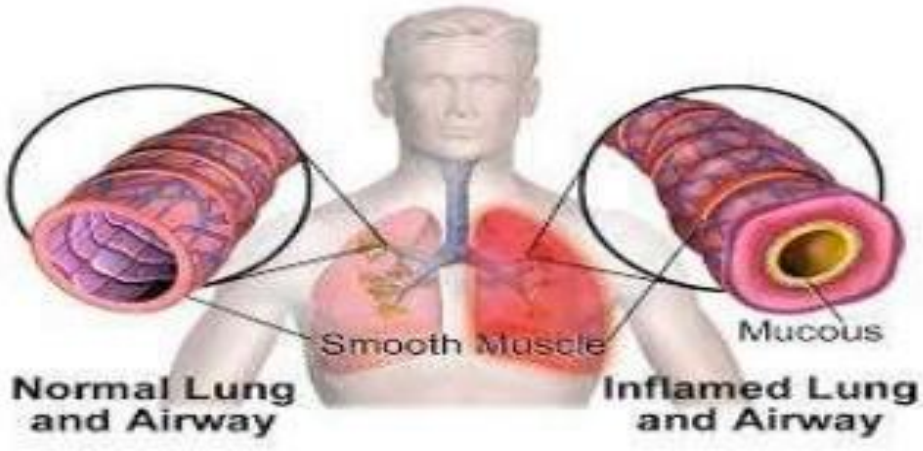
ASHTHMA

ASTHMA DEFINITION

Asthma is defined as a chronic inflammation disease of airway that is characterised by increase responsiveness of tracheobronchial tree to a multiplicity of stimuli.

Extrinsic: episodic , atopy

Intrinsic: perennial , status asthmaticus.



CAUSES

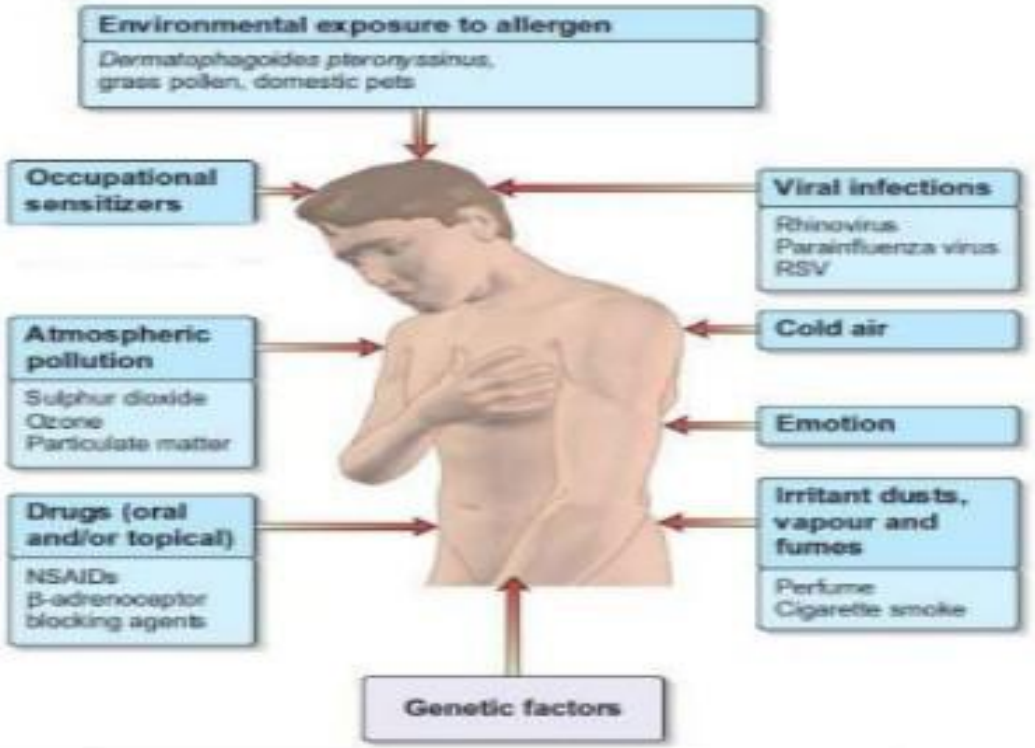
Asthma may be triggered because of :

1)Environmental Factors:

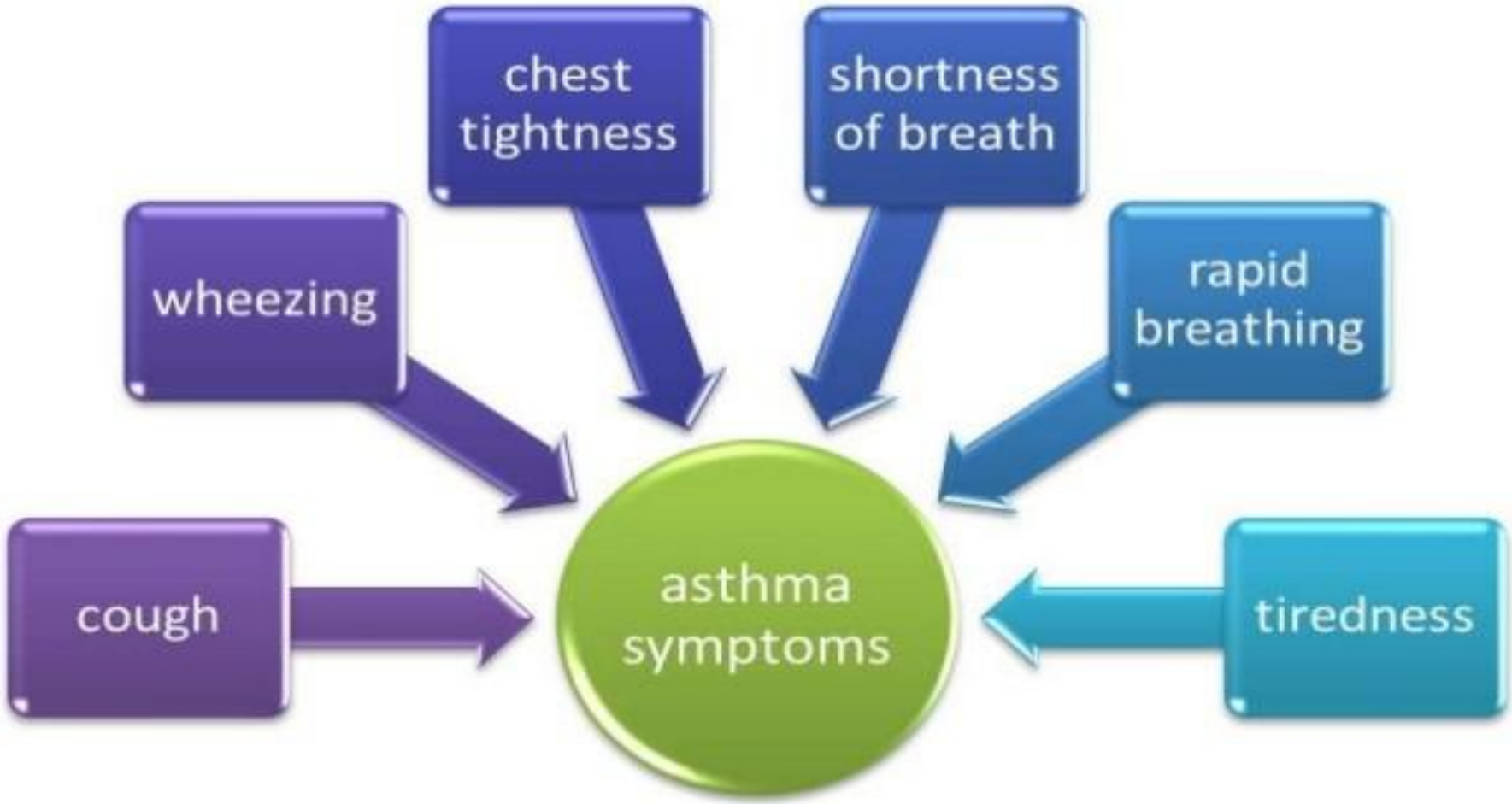
- Air pollutants
- Smoking
- Dust
- Pets
- Chemicals

2)Genetic Factors:

- Family history
- Certain genes



SYMPTOMS


chest tightness
shortness of breath
wheezing
rapid breathing
cough
asthma symptoms
tiredness

ETIOLOGY OF ASTHMA:

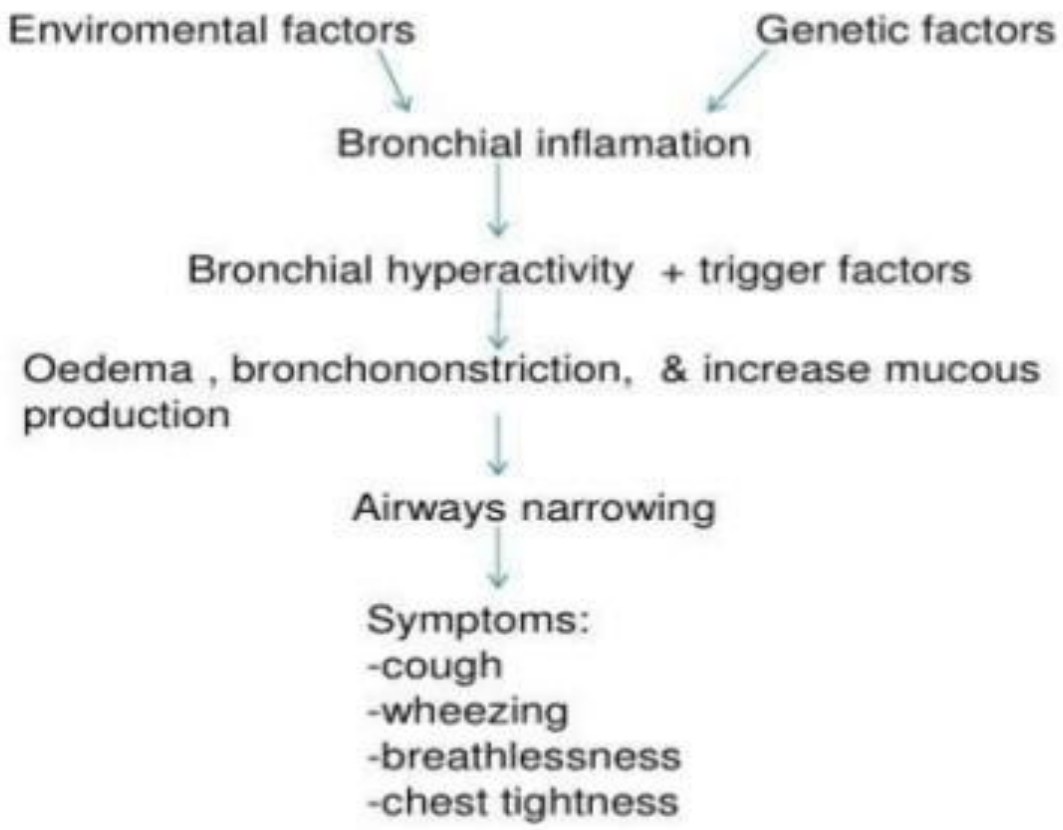
- **Genetic factors**
- **Environmental factors**
  a) House dust mites
  b) Exposure to tobacco smoke.
  c) Predisposed to animals, pollens moulds and dust.
- **Dietary changes** – junk food and fast food contain MSG

- **Lack of exercise** - Less stretching of the airways
- **Occupational exposure**
  - Irritants in the workplace : chemicals, dusts, gases, moulds and pollens. These can be found in industries such as baking, spray painting of cars, woodworking, chemical production, and farming.
- **Atopic diseases** – eczema and allergic rhinitis.
- **Maternal status** – both physical and mental conditions like anaemia and depression in the mother are associated with asthmatic stress for the child.
- **Early antibiotic use** – babies who are given antibiotics may be 50% more likely to develop asthma by the age of six

TYPES

- Extrinsic Asthma (Allergic)
- Intrinsic Asthma (Non- Allergic)
- Mixed Asthma (Extrinsic and Intrinsic)
- Occupational Asthma
- Drug Induced Asthma
  - Aspirin Induced Asthma
  - NSAID Induced Asthma
- Exercise Induced Asthma
- Cough Variant Asthma
  - Very Common (Especially in children)

Pathogenesis of asthma



Classification

- Bronchodilators
  - β Sympathomimetics: Salbutamol, Terbutaline, Bambuterol, Salmeterol, Formoterol, Ephedrine.
  - Methylxanthines: Theophylline (anhydrous), Aminophylline, Choline theophyllinate, Hydroxyethyl theophylline, Theophylline ethanolate of piperazine, Doxophylline.
  - Anticholinergics (muscarnic receptor antagonist): Ipratropium bromide, Tiotropium bromide.
- Leukotriene antagonists: Montelukast, Zafirlukast.
- Mast cell stabilizers: Sodium cromoglycate, Ketotifen.
- Corticosteroids
  - Systemic: Hydrocortisone, Prednisolone and others.
  - Inhalational: Beclomethasone dipropionate, Budesonide, Fluticasone propionate, Flunisolide, Ciclesonide.
- Anti-IgE antibody: Omalizumab

BRONCHODIALATORS

A **bronchodilator** is a substance that dilates the bronchi and bronchioles, decreasing resistance in the respiratory airway and increasing airflow to the lungs. Bronchodilators may be endogenous (originating naturally within the body), Bronchodilators are either short-acting or long-acting.

e.g : Salbutamol, Theophylline, Ipratropium bromide.

M.O.A :

- Increase levels of energy- producing cAMP.
- This is done competitively inhibiting phosphodiesterase (PDE), the enzyme that breaks down cAMP.
- Result: decreased cAMP levels, smooth muscle relaxation bronchodialation, and increased airflow.

Contd…..

Therapeutic uses:

- Dilation of airway in asthma, chronic bronchitis, & emphysema
- Mild to moderate cases of asthma
- Adjunct therapy for the relief of pulmonary edema.

Side effects:

- Nausea , vomiting , anorexia
- Gastroesophagal reflux during sleep
- Sinus tachycardia , extrasystolic , palpitations , ventricular dysrhythmias
- Transient increased urination.

LEUKOTRIENE ANTAGONISTS

An Leukotriene antagonists is a drug which functions as a leukotriene-related enzyme inhibitor (arachidonate 5-lipoxygenase) or leukotriene receptor antagonist and consequently opposes the function of these inflammatory mediators; leukotrienes are produced by the immune system. Leukotriene receptor antagonists, such as montelukast, zafirlukast can be used to treat these diseases. They are less effective than corticosteroids for treating asthma,but more effective for treating certain mast cell disorders.

M.O.A:

Montelukast , zafirlukast are competitively prevent the bronchoconstrictor effects of leukotrienes

- By blocking their receptor
- Prevent leukotrienes from attaching to receptor on cells in the lungs and in circulation
- Blocking the inflammation in the lungs.

Contd…..

Kinetics:

The half life of Leukotriene antagonists is less than 5 minutes.

Side effects:

- Headache
- Stomach pain, heartburn, upset stomach, nausea, diarrhea
- Tooth pain
- Tired feeling
- Fever, stuffy nose, sore throat, cough, hoarseness
- Mild rash.

Uses:

Prophylaxis and chronic treatment of asthma.

Mast cell stabilizers
Cromolyn - Nedocromil

- Act by stabilization of mast cell membrane
- Have poor oral absorption
- Given by inhalation
- Not bronchodilators
- Not effective in acute attack of asthma
- Prophylactic anti-inflammatory drugs
- Children respond better than adults

Mast Cell Stabilizers

- Intal (cromolyn)

Blocks histamine from mast cells esp.

For exercise-induced asthma - ok for kids > 2 years

- Tilade (nedocromil)

Blocks eosinophils, neutrophils, macrophages AND mast cells

Use with corticosteroids, only for those over 12 years old

Uses

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

Side effects

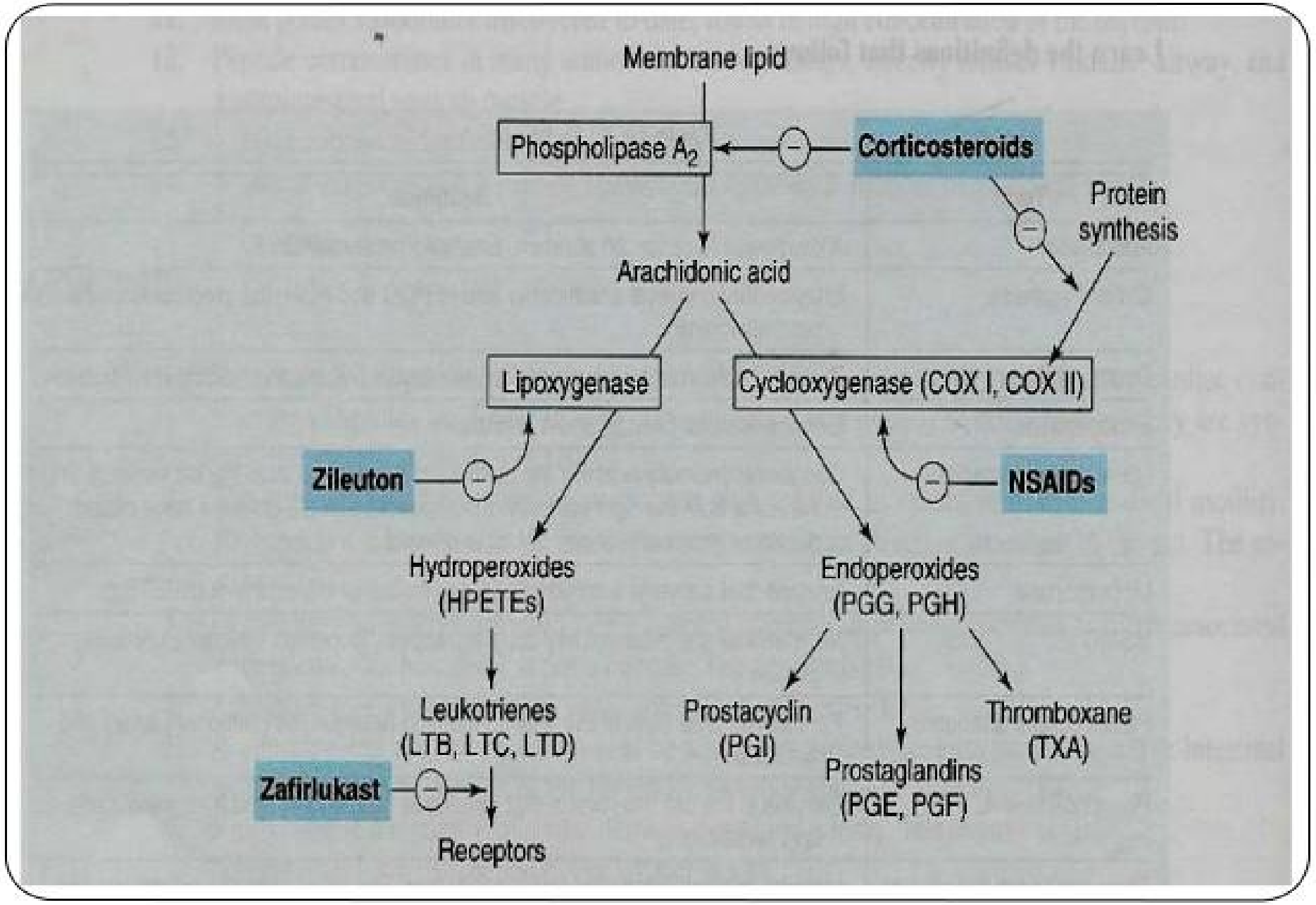
- Bitter taste
- minor upper respiratory tract irritation (burning sensation)

Corticosteroids

- Are not bronchodilators
- Given as prophylactic medications, used alone or combined with beta-agonists

Mechanism of action

- Inhibition of phospholipase A2 → ↓ prostaglandin and leukotrienes
- Mast cell stabilization →↓ histamine release
- Upregulation of β2 receptors


Membrane lipid
Phospholipase A_2
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

Side effects of systemic corticosteroids

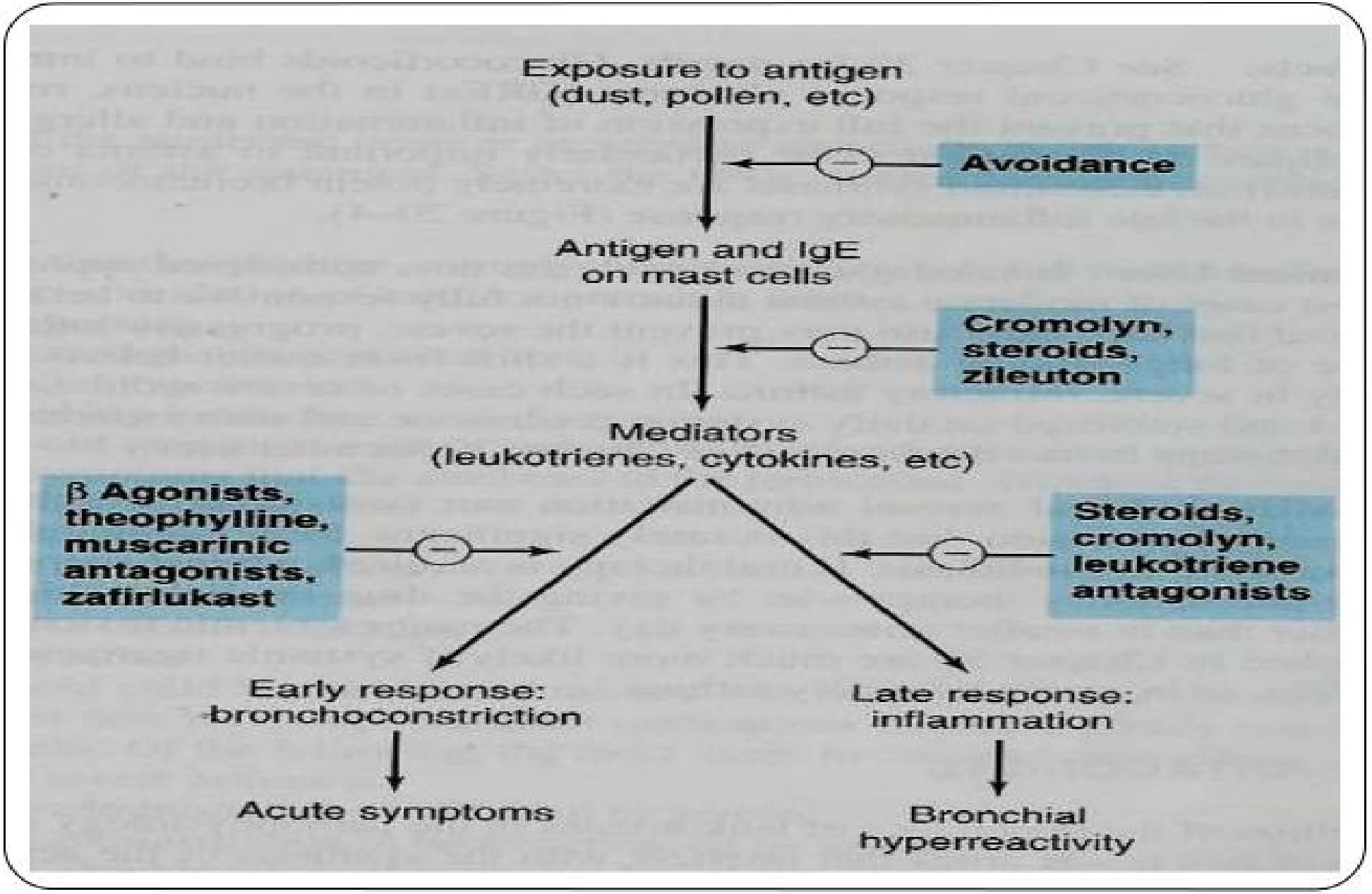
- Adrenal suppression
- Growth retardation in children
- Osteoporosis
- Fluid retention, weight gain, hypertension
- Hyperglycemia
- Susceptibility to infections
- Glaucoma
- Cataract
- Fat distribution, wasting of the muscles
- Psychosis

Anti-IgE antibody
Omalizumab

- A monoclonal antibody directed against human IgE

- It binds to the IgE on sensitized mast cells and prevents activation by asthma triggers and subsequent release of inflammatory mediators

- Expensive-not first line therapy


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

Recent Advances in the Treatment of Asthma

- Novel class of bronchodilators
- Immunomodulatory therapies
- Newer anti- inflammatory therapies
- Mediator antagonists
- Miscellaneous approaches
  - Cytokine modifiers
  - Chemokine Receptor antagonist.

Aknowledgment

References

1)Essentials of Medical Pharmacology,6 edition, K.D Tripathi,Pg 213-22

2)Text book of Pathology ,Sixth edition,Harsh Mohan,Pg 483-484