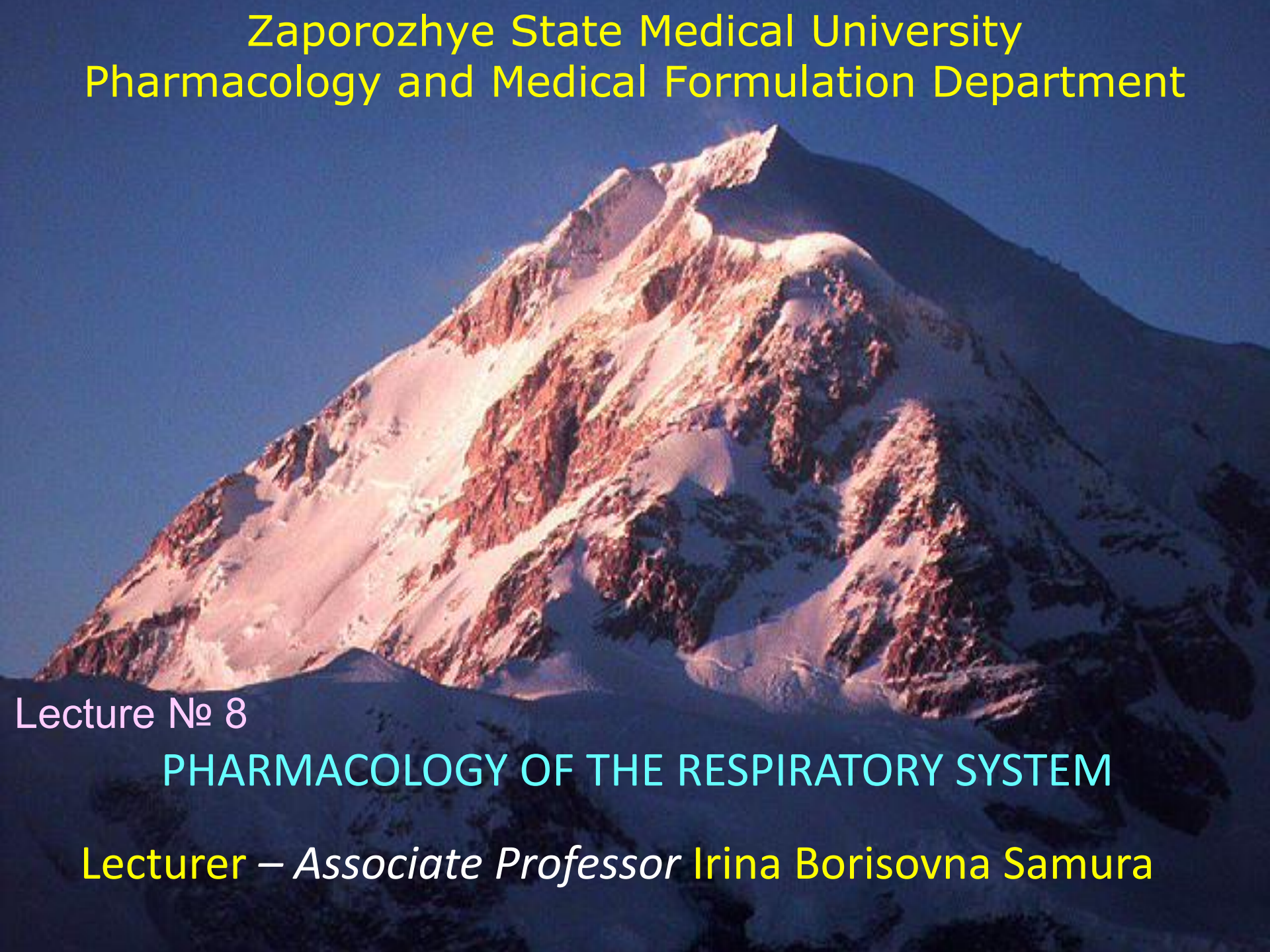
Zaporozhye State Medical University
Pharmacology and Medical Formulation Department



Lecture № 8

PHARMACOLOGY OF THE RESPIRATORY SYSTEM

Lecturer – *Associate Professor* Irina Borisovna Samura

Respiratory Stimulants

1. Activating Respiratory Center Directly:

Caffeine

Bemegride – amp. 0.5% - 10 ml

Etimizol – amp. 1.5% - 3 ml, Tab. 0.1 g

2. Reflex Action:

Cytiton

Lobeline hydrochloride

Ammonia solution

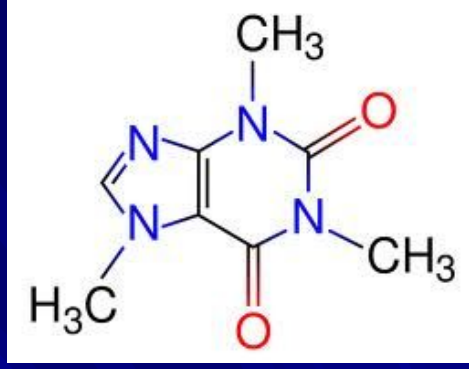
3. Mixed Type of Action:

Cordiamin (***Nikethamide***) – amp. 1 ml, vial 15 ml

Sulfocamphocaine – amp. 10% - 2 ml

Carbogen (***Carbon dioxide***) **-** gas bottles

Mechanisms of Action of Caffeine



1). Blockade of *Phosphodiesterase* => and ⇑*cGMP*

2) Blockade of *Adenosine Receptors*

ADENOSINE –

- an Inhibitory Transmitter of the CNS
- inhibits Adenyl Cyclase activity, causing Contraction of Airway Smooth Muscle

Cordiamin (*Niketamide*) amp. 1 ml, vial 30 ml – an analeptic of ***mixed*** **action**

- **Direct Exciting influence** on **Respiratory Center**
- **Stimulates N-Receptors of Carotid Sinus**

- Acceleration and Deepening of Respiration
- **↑HR, ↑BP**

Clinical uses:

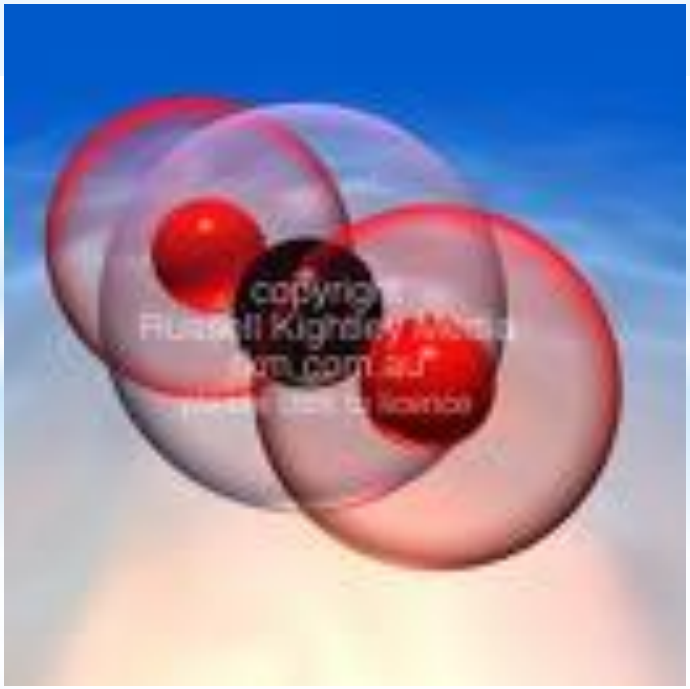
Respiratory failure in Shock, Collapse, Asphyxia;
Respiratory depression in Infectious diseases;
Prophylaxis of lung atelectasis and pneumonia

Adverse effects: clonic seizures, face hyperemia

Carbogen – is a mixture of **93-95% O_2** with *Carbon dioxide* **5-7% CO_2**

It is used in anesthesia for inhalation.

Addition CO_2 to the O_2 => *stimulation* of *Respiratory Center* and much better using of O_2



Clinical Uses of Breathing Stimulants

Acute Respiratory Failure :

- **Asphyxia** (*Respiratory Arrest*) **in** ***newborns*** and during ***surgical operations***
- **Aggravation** of

  Chronic Obturating Bronchial Diseases with

  sleepiness, inability to cough out
- **Respiratory depression** during

  Infectious Diseases, Shock, Syncopal Conditions
- During ***surgical operations***
- **Poisons** with ***Hypnotic drugs, Opioid Analgesics, General Anesthetics***

Antitussive Drugs

I. Central Cough Suppressants:

1. With opioid mechanism of action:

Codeine

Ethylmorphine

Dextromethorphan

2. With non-opioid mechanism of action:

Glaucine

Tusuprex

Broncholytin

II. Peripherally Acting Drugs:

Libexin, Falimint

Codeine (***Methylmorphine***) - an opioid alkaloid

Analgesic properties –

agonist activity at the ***opiate receptors***

Antitussive action – a direct suppressive action on

the ***cough center*** and **mucosal secretion**.

Delay gastric empting,

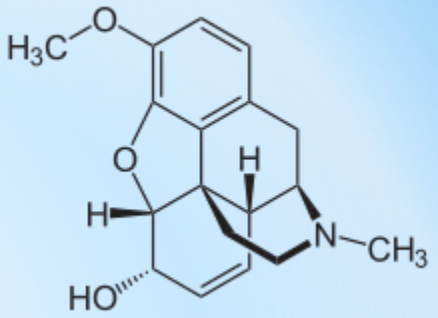
- Plasma *Amylase* and *Lipase* levels,
- Biliary tract pressure resulting from contraction of the sphincter of Oddi.

May produce **dependence** (*psychiatric and physical*).

Adverse effects: euphoria, hypotension, bradycardia, constipation, urine retention, physical dependence

- Tablets Codeine: 0.015 g

  with *Sodium Bicarbonate*



- Tablets “Codterpine”:

  Codeine 0.015 g

  Sodium Bicarbonate 0.25 g

  Terpine hydrate 0.25 g

- ”Tablets for Cough”:

  Codeine 0.02 g

  Sodium Bicarbonate 0.2 g

  Thermopsis grass 0.01 g

  Licorice root 0.2 g.

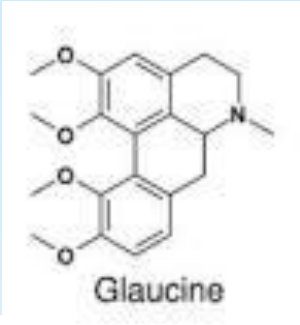
Glaucine hydrochloride – *Tab. 0.05 g –*

It is an **alkaloid** from the **Yellow Poppy** plant ***Glaucine*** (***Glaucium Flavum***) and may also **be synthetically derived**.

It is a powerhouse ingredient in the reduction of cough.

Mechanism of action:

- inhibits the ***Central Link*** of the ***Cough Reflex.***



Broncholytin - ***Syrup 125 ml –***

a complex antitussive drug.

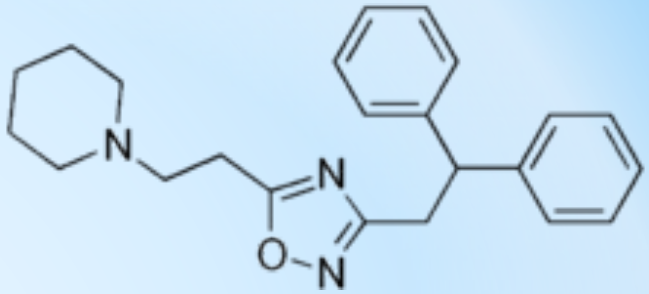
125 ml of syrup contains:

Glaucine 0.125 g

phedrine 0.1 g

asil Oil 0.125 g

Libexine (*Prenoxdiazine*)- *Tab.* 0.1 g - a synthetic **Antitussive of Peripheral Action**



Mechanism of action:

- inhibits the ***Peripheral Link*** of the ***Cough Reflex***.
- Anesthesia of Mucous Membrane of upper Respiratory Tract
- Broncholytic properties

EXPECTORANTS

I. BRONCHOSECRETOR DRUGS:

1. **Reflex** type of action:

Thermopsis *Grass* ***Infusion***: (0.6 – 180 ml)

Althaea *Root* ***Decoction*** : (6.0 – 180 ml)

2. **Resorptive** type of action:

Potassium Iodide [KI]: *0.3-1 g PO as*

3% solution 1 tbsp. 3-4 times a day.

Sodium Bicarbonate [$NaHCO_3$]

Mucaltin (*tab. 0.05 g*)

II. **Mucolytic Drugs** – convert ***sticky*** and ***viscous*** ***sputum*** to more liquid one and **promote** its **easier release**.

1. Activating Hydrolytic Enzymes in Sputum:

Acetylcysteine *(ACC)* - *amp. for inhalation 20%-10 ml, amp. for injection 10%-2 ml , tab 0.5 mg*

2. Activating Hydrolytic Enzymes and Endogenous Surfactant Production:

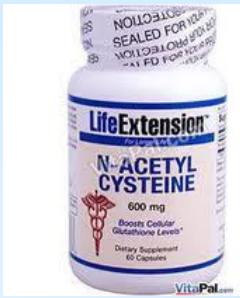
Bromhexine -*Tab. 0.004 and 0.008 g*

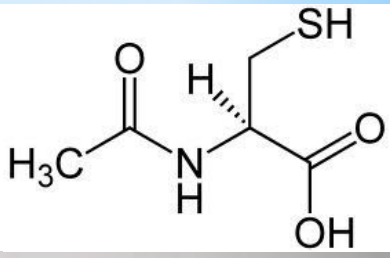
Ambroxole -*Tab. 0.03 g; syrup 0.3%-100 ml*

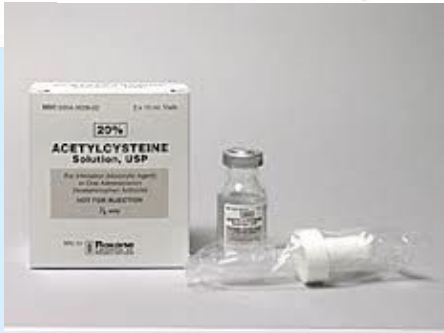
Acetylcysteine (*ACC*) -

an **mucolytic of direct action**

It is administered by *Nebulazation, PO, Direct Application, or Intratracheal Instillation*.







<u>Mechanism of Action:</u>

ACC splits the disulfide (-S-S-) bonds of mucoproteines, responsible for **increased viscosity** of **mucus secretions** in the **lungs** - secretions become *less viscous* and *more liquid*.

ACC is a *Paracetamol* antidote.

<u>The mechanism</u>:

- **Restores** hepatic stores of **Glutatione** – important in biological oxidations and the activation of some enzymes.

  Formula: $C_{10}H_{17}N_3O_6S$

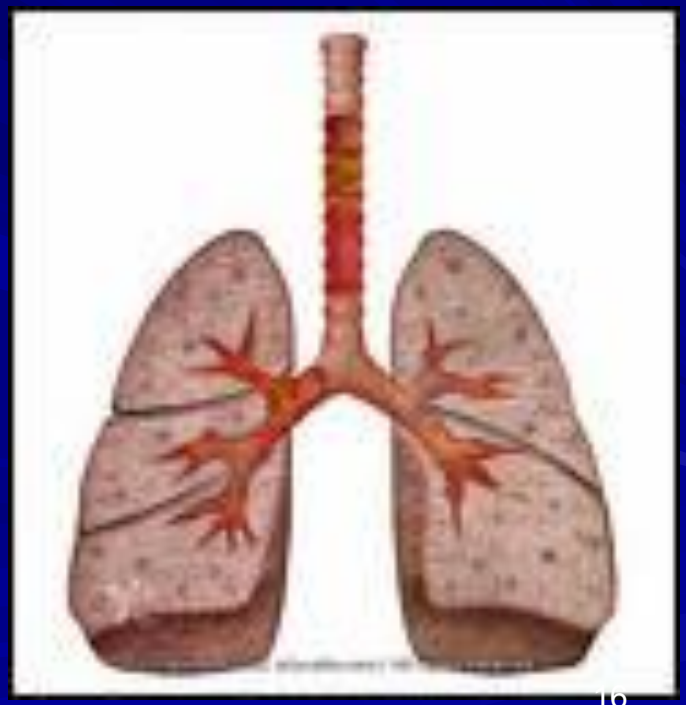
- **Inactivates** the Toxic Metabolites

  Preventing Liver Damage

ANTIDOTE

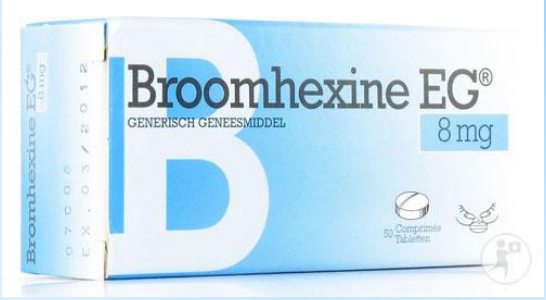
Clinical uses of ACC:

- Acute and chronic broncho-pulmobary diseases
- Tracheostomy care
- Pulmonary complications of surgery
- Diagnostic bronchial studies



Bromhexine and ***Ambroxole*** –

are Mucolytic and Expectorant Agents:



Mechanism of Action:

=> **Depolymerization** of ***Mucoproteines*** and ***Mucopolysaccharides*** of **expectoration that induces its liquefaction.**

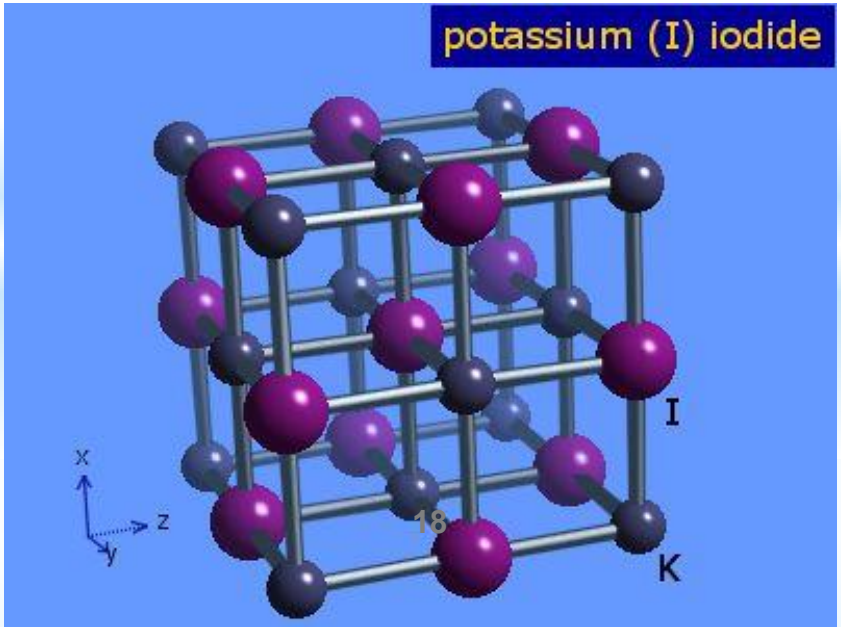
They also stimulate production of **Surphactant** - endogenous **Superficially Active Substance** produced in alveolar cells.

- **Normalize** Secretion of Bronchial Glands,
- **Improve** reological properties of ***sputum***,
- **Reduce** its viscosity,
- **Relieve** *excretion* of *sputum* from bronchi

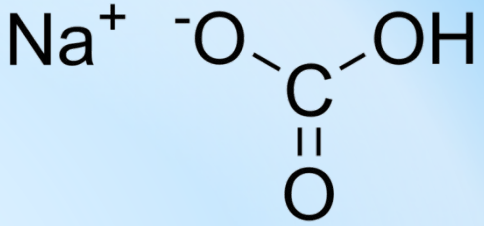
Potassium Iodide is an **Expectorant** and **Antihyperthyroid Agent**.

It reduces viscosity of mucus by increasing respiratory tract secretions.

In addition it acts directly on the **Thyroid Gland** to inhibit synthesis and release of **Thyroid Hormone**.



Sodium Bicarbonate -



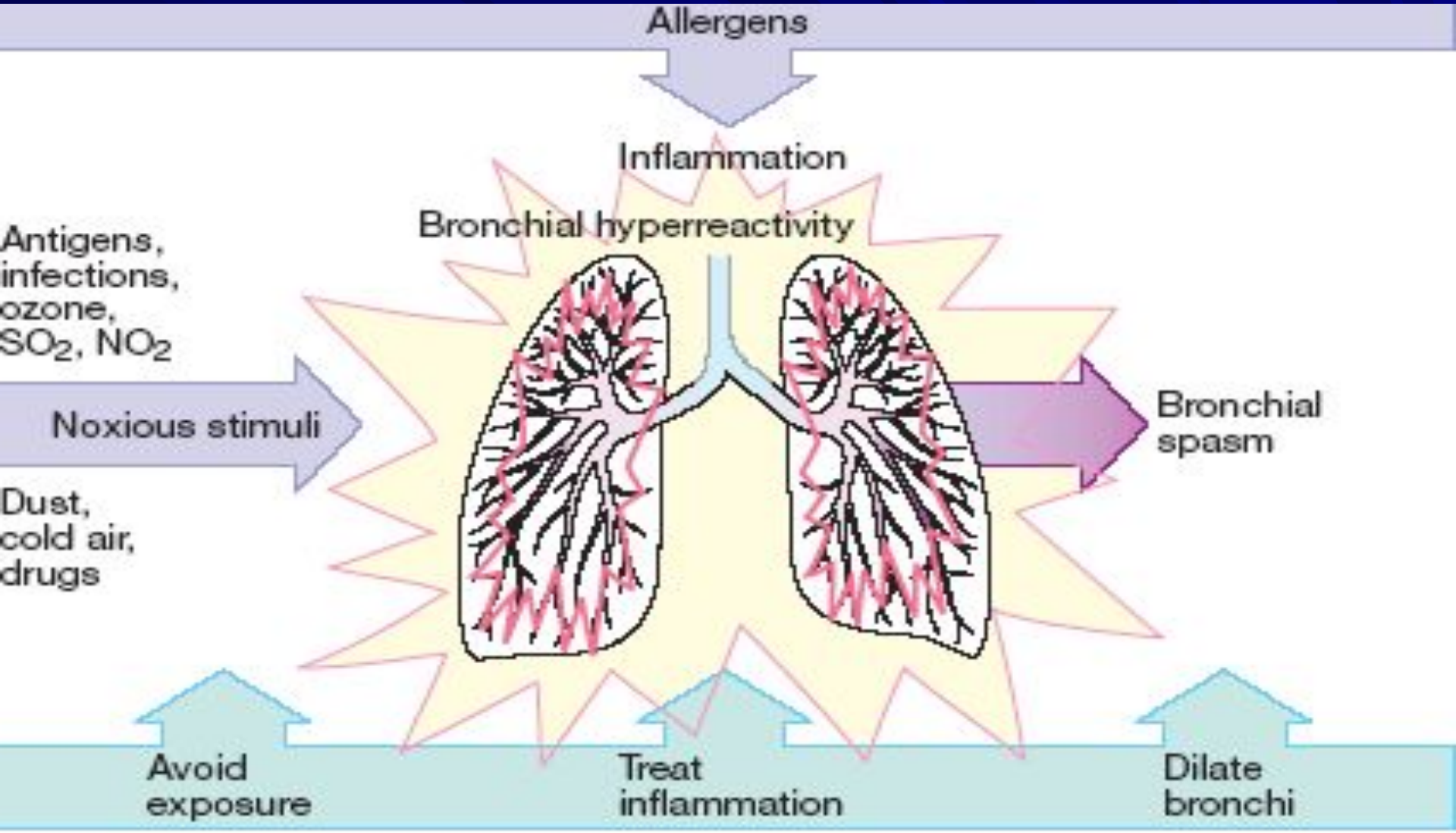
- Viscosity of mucus
- Bronchial secretions

Sodium Bicarbonate abuse have been associated with **Hypokalemic Hypochloremic Metabolic Alkalosis**.

Hypernatremia => water retention, weight gain, and edema, which may be important in patients with **CHF**, Renal Insufficiency, or Severe Liver Disease.

Metabolic side effects have included metabolic alkalosis, hypernatremia/hyperosmolarity, hypochloremia, and hypokalemia.

Side effects have rarely included **intravascular volume expansion** with resultant **Hyporeninemia** and **Hypoaldosteronemia**: the **plasma K+** may be **elevated**.



Bronchial asthma, pathophysiology and therapeutic approach

BRONCHODILATORS

1. Agents stimulating β_2 – adrenoreceptors of bronchi:

a) Selective β_2-adrenomimetics (AMs):

β_2 -AMs of Short action (4–6 hours):

Salbutamol

Terbutaline

Fenoterol

β_2 -AMs of Long action (> 12 hours):

Salmeterol

Formoterol

b) Non-selective Adrenomimetics:

Ephedrine, Adrenaline hydrochloride,

Isadrin, Orciprenaline sulfate (*Alupent*)

2. **Methylxanthines** – **Spasmolytics of direct action:**

a) **Theophylline** preparations with **short** period of action:

Theophylline

Euphylline (*Aminophylline*)

Oxtriphylline

b) **Theophylline** preparations with **long** period of action :

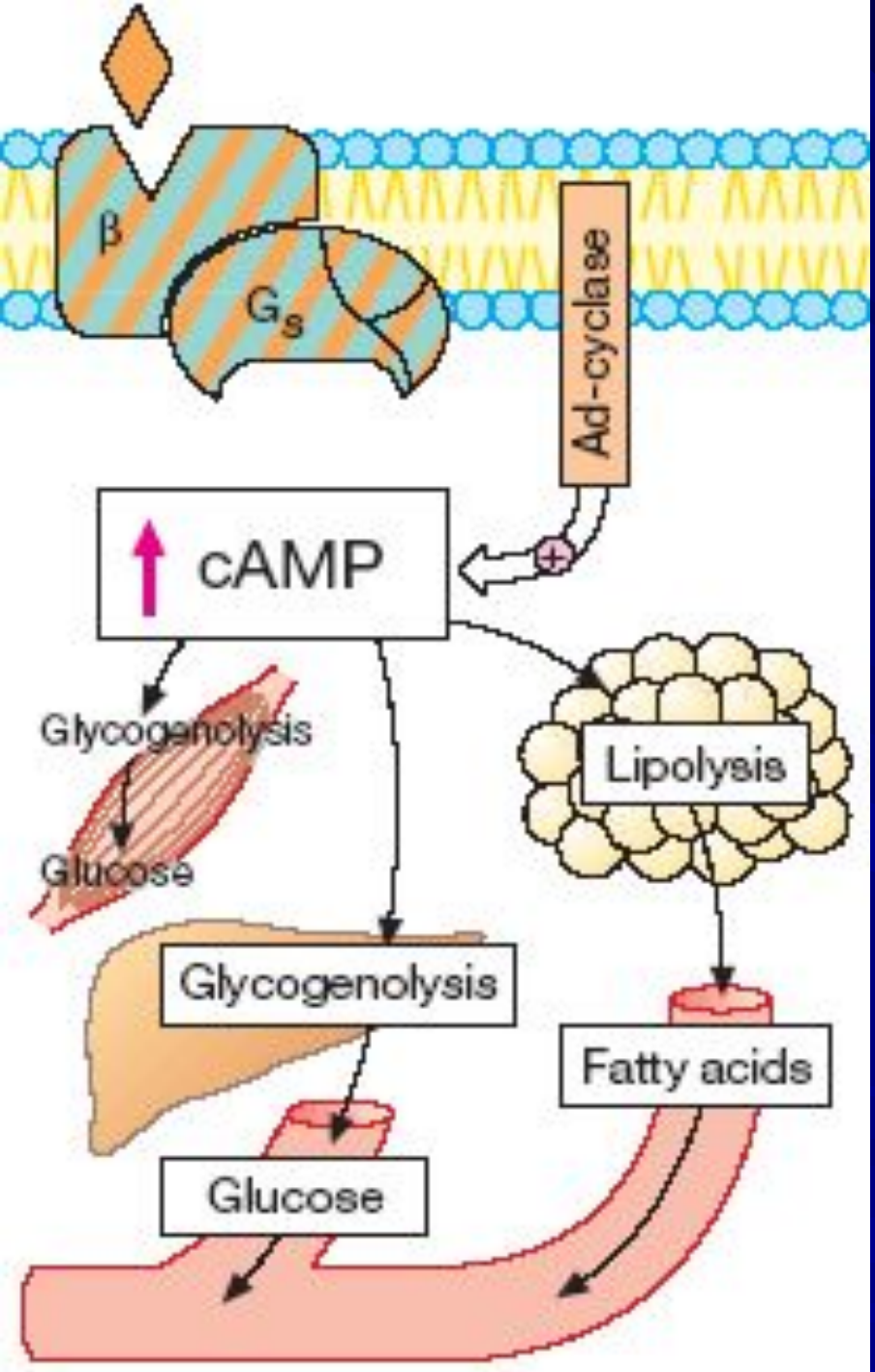
Theobilong, Theodur, Theotard, Durophyllin

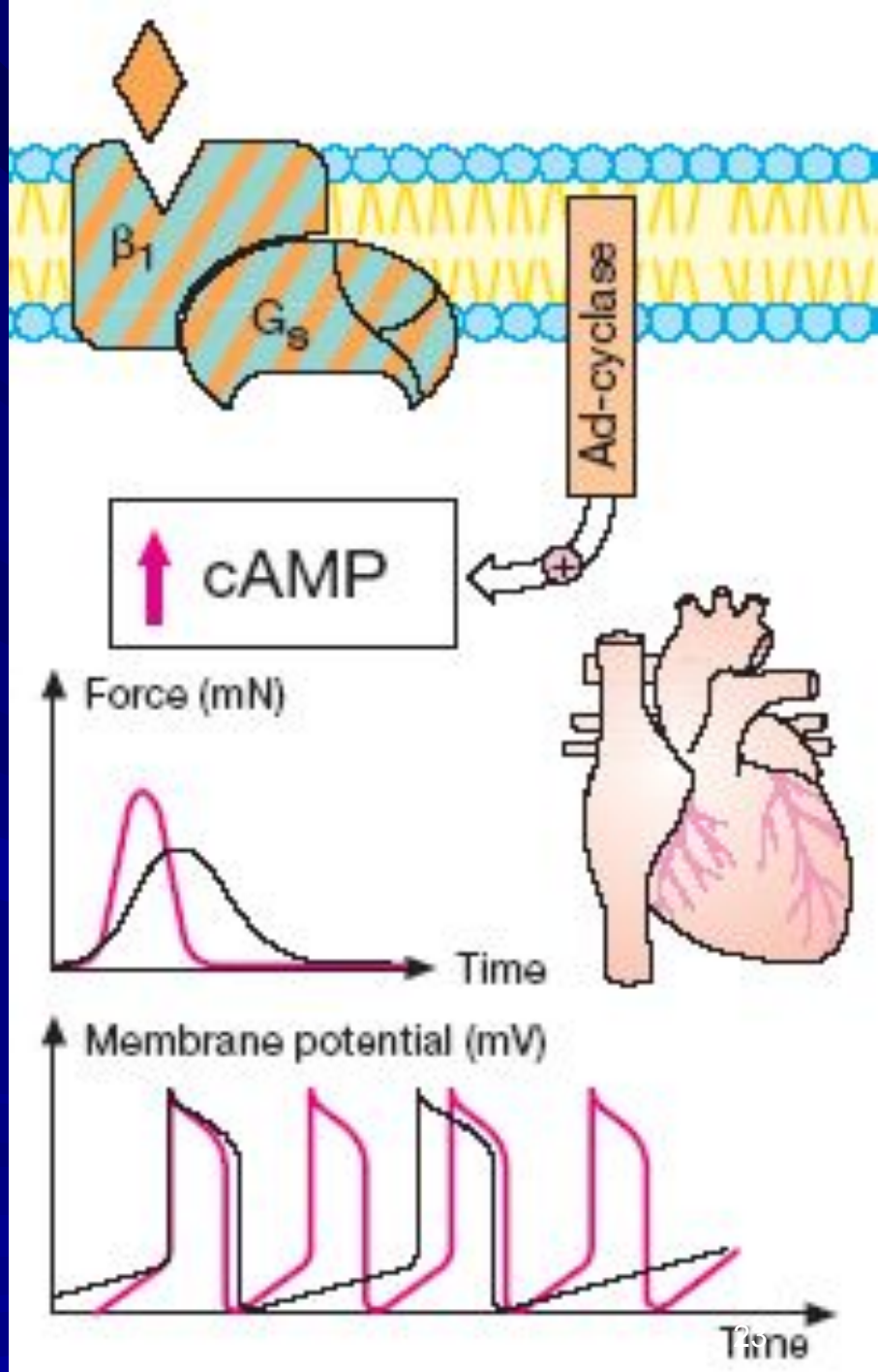
3. **M-cholinoblockers**:

Ipratropium bromide (*Atrovent*)

Tiotropium bromide

Oxitropium bromide


β
Gs
Ad-cyclase
cAMP
Glycogenolysis
Glucose
Lipolysis
Glycogenolysis
Fatty acids
Glucose


β1
Gs
Ad-cyclase
cAMP
Force (mN)
Time
Membrane potential (mV)
Time

Salmeterol and ***Formoterol*** - have **lipophilic** properties

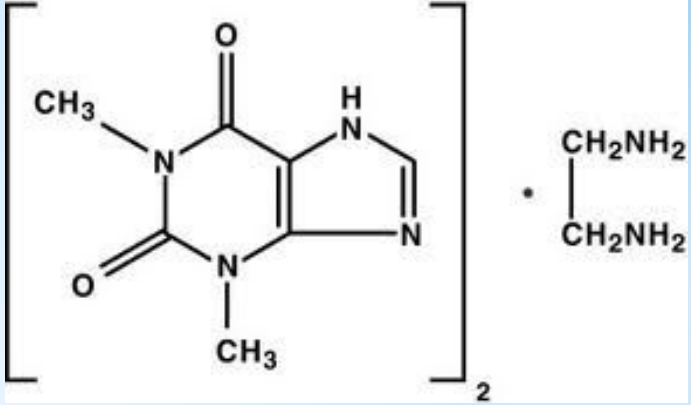
Salbutamol and **Fenoterol** have minor length (11 Angstrem**)** and **hydrophilic** properties.

These comparatively quickly "**wash out**" from receptor's area and their duration lasts 4-6 hours.

Salmeterol is long (25 Angstrem) molecule and exceeds *Salbutamol* in lipophility by dozens times.

The long chain is strongly attaching to the cell membrane and active center of the drug is capable to *activate receptor repeatedly* providing bronchodilation for 12 hours.

Aminophylline (*Euphylline*):
Theophylline 79%
Ethylenediamine 21% complex



Theophylline:

- inhibits PDE => ↑cAMP
- blocks Adenosine receptors

Anti-Inflammatory action:

It inhibits the late response to *antigenic challenge*, and withdrawal of *theophylline* causes worsening of asthmatic symptoms, a fall in spirometry, and significant in CD4+ and CD8+ Lymphocytes in bronchial biopsies

Clinical uses of Euphylline:

- Asthma, including IV in
  - Acute Severe Asthma
- Chronic Obstructive Pulmonary Diseases
- Acute Bronchospasm
- Left-Sided Heart Failure
- Severe Bronchospasm in Infants

Drugs with Anti-Inflammatory Activity

I. Steroid Anti-Inflammatory Drugs (SAIDs) – **Glucocorticoids:**

1. Natural - Hydrocortisone acetate

2. Synthetic with resorptive action –

Prednisolone, Dexamethasone, Triamcinolone

3. Synthetic with local action –

Beclometasone, Budesonide, Flunisolide, Fluticasone

II. Mast cell stabilizers:

Cromolyn sodium (*Intal -caps for inhalation 0.2 g*)

Nedocromil (*Nedocromil sodium – aerosol dosed: 2 mg/dose*)

Ketotifen (*tab. 1 mg*)

III. Leukotriene Modifiers:

1. Inhibitors of 5-lipooxygenase: Zileuton

2. Leukotriene Receptor Blockers: Zafirlukast, Montelukast

Mechanism of action of Glucocorticoids

Steroid hormones are lipid soluble and cross cell membranes easily.

- Once inside the cell, the hormone molecules bind with specific receptor proteins.
- The hormone–receptor complex enters the **nucleus** of the cell where it activates **Gene Expression –**

nucleic acids (DNA and RNA) and the Genetic Code to synthesize new proteins.

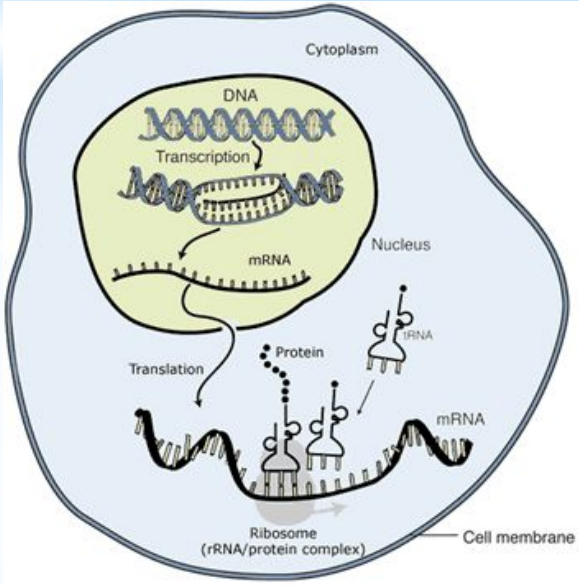


Image adapted from: National Human Genome Research Institute.

For Anti-inflammatory Action **GCs produce**:

· **Inhibition of transcription of the genes** for:

COX-2, **Cytokines** (***interleukins***), cell adhesion molecules and **the inducible form of *Nitric Oxide* synthase**;

· **Block** of **vitamin D_3-mediated** induction of the **osteocalcin gene** in **osteoblasts** and **modification of transcription** of the **Collagenase Gene**;

· **Increased synthesis** of **Annexin-1** (*Lipocortin-1*), which is important in the **negative feedback** on the hypothalamus and anterior pituitary and has **anti-inflammatory actions**.

!! **Annexin-1** blocks the release of ***Arachidonic Acid***, the **precursor** of the PGs and leukotrienes.

Pharmacological Effects of Glucocorticoids:

- Prostaglandin production due to decreased expression of COX-2;
- Generation of Cytokines – *IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8*, TNF-γ and cell adhesion factor – through **inhibition** of **transcription** of the **relevant genes**;
- level of ***Complement Components*** in the plasma;
- Generation of *Nitric Oxide,* IgG;
- **Histamine** release from basophils.

The anti-inflammatory effect of GCs takes **several hours** to become evident since **formation** of **Annexin-1** and other **active proteins** is relatively slow.

Glucocorticoids - do not relax airway smooth muscle directly but:

- Stimulate the synthesis of enzymes needed to inhibit Inflammatory Response
- Number and Activity of cells involved in airway inflammation:

  Macrophages, Eosinophils, and T-lymphocytes
- Suppress the Immune System by reducing activity and volume of the lymphatic system

Glucocorticoids

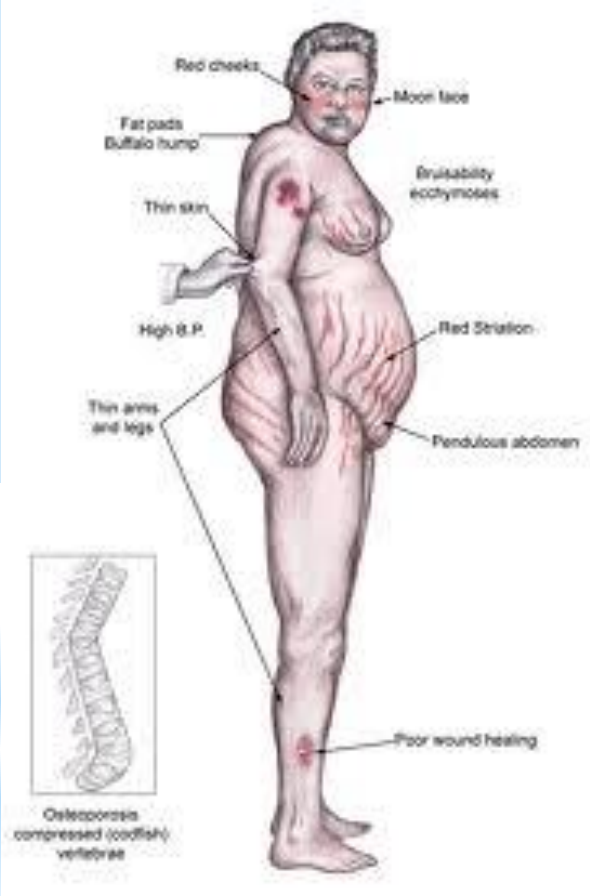
Beclometasone

Butesonide

Fluticasone

- are given by inhalation with metered-dose inhaler, the full effect being attained only after several days of therapy.

ADVERSE EFFECT OF GCs:



Local Effects:

Oropharyngeal Candidiasis – **Thrush**

Systemic Effects:

- BP, Edema, CHF, Thromboembolism, Thrombophlebitis,
- Cushingoid State (*moonface, buffalo hump, central obesity*),
- Peptic Ulceration,
- Increased Appetite,
- Muscle Weakness,
- Osteoporosis, Hirsutism,
- Growth Suppression in Children.

Cromolyn sodium (*caps. 20 mg for inhalation*) and **Nedocromil** (*aerosol: 2 mg/dose*) stabilize mast cells and prevent the release of **bronchoconstrictive** and **inflammatory** substances when mast cells are confronted with allergens and other stimuli.

They are effective prophylactic anti-inflammatory agents, but are not useful in managing acute asthmatic attack because they are not direct bronchodilators.

Mechanism of action:

- **stabilize** the **mast cell membrane** and **inhibits release** of the **spasmogenic mediators** of **Type I** allergic reaction, including ***Histamine*** and *slow reacting substance of anaphylaxis* (SRS-A) from sensitized must cells.

Ketotifen (*tab. 1 mg*), a *cromolyn* analog,

is an antihistaminic (H_1) with some cromolyn like action.

Mechanism of action:

- It inhibits stimulation of immunogenic and inflammatory cells (*mast cells, macrophages, eosinophils, lymphocytes, neutrophils*) and mediator release.
- It is believed to inhibit airway inflammation induced by platelet activating factor (PAF).

Clinicla uses: bronchial asthma, rhinitis, atopic dermatitis, conjunctivitis, urticaria, food allergy, migraine.

Adverse effects:

sedation, dry mouth, dizziness, nausea, weight gain.

Montelukast (*tab. 0.01 g*) and

Zafirlukast (*Tab. 0.02 and 0.04 g*):

competitively inhibit cysteinyl Leukotriene receptors.

Leukotriene **B_4** is a potent neutrophil chemoattractant,

LTC_4 and **LTD_4** produce bronchoconstriction, mucosal edema.

All the leukotriens (**LTC_4, LTD_4** and **LTE_4**) act

on **the same cysteinyl-leukotriene receptor**.

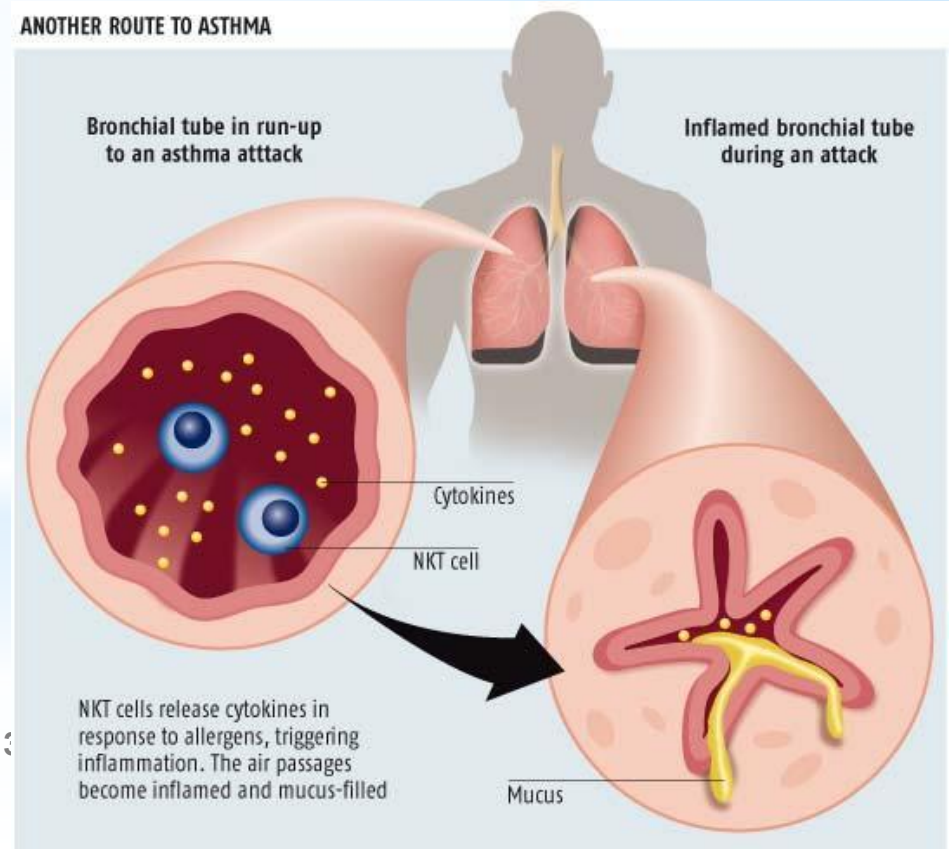
Zafirlucast and Montelucast relax the airways in mild asthma, the bronchodilator activity being *one third*

that of *Salbutamol*.

They ↓ Sputum Eosinophilia.

Zafirlukast and **Montelukast** – are not a cure-all for asthma; their main use is as add-on therapy for:

- Mild-to-moderate asthma – that is not controlled by an 'as required' short-acting β_2-agonist + Inhaled GC
- *Exercise-induced bronchospasm*
- *Aspirin*- induced asthma




Thank You for Attention !