

Zaporozhye State Medical University
Pharmacology and Medical Formulation Department

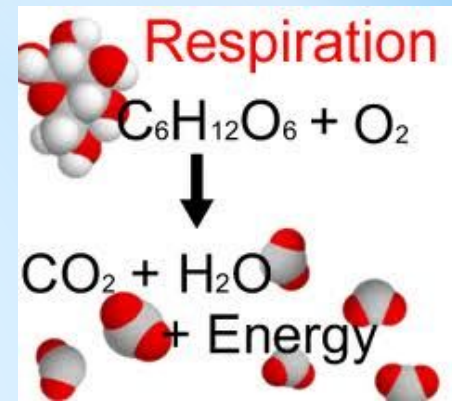


Lecture № 8

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

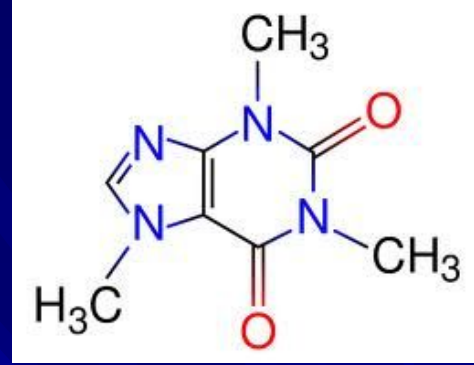
Sulfocamphocaine – amp. 10% - 2 ml

Carbogen (*Carbon dioxide*) - gas bottles



Mechanisms of Action of Caffeine

- 1). Blockade of *Phosphodiesterase* => and \uparrow *cGMP*
- 2) Blockade of *Adenosine Receptors*



ADENOSINE –

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



Contraction of



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% O₂** with
Carbon dioxide **5-7% CO₂**

It is used in anesthesia for inhalation.

Addition **CO₂** to the **O₂** => *stimulation* of
Respiratory Center and much better using of O₂



Clinical Uses of Breathing Stimulants

Acute Respiratory Failure :

- ▶ **Asphyxia** (*Respiratory Arrest*) in *newborns* and during *surgical operations*
- ▶ **Aggravation of**
Chronic Obstructive Pulmonary 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.**

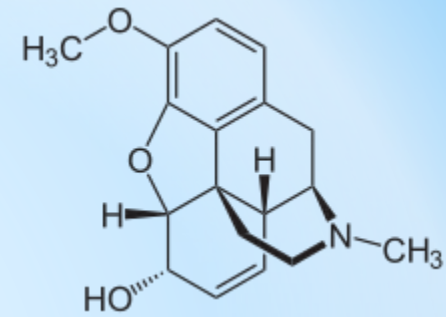
Delay gastric emptying,

- 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* –

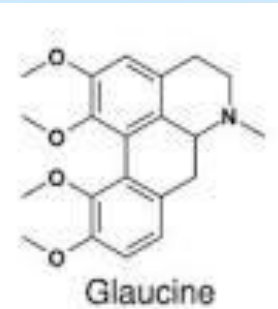
It is an **alkaloid** from the **Yellow Poppy** plant
Glaucine (*Glaucium Flavum*) and may
also be **synthetically derived**.



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

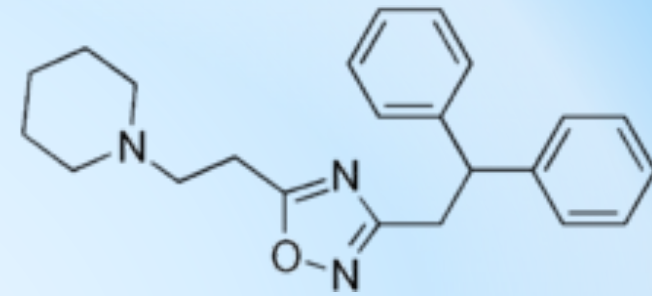
ephedrine 0.1 g

basil 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 [NaHCO₃]

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:

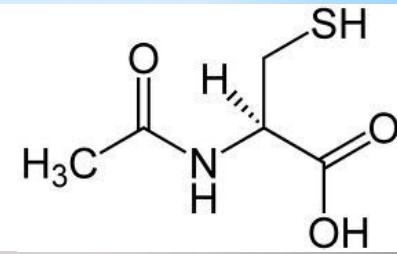
Bromhexine -*Tab. 0.004 and 0.008 g*

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

Acetylcysteine (ACC) -

an **mucolytic** of direct action

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



Mechanism of Action:

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





ACC is a *Paracetamol* antidote.

The mechanism:

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

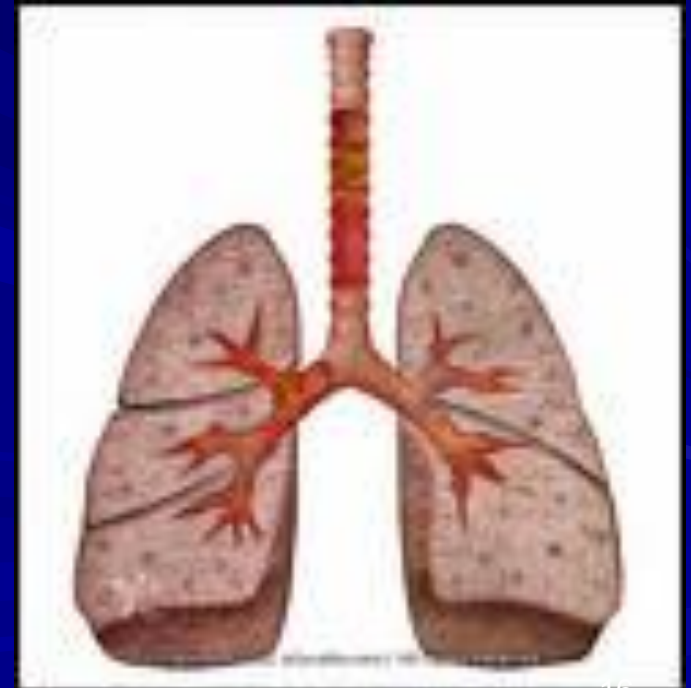
Formula: $C_{10}H_{17}N_3O_6S$

- Inactivates the Toxic Metabolites
Preventing **Liver Damage**



Clinical uses of ACC:

- Acute and chronic broncho-pulmonary 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.

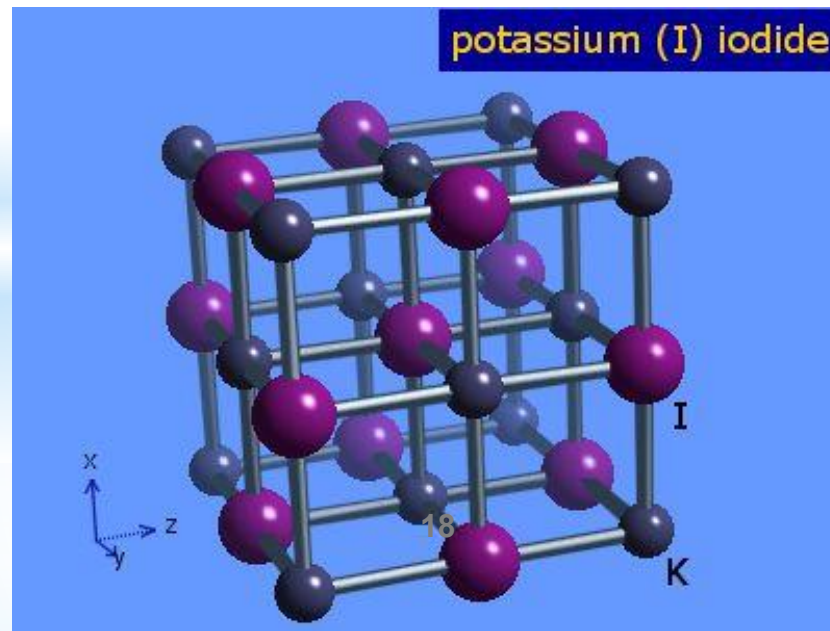
- Normalize** Secretion of Bronchial Glands,
- Improve** reological properties of *sputum*,
- Reduce** its viscosity,
- Relieve** excretion of *sputum* from bronchi



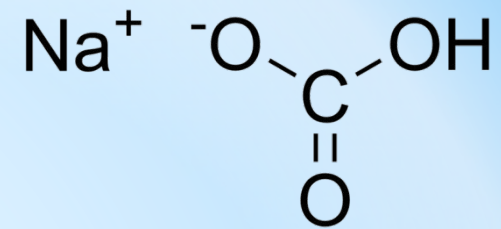
Potassium Iodide is an **Expectorant** and
Antihyperthyroid Agent.

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.**

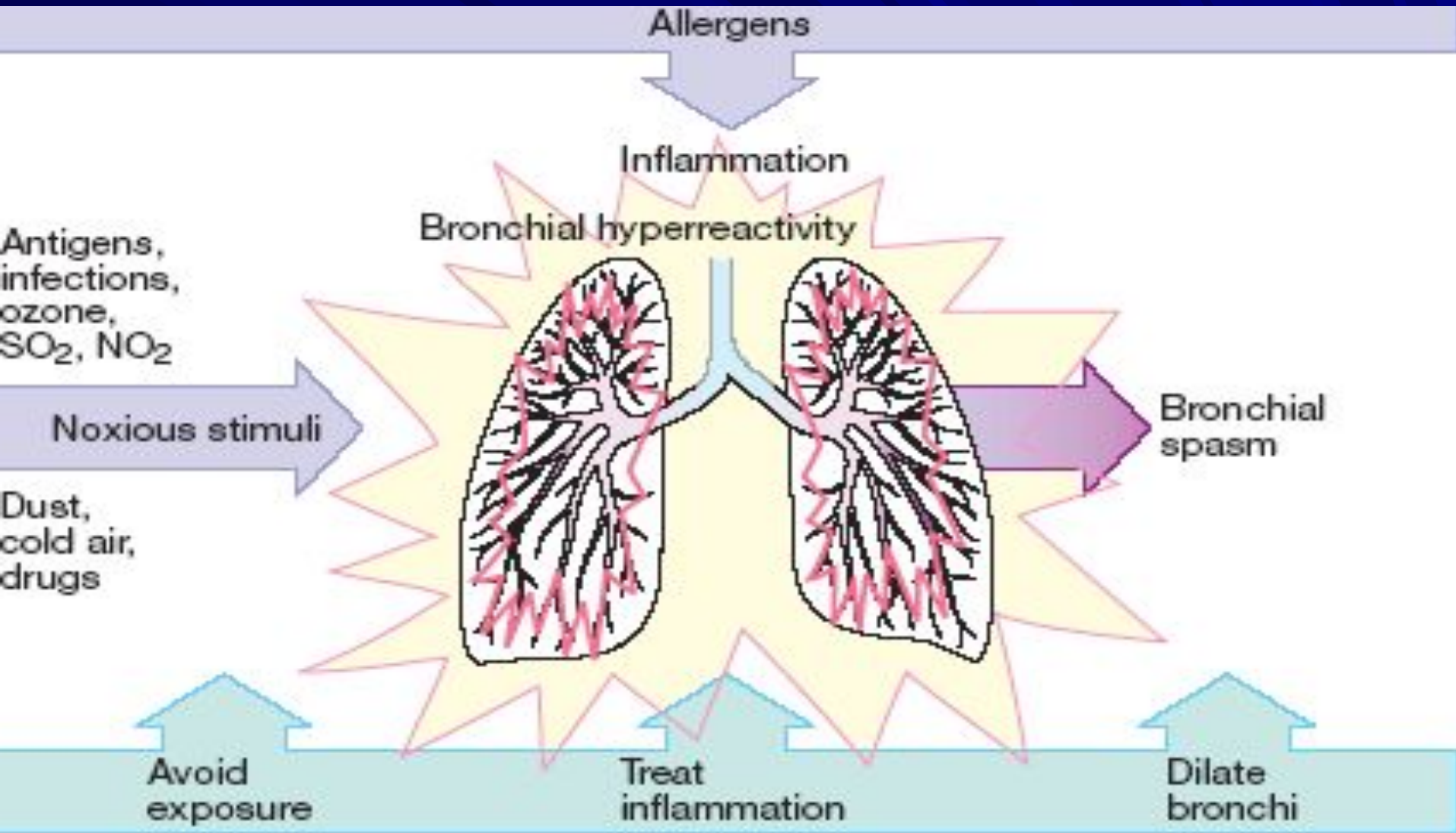
Metabolic side effects have included metabolic alkalosis, hypernatremia/hyperosmolarity, hypochloremia, and hypokalemia.

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 :

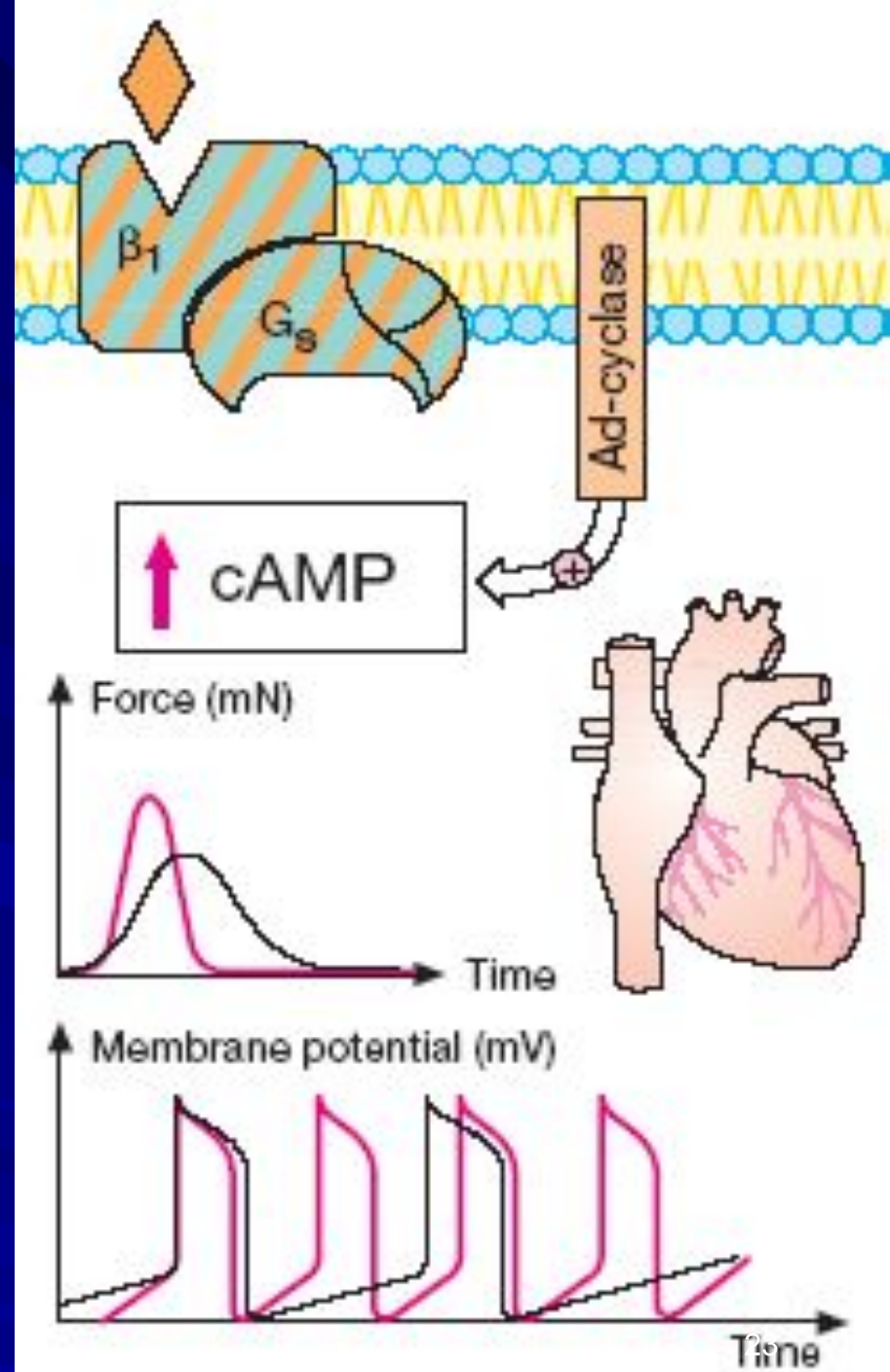
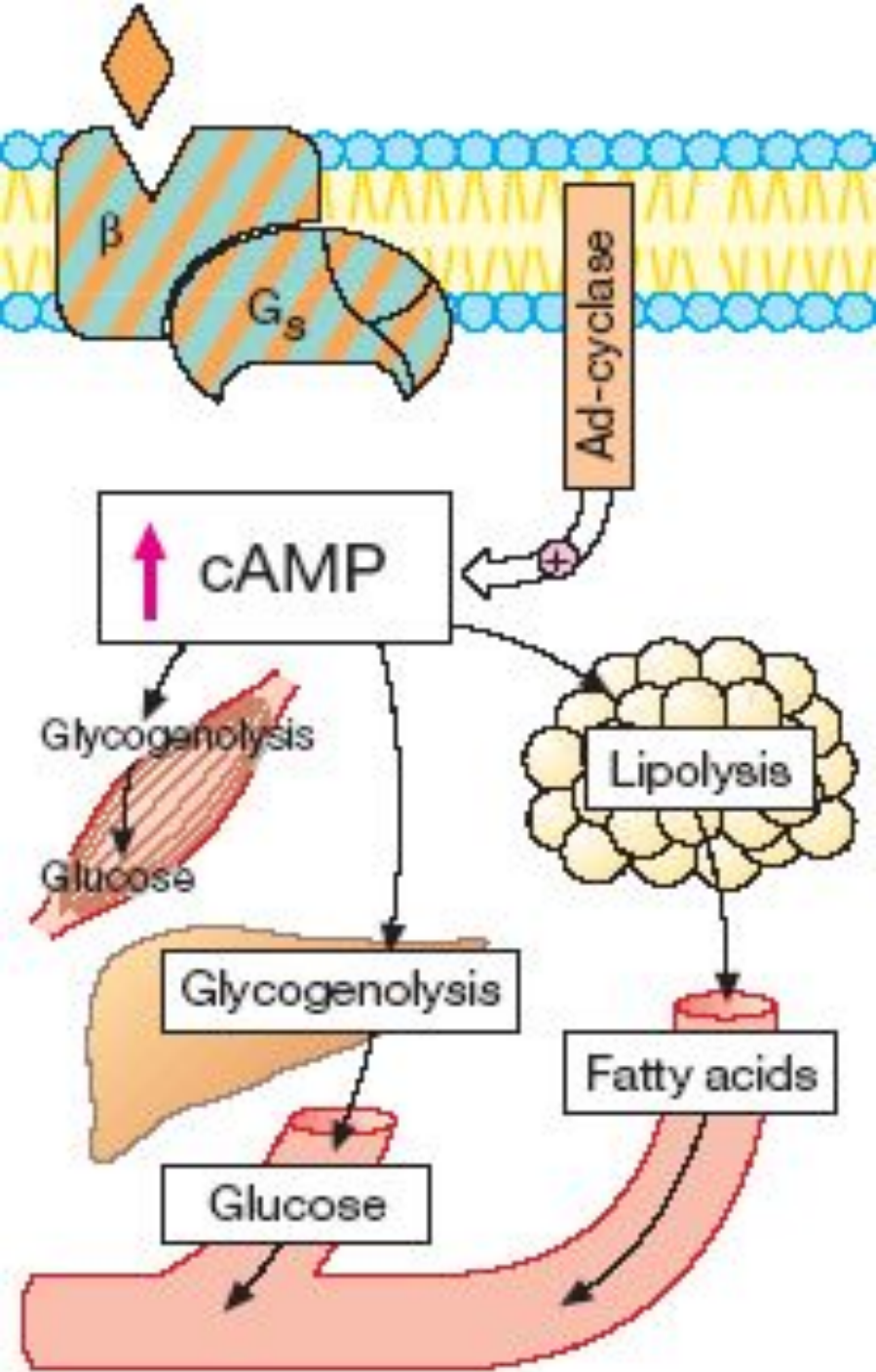
Theobilong, Theodur, Theotard, Durophyllin

3. M-cholinoblockers:

Ipratropium bromide (*Atrovent*)

Tiotropium bromide

Oxitropium bromide



Salmeterol and **Formoterol** - have **lipophilic** properties
Salbutamol and **Fenoterol** have minor length (11 Angstrom)
and **hydrophilic** properties.

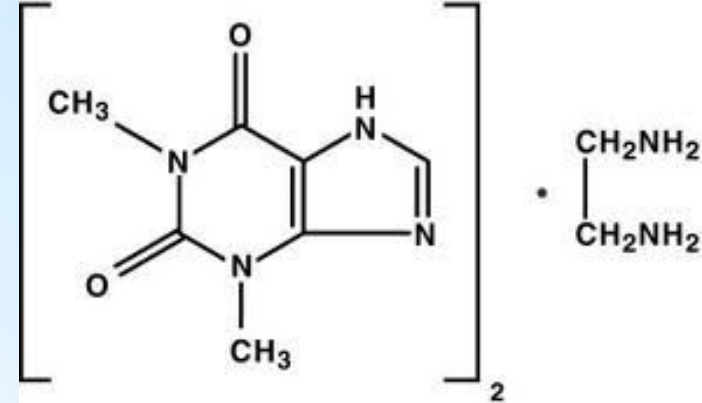
These comparatively quickly “**wash out**” from receptor’s area
and their duration lasts 4-6 hours.

Salmeterol is long (25 Angstrom) molecule and exceeds
Salbutamol in lipophilicity 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 => \uparrow 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*)

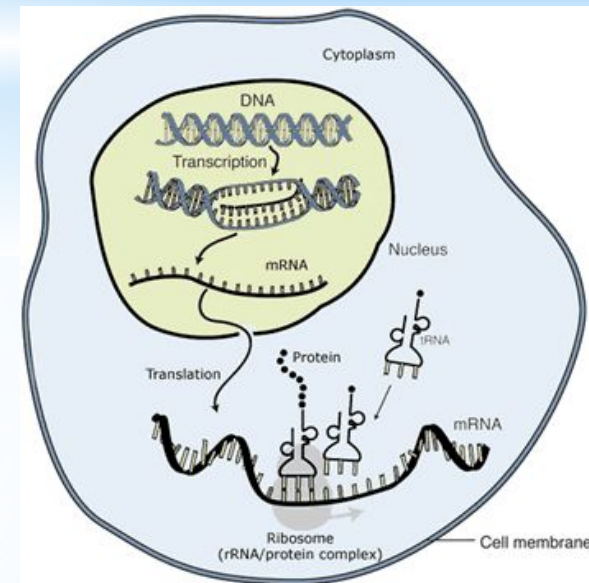
III. Leukotriene Modifiers:

1. Inhibitors of 5-lipoxygenase: **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.



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 D₃-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

Budesonide

Fluticasone

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



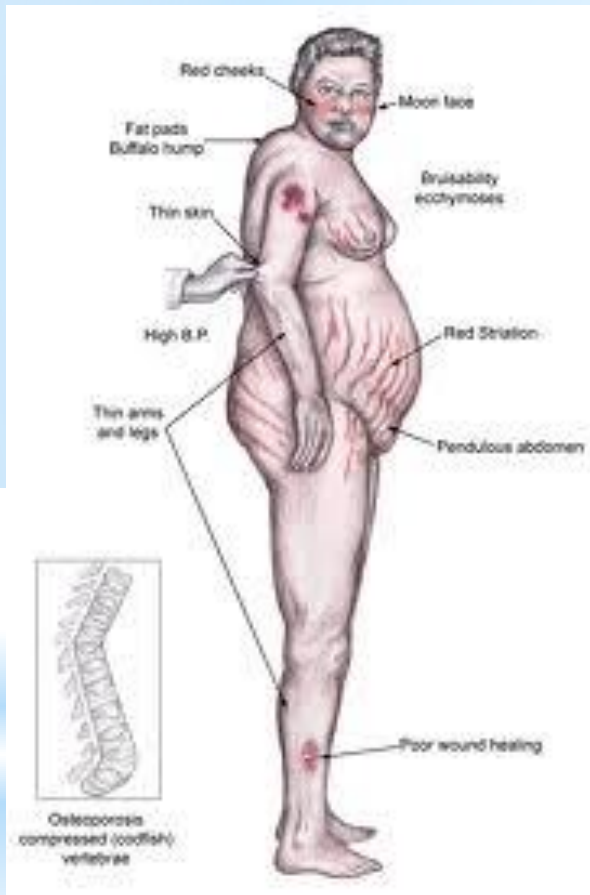
ADVERSE EFFECT OF GCs:

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 mast 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).

Clinical 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.



MONTELUKAST COUPON
Pharmacy Instructions
Submit a primary claim using the following pharmacy processing information.
For processing questions and comments please call the Pharmacy Helpline below.
Member ID: Enter Year & Time (Example: Year 2012; Time 9/14; Enter ID 2012914)
RxPCN: 7777
RxBIN: 610709
RxGRP: RXCOUPON
THIS IS NOT INSURANCE
Customer Service: 800-726-4232 Pharmacy Helpline: 877-321-6755
Pharmacy Coupons.com

Leukotriene B₄ is a potent neutrophil **chemoattractant**,
LTC₄ and **LTD₄** produce **bronchoconstriction**, **mucosal edema**.
All the leukotriens (**LTC₄**, **LTD₄** and **LTE₄**) act
on **the same cysteinyl-leukotriene receptor**.

Zafirlucast and **Montelukast** relax the airways in mild asthma,
the bronchodilator activity being *one third*
that of **Salbutamol**.

They Sputum Eosinophilia.

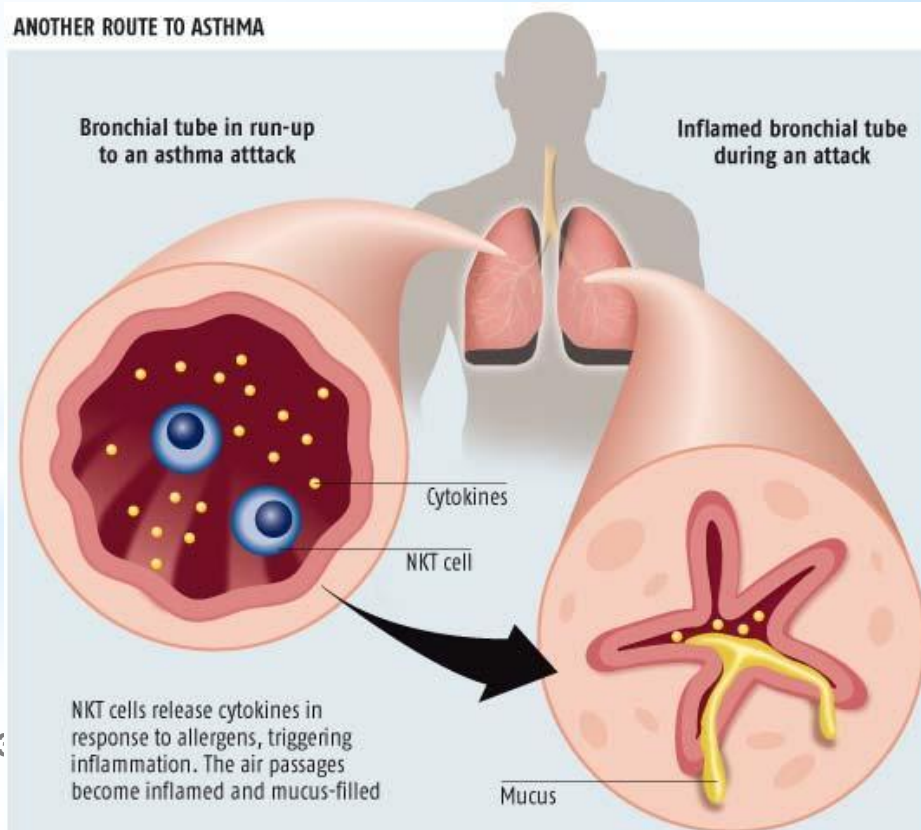


Zafirlukast and **Montelukast** – are not a cure-all for asthma;
their main use is as **add-on therapy** for:

- **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*



ANOTHER ROUTE TO ASTHMA



A wide, snow-covered road with numerous parallel tire tracks leads from the foreground towards a range of snow-capped mountains in the distance. The sky is a clear, bright blue. The overall scene is a winter landscape.

Thank You for Attention !