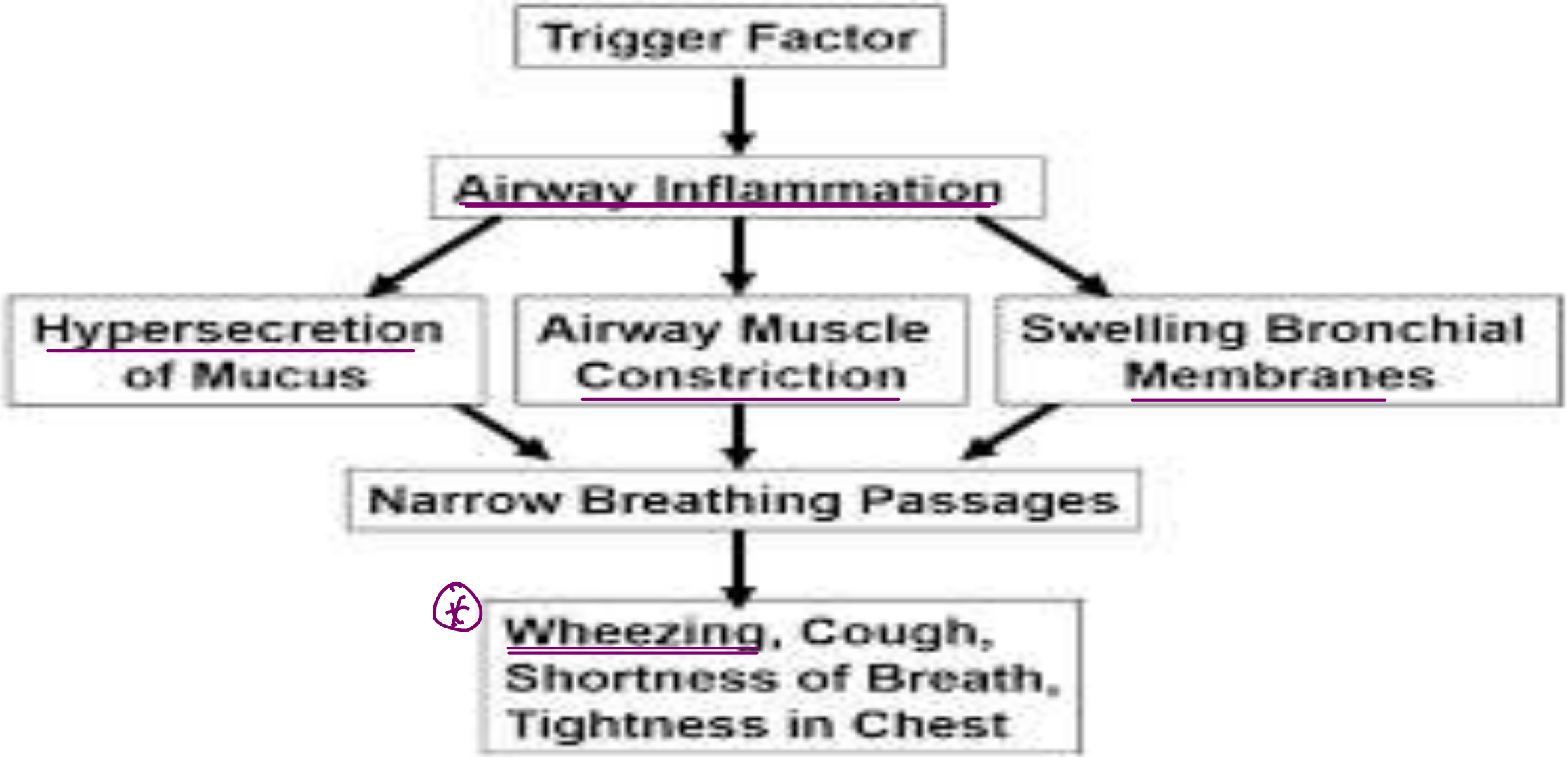
- **Inflammatory disease** characterized by **reversible airway obstruction** due to **bronchoconstriction, mucosal edema, cellular infiltration, and viscid secretions**

irreversible: COPD

- Manifested clinically by **paroxysms** of dyspnea (1), cough (2) and wheezes (3) → most important landmark

صوت الصفير


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

- selective B2 agonist
- Methylxanthines
- Anticholinergics [M · Antagonist]

Breath Calm and Stay Alive
B2 Agonist — Corticosteroids — Supportive — Anti inflamatory

2- Anti-inflammatory drugs

- Corticosteroids
- Mast cell stabilizers
- Omalizumab
- Leukotriene antagonists → main mediator in Bronchial Asthma

3- Supportive treatment

- Mucolytics & expectorants → (طارد بلغم) — Lysis ←
- Antimicrobials → inflamation with infection
- Oxygen inhalation

Bronchodilators

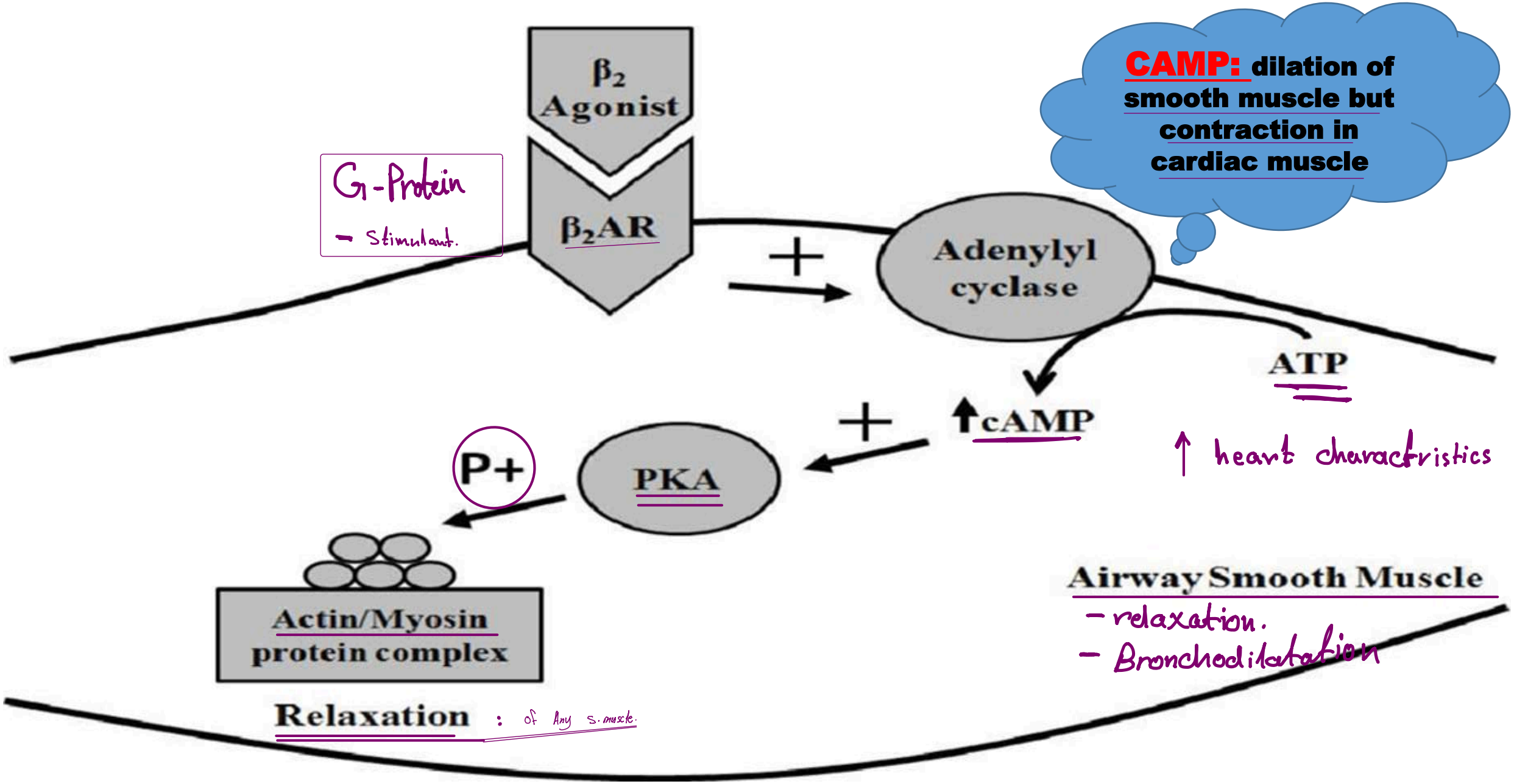
1- β_2 agonists

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

Antidot for Histamine

Selective β_2 agonists:

- **Short-acting:** salbutomal, terbutaline (4-6 H) 3/day
- **Long acting:** salmeterol and formeterol (12 H) 2/day


CAMP: dilation of smooth muscle but contraction in cardiac muscle
β2 Agonist
G-Protein
- Stimulant.
β2AR
+
Adenylyl cyclase
ATP
cAMP
↑ heart characteristics
+
P+
PKA
Actin/Myosin protein complex
Airway Smooth Muscle
- relaxation.
- Bronchodilatation
Relaxation : of Any S. 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 → better

1) Terbutaline: Short acting beta2 agonist (SABA)

- Like salbutamol but has a delayed onset of action (15 minutes)

Quick releiver

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:

1) ▪ Tremors → [↑ Ach release] → increase transmition at Neuromuscular junction

2) ▪ Tachycardia: Arrhythmia may occur in patients with underlying cardiac diseases eg, ischemic heart disease

[Any drug will loss slectivity when the dose ↑↑]

3) ▪ Tolerance → [No response]

4) ▪ Hypokalemia · uptake from blood to tissue → ↑k

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)

High Toxicity

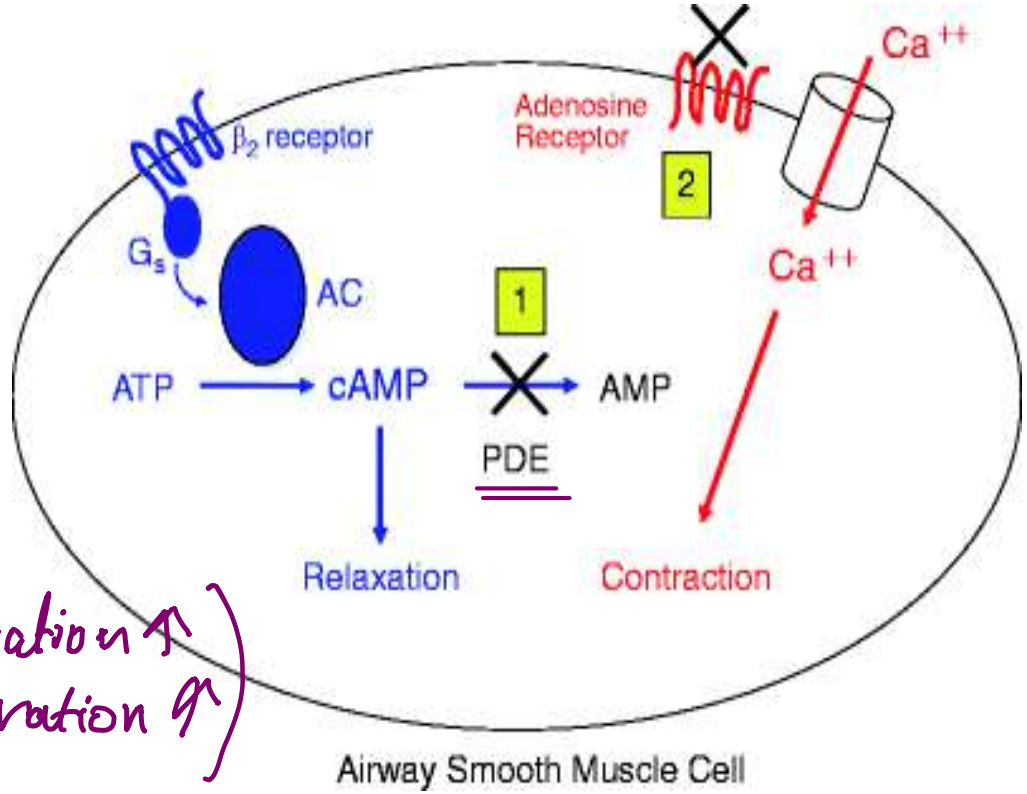
short - Acting

long Acting

Mechanism of action:

CAMP↑ → [Bronchodilatation.]

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

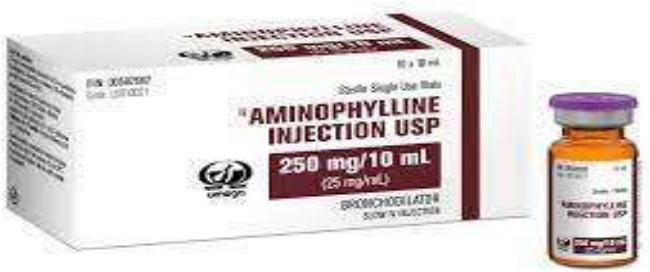


Pharmacokinetics:

↑↑ Lipid soluble

Side effect: Palpitation
- Hypotension
- tachycardia
- Arrythmia.

- 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



- Block of Adenosine Rec will Cause Bronchodilate

Pharmacological actions:

- **Relaxation of the smooth muscle** (bronchial, intestinal, biliary, ureteric and vascular smooth muscles "except cerebral blood vessels" → vasodilatation and hypotension)
  - Vasoconstriction here.
- **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

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

3- Muscarinic (M) Antagonists

M3: contraction

↳ Non ionized, ✓ Pass B.B.

- **Atropine (tertiary amine)** blocks bronchial M receptors, but it is **not effective in bronchial asthma** because:
  1. Cholinergic pathways play a minor role in the pathogenesis of bronchial asthma
  2. Non-selective effects:
     - Dryness of bronchial secretions (injury)
     - ↓? Muco-ciliary function

- **Ipratropium bromide:** (Same Atropine, More selective)

  - ✔ Quaternary ammonium derivative of atropine (ionized)
  - ✔ 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

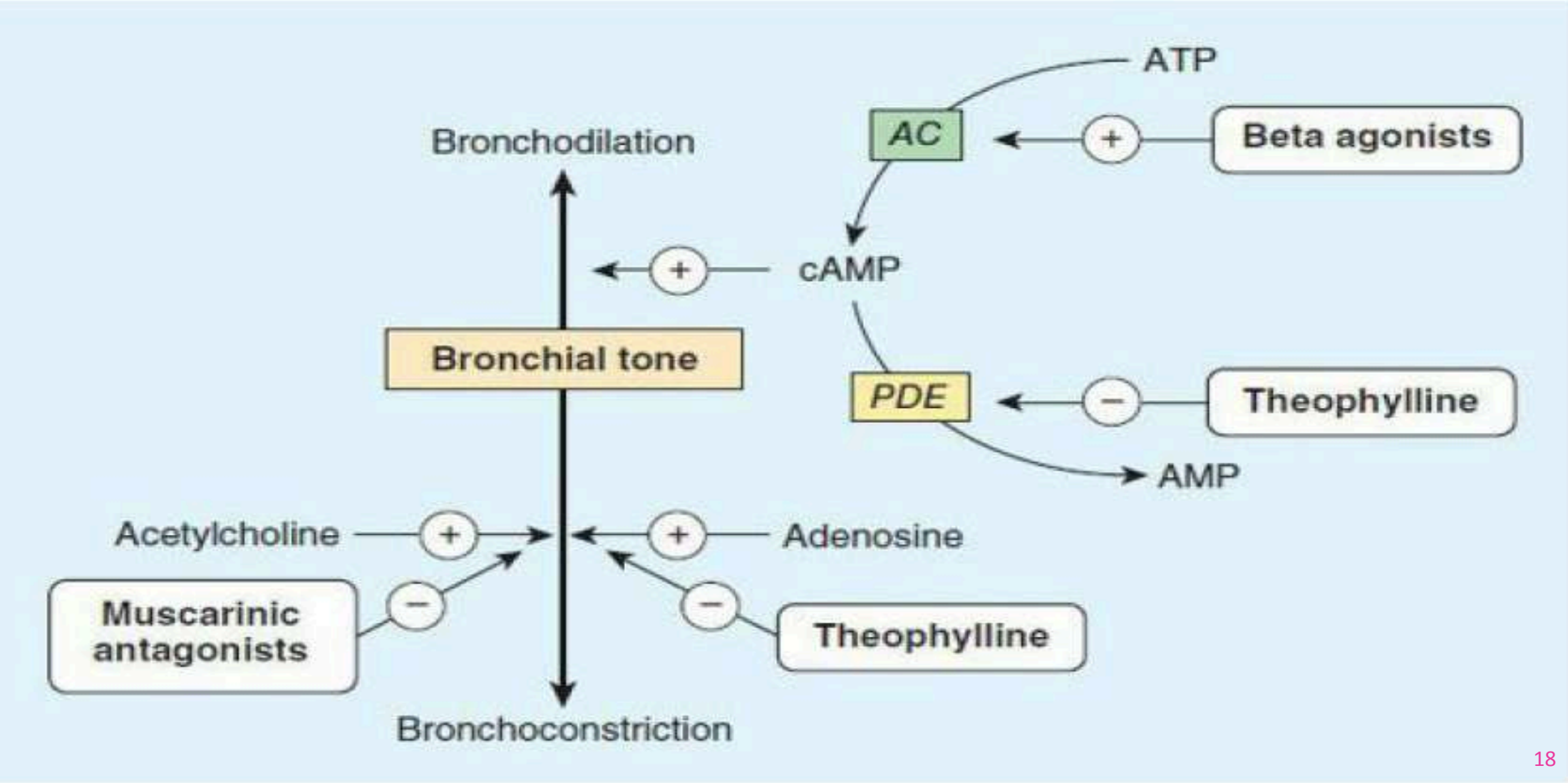
- **Tiotropium** differs from ipratropium in the following

  ✔ **Long-acting** (given once/day)

  ✔ Given by inhalation

  ✔ Approved for treatment of **COPD with no cardiac adverse effects.**

Bronchodilators



Anti-Inflammatory Drugs

→ mainly in between Attack for long lasting

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 → ليلي
  → severe inflamation
- ✔ Acute severe asthma

Preparations:

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

B. **Parenteral: methylprednisolone, hydrocortisone**, dexamethasone, 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

(Cu, Bu)

- **They include:**

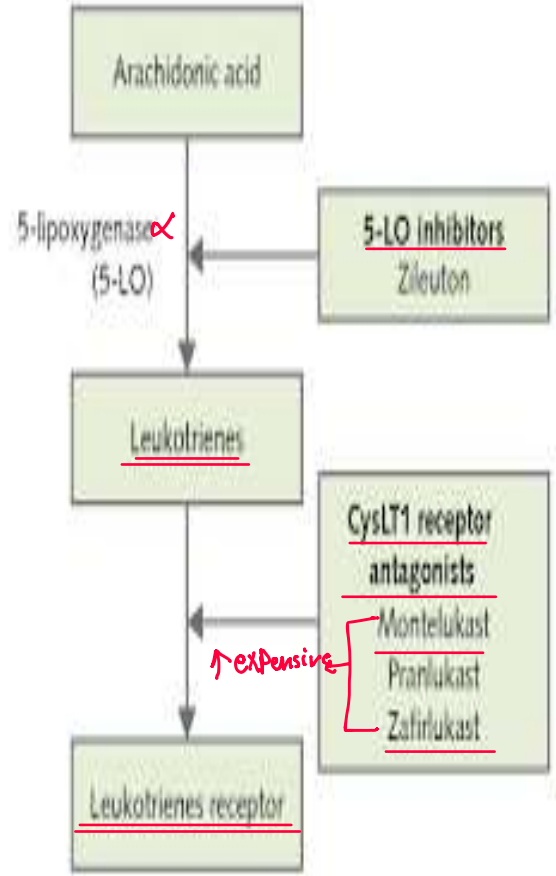
1. **LT receptor antagonists** (Montelukast & zafirlukast)
2. **5-LOX inhibitors** (zileuton): ↓ LTs synthesis ↓

- **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

. are inflimation of vesseles

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

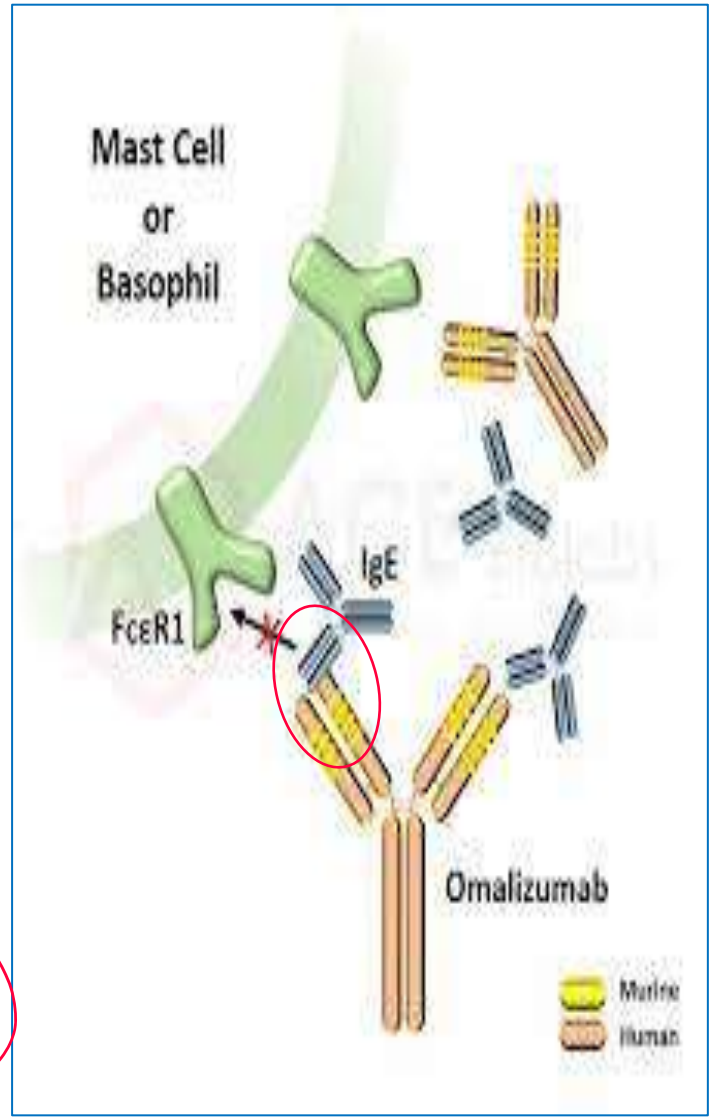
✔ **Mechanism:** stabilization of mast cell membrane (possibly by blocking calcium influx) ↓ release of allergic mediators eg, histamine & LTs.

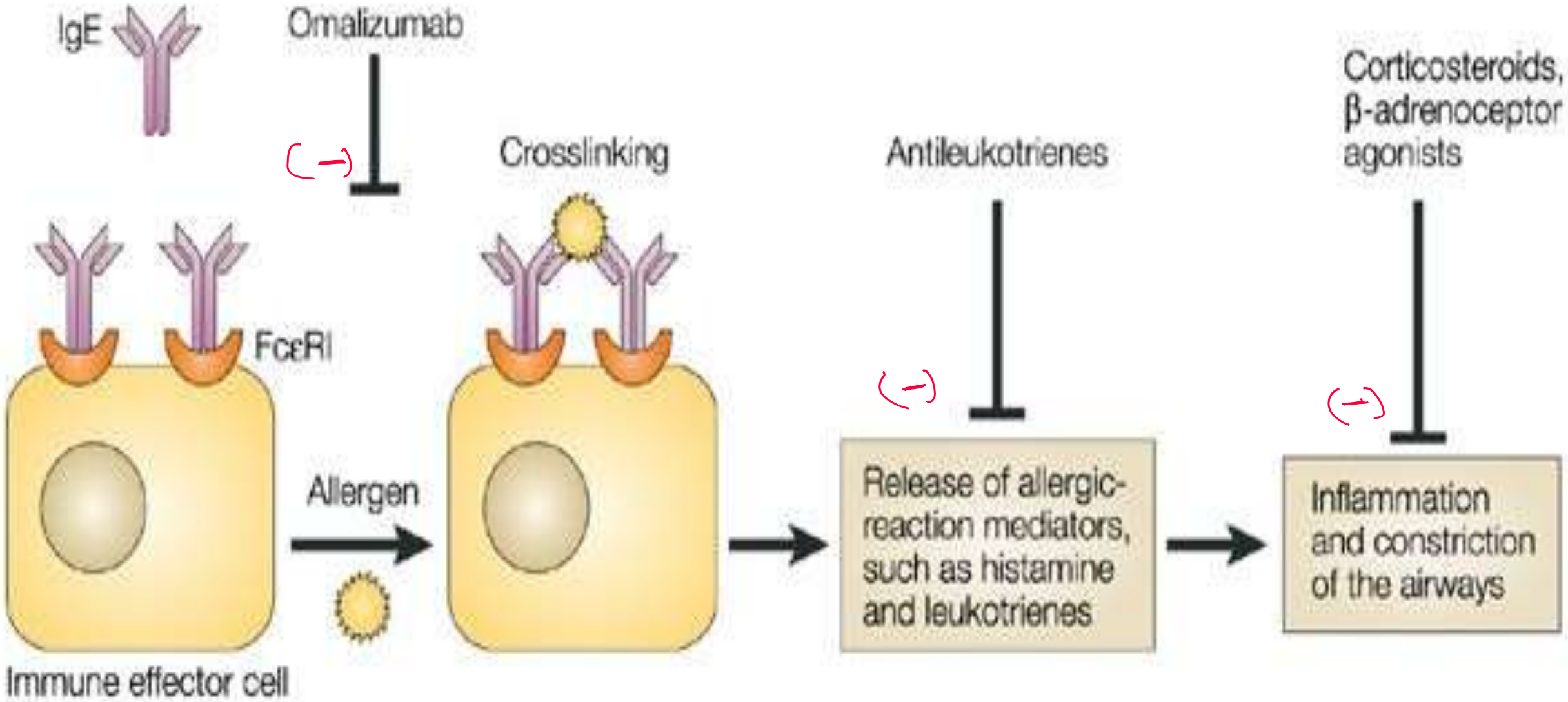
- ✔ They are useful chiefly for asthma prophylaxis, particularly children & young adults
- ✔ Ketotifen has additional antihistamine effect
- ✔ **Route:**
  - **Disodium cromoglycate:** inhalation
    - ❖ It is also available as nasal spray for **allergic rhinitis & as eye drops for allergic conjunctivitis**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

4-Omalizumab

→ most recent drug

- ✔ 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 , Not Bronchodilator.





Nature Reviews | Drug Discovery

Bronchial Asthma Prophylaxis

- ✔ **Control of predisposing factors** (برد , exercise)
- ✔ **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:** ... أقوى دوا من كل نوع - emergency.

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

less than 3 weeks.

لح أعطيه كمان :-

Magnesium Citrate (Mg Citrate)

- Powerful s. muscle relaxent

References

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تقبل الله شهداء
أهل غزة
ورفع منزلتهم،
لاتنسوهم من
دعائكم