# Drugs used in the treatment of respiratory system diseases

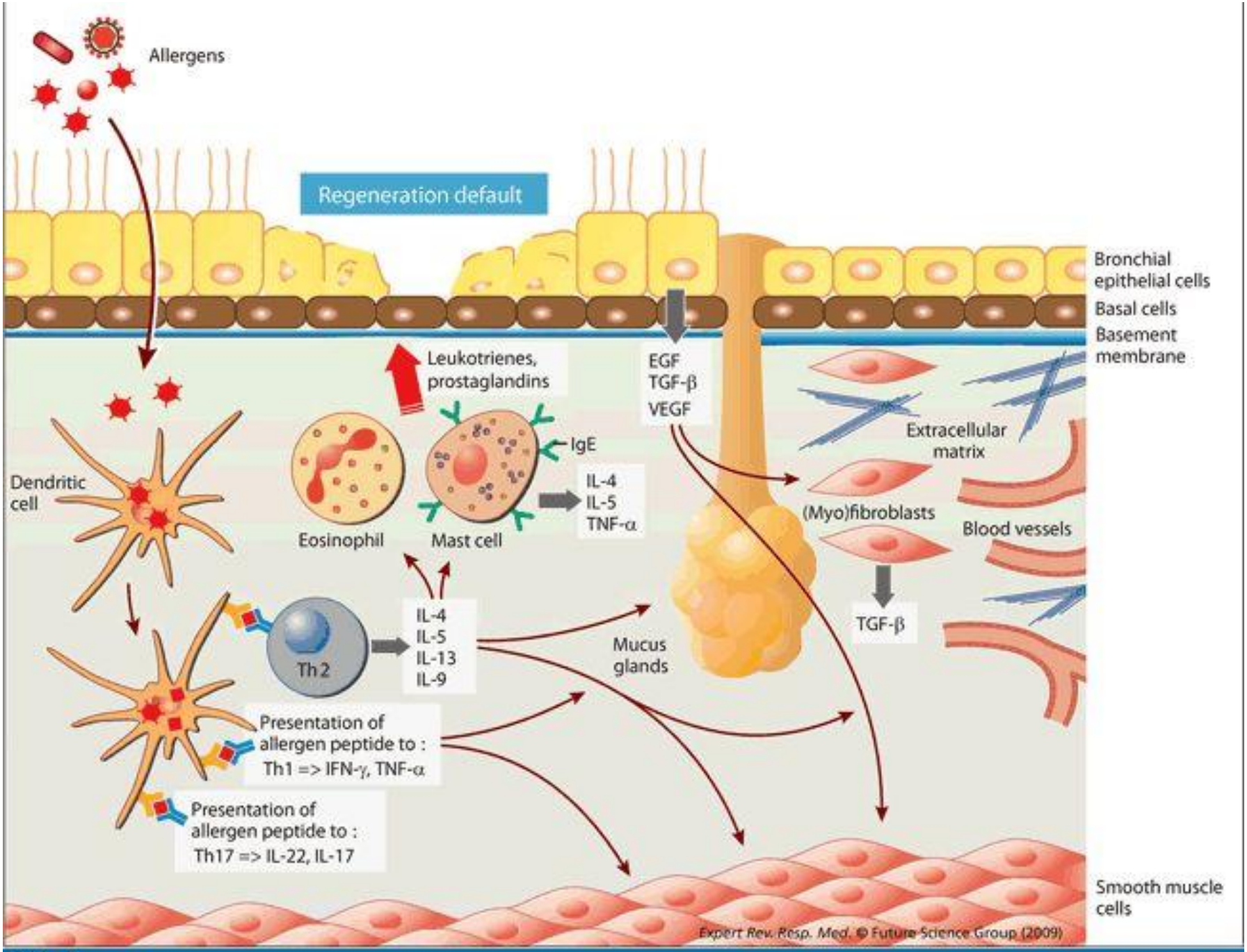
## Antiasthmatic drugs

# Asthma

Asthma is a chronic inflammatory disorder which is accompanied by bronchi contraction, increased release of sticky mucus, edema and exfoliation of the epithelium of the bronchi.

**The most common form of asthma is allergic asthma (atopic or extrinsic asthma).** It is associated with environmental allergens, such as plant pollens, house dust mites, domestic pet dander, molds, and foods.

**The less common form, intrinsic asthma, has no known allergic cause and usually occurs in adults older than 35 years.** Intrinsic asthma may result from an autonomic dysfunction characterized by excess cholinergic and/or tachykinin activity, but this hypothesis has never been proven.



# Antiasthmatic drugs

**Astma** symptoms are caused by bronchoconstruction and inflammation, and approaches to treatment are directed at both these physiological problems.

**Therefore, drugs that affect adrenergic/cholinergic bronchial smooth muscle tone and drugs that inhibit the inflammatory process are used to treat and control asthma symptoms.**

In the normal lung, bronchiole smooth muscle tone results from the balance between the bronchoconstrictive effects of the cholinergic system and the bronchodilating effects of the adrenergic system on the smooth muscles of the bronchioles.

**Pharmacological treatment of asthmatic bronchoconstriction consists of either increasing adrenergic tone with an adrenergic agonist (**or phosphodiesterase inhibitors) **or inhibiting cholinergic tone with anticholinergic agent**.

**The inflammatory effects** seen in asthma result from the release of physiologically active chemicals from a variety of inflammatory cells.

**Pharmacological treatment, therefore, uses:**

- anti-inflammatory drugs (corticosteroids),
- mast cell stabilizers,
- leukotriene modifiers, and
- IgE monoclonal antibodies.

# Therapeutic management

Therapeutic management of asthma requires the use of quickly acting drugs to relieve an acute attack as vell as drugs that control symptoms over the long-term.

The quick-reliever medication is almost always an inhaled short-acting $\beta_2$-adrenergic agonist, whereas controller drugs are inhaled corticosteroids, long-acting $\beta_2$-agonists, leukotriene modifiers, cromolyn sodium, and/or methylxanthines.

The dose, route of administration, and number of controller drugs depends on the severity of the patient's disease (Table).

# Stepwise medication management of asthma (1)

**All patients: short-acting inhaled β2-agonists as needed for acute episodes**

| Severity classification | Long-term control |
|---|---|
| Mild intermittent (Step 1) | **No daily medication needed**<br>A course of systemic steroid may be necessary to treat a severe episode |
| Mild persistent (Step 2) | **Low-dosed inhaled steroid**<br>**Other treatment option**:<br>Cromolyn/nedocromil OR<br>Leukotriene modifier OR<br>Sustained-release theophylline |

# Stepwise medication management of asthma (2)

| | |
|---|---|
| Moderate persistent (Step 3) | **Low- to medium-dose inhaled steroid** + an inhaled long-acting β2-agonist |
| | **Other treatment option**:<br>Medium-dose inhaled steroid + cromolyn/nedocromil OR<br>Medium-dose inhaled steroid + Leukotriene modifier OR<br>Medium-dose inhaled steroid + Sustained-release theophylline |
| Severe persistent (Step 4) | **High-dosed inhaled steroid** + a long-acting bronchodilator + one or more of the following:<br>Oral long-acting $\beta_2$-agonist<br>Sustained-release theophylline<br>Oral steroid<br>Leukotriene modifier |

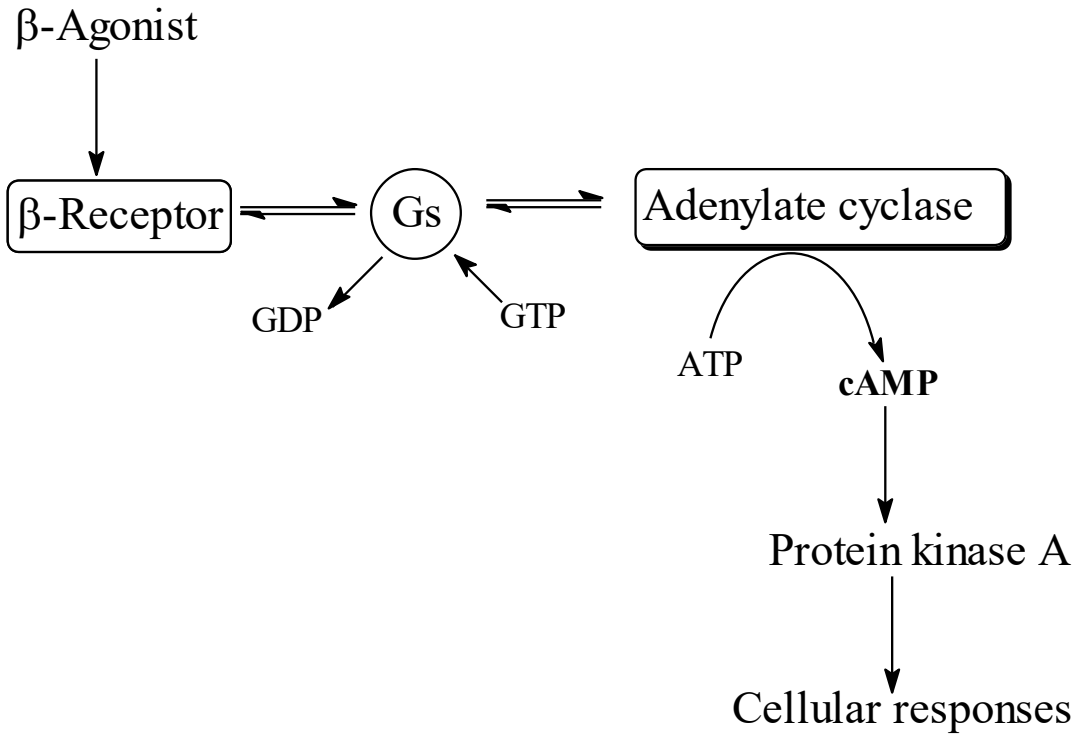
# Mechanism of action of the β-adrenergic agonists

All the β-adrenergic receptors are coupled to adenylate cyclase via specific G-stimulatory proteins (Gs).

When agonist binds to the β-adrenergic receptors, the α-subunit migrates through the membrane and stimulates adenylate cyclase to form cyclic adenosine monophosphate (cAMP) from ATP.

Once formed in the cell, cAMP activates protein kinase A, which catalyzes the phosphorylation of numerous proteins, thereby regulating their activity and leading to characteristic cellular responses.

The intracellular PDE hydrolyzes cAMP to form AMP and terminates its action.

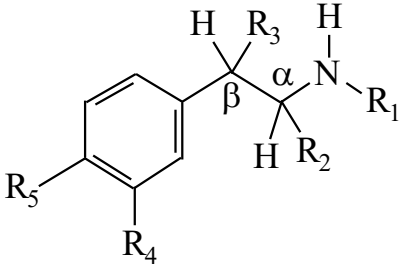


Physiological response in relationship to β-receptor subtype and organ site

| Receptor subtype | Organ location | Response |
|---|---|---|
| $\beta_1$ | Heart | Increased rate and force<br>Increased conduction velocity |
| $\beta_2$ | **Bronchiale smooth muscle**<br>Intestine<br>Liver<br><br>Uterus<br>Lungs | **Dilation**<br>Decreased motility<br>Increased gluconeogenesis<br>Increased glycogenolysis<br>Contraction<br>Bronchial dilation |
| $\beta_3$ | Fatty tissue | Lipolysis |

# Adrenergic agonist structure – activity relationships (1)

The fundamental pharmacophore for all adrenergic agonists is a substituted β-phenylethylamine.




The nature and number of substituents on the pharmacophore influences whether an analogue will be direct-acting or indirect-acting or have a mixture of direct and indirect action.

In addition, the nature and number of substituents also influences the specifity for the β-receptor subtypes.

Direct-acting adrenergic agonists bind the β-adrenergic receptors producing a sympathetic response.

# Adrenergic agonist structure – activity relationships (2)

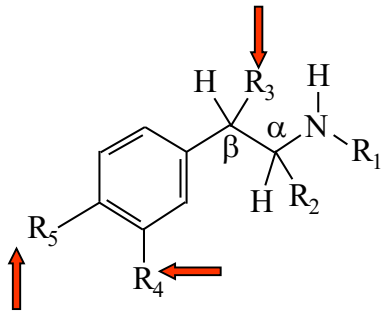
Indirect-acting agonists cause their effect by a number of mechanisms.

They can:

- stimulate the release of NE from the presynaptic terminal,
- inhibit the reuptake of released NE,
- or inhibit the metabolic degradation of NE by neuronal MAO.

Mixed-acting agonists have both direct and indirect abilities.

# Relationship of substituents to adrenergic agonist mechanism of action (1)




Adrenergic agonist pharmacophore

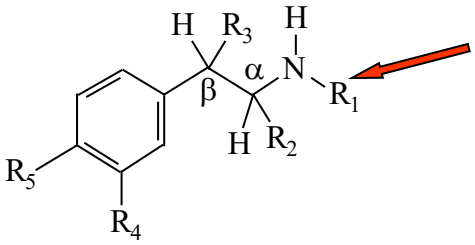
| Action | $R_3$ | $R_4$ | $R_5$ |
|---|---|---|---|
| Direct[1] | OH | OH | OH |
| or | OH | OH | H |
| Indirect[2] | H | H | H |
| or | H | H | OH |
| Mixed[3] | H | OH | OH |
| or | OH | H | OH |

[1] β-OH ($R_3$) necessary for direct action, optimal if in the R-configuration; *m*-OH ($R_4$) also necessary for direct action;
*p*-OH ($R_5$) can be an H or OH, however catechol is optimal.

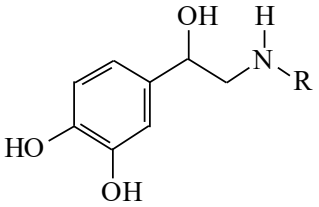
[2] Without the catechol OH's ($R_4$ and $R_5$) or β-OH ($R_3$) there is little affinity for the β-receptor;
*p*-OH doesn't contribute to β-receptor binding affinity.

[3] β-OH ($R_3$) or *m*-OH ($R_4$) contribute to direct action.

## Relationship of substituents to adrenergic agonist mechanism of action (2)




The substituents on the amino group (**$R_1$**) determines α- or β-receptor selectivity.



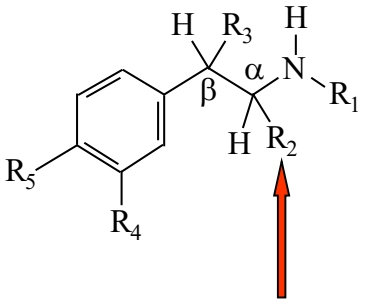

When the N-substituent was changed from hydrogen (NE) to methyl (EPI) to isopropyl, the receptor affinity went from nonselective for NE/EPI to β-selective for (ISO).

| | |
|---|---|
| Norepinephrine (NE) | R = H |
| Epinephrine (EPI) | R = $CH_3$ |
| Isoproterenol (ISO) | R = -$CH(CH_3)_2$ |

**If $R_1$ is *t*-butyl or aralkyl, there is complete loss of α-receptor affinity, and the β-receptor affinity shows preference for the $\beta_2$-receptor.**

Receptor selectivity is dose related, and when the dose is high enough, all selectivity can be lost.

# Relationship of substituents to adrenergic agonist mechanism of action (3)




Substituents on the α-carbon ($R_2$) other than hydrogen will show an increased duration of action, because they make the compound resistant to metabolism by MAO.

In addition, if the substituent is ethyl, there is a selectivity for the $\beta_2$-receptor, which is enhanced by a bulky N-substituent.

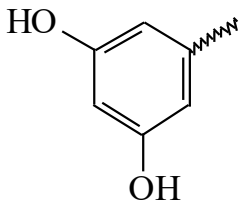
Interestingly, α-methyl substitution shows a slight β-receptor enhancement and only for the *S*-configuration.

## Relationship of substituents to adrenergic agonist mechanism of action (4)

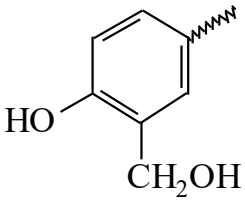
For an adrenergic agonist to demonstrate significant $\beta_2$-receptor selectivity, there needs to be in addition to the bulky N-substituent an appropriately substituted phenyl ring.

The currently marketed adrenergic agonist contain a resorcinol ring, a salicyl alkohol moiety, or a *m*-formamide group.

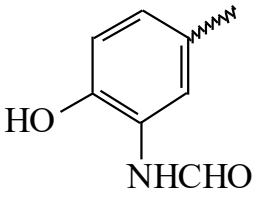
In addition, these ring configurations are resistant to COMT metabolism and will increase the duration of action.




Resorcinol




Salicyl alkohol




N-formamide

# β-Adrenergic drugs

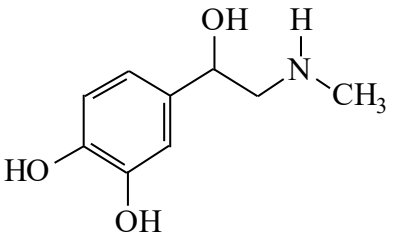
- β-Adrenergic drugs are used as drugs of first choice in paroxysmal bronchospasm.
- β-Adrenergic drugs are used most often as inhalants. In acute cases of asthma β-mimetics are also administered parenterally. Although when these drugs are used parenterally the relaxing effect is produced the most rapidly, this manner of administration can cause dangerous complications in the cardiovascular system.
- The use of β-mimetics as oral drugs is limited because the dosage of an oral drug should be many times greater than of an inhalant and adverse effects are stronger. In night asthma, depot preparations are mainly used orally. β-Adrenergic drugs differ in terms of selectivity of action on β-receptors, the time and power of action and the intensity of adverse effects.

Non-selective β-adrenergic drugs are used in bouts of acute bronchospastic dyspnoea because of their immediate and highly effective action and the possibility of parenteral administration.

Selective and non-selective β-adrenergic drugs differ mainly in their side effects. When selective β-adrenergic drugs are administered, much less dangerous cardiologic complications are observed.

# α,β-Adrenergic agonists

*Epinephrine* (*Adrenalin*); Epi Pen




The combination of the catechol nucleus, the β-hydroxyl group, and the N-methyl give EPI a direct action and a strong affinity for all adrenergic receptors.

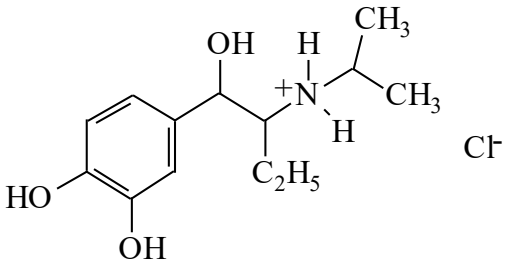
Epinephrine usually is administered slowly by IV injection to relieve acute asthmatic attacks not controlled by other treatments.

Intravenous injection produces an immediate response.

Adverse effects include palpitations, tachycardia, sweating, nausea and vomiting, respiratory difficulty, dizzines, tremor, apprehension and anxiety.

# $\beta_1,\beta_2$-Adrenergic agonists

Isoetharine, Metaproterenol, Terbutaline, Bitolterol

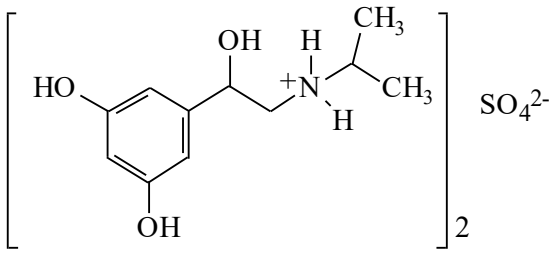



***Isoetharine hydrochloride***

The α-ethyl group confers $\beta_2$-selectivity, and the β-hydroxyl group and catechol nucleus make this a direct-acting drug.

It is susceptible to COMT metabolism; however, the α-ethyl group inhibits MAO. Therefore, one would expect some oral activity.

Isoetharine is dispensed as a solution only for inhalation administration to treat reversible bronchospasm of asthma.




## *Metaproterenol sulfate*

ALUPENT, METAPREL

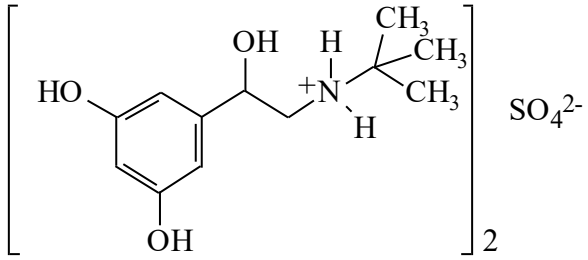
Metaproterenol is a direct-acting resorcinol analogue of isoproterenol.

The N-isopropyl is β-directing, and the combination with the resorcinol ring system enhances the selectivity for the $\beta_2$-receptors. It is the least potent of the $\beta_2$-selective agonists, however, most likely because of the poor $\beta_2$-selectivity of the isopropyl group. It has good oral bioavailability being resistant to COMT and only slowly metabolized by MAO.

When administered orally, it has an onset of approximately 30 min with a 4-hour duration.

Inhaled metaproterenol can have an onset as quick as 5 min; however, it can be as long as 30 min in susceptible individuals.

Metaproterenol is available in tablet, syrup, and inhalation dosage forms and is recommended for bronchial asthma attacks and treatment of acute asthmatic attacks in children 6 years of age and older (5% solution for inhalation only).




***Terbutaline sulfate***

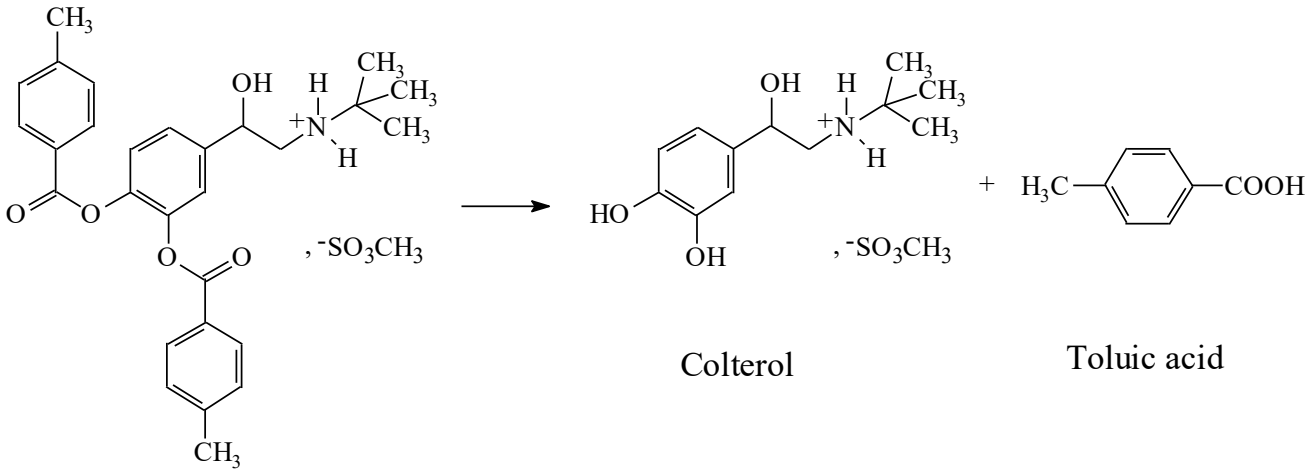
BRETHINE, BRETHAIRE

Terbutaline is N-*t*-butyl analogue of metaproterenol and, as such, woud be expected to have a more potent $\beta_2$-selectivity.
When compared to metaproterenol, terbutaline has a threefold greater potency at the $\beta_2$-receptor.

Like metaproterenol, it is resistant to COMT and slowly metabolized by MAO, therefore having good oral bioavailability with similar onset and duration.

Terbutaline is available as tablets and solutions for injection and inhalation.

***Bitolterol mesylate*** (TORNALATE) is a prodrug that releases colterol on activation by esterases in the lung.




Colterol is a direct-acting agonist, and the N-t-butyl group makes it $\beta_2$-selective with a binding potency equivalent to that of isoetharine and terbutaline.

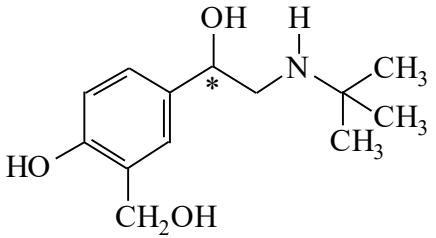
The ester form is lipophilic, which helps to keep it local in the lung and resistant to COMT, which tends to increase its duration of action. Onset begins 2 to 4 min after administration, and the effect can last as long as 8 hours.

# $\beta_2$-Selective agonists

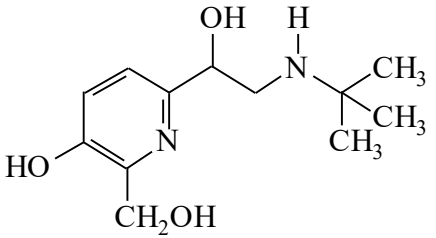
- **If $\beta_2$-adrenergic receptor agonists are administered as inhalants, they relax the bronchi immediately after inhalation.**
- **A maximal effect is achieved after 10-15 min. Action lasts from 4 to 6 hours, depending on the kind of preparation.**
- **Side effects depend on dosage and the way of administration.**
- **Side effects are not significant if such drugs are used as inhalants, but when they are administered orally or parenterally they can cause hypokalaemia.**

# Short-acting $\beta_2$-selective agonists

## Albuterol, Pirbuterol, Fenoterol




d,l-Albuterol (PROVENTIL, VENTOLIN
Levalbuterol (XOPENEX)



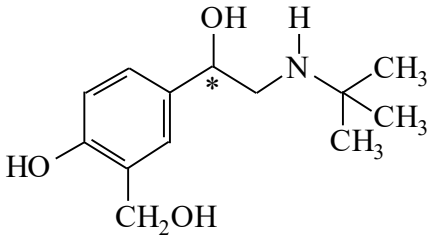

Pirbuterol (MAXAIR)

Albuterol has the N-*t*-butyl and a salicyl alkohol phenyl ring, which gives it optimal $\beta_2$-selectivity. It is resistant to COMT and slowly metabolized by MAO, giving it good oral bioavailability. Its onset by inhalation is within 5 min, with a duration of action between 4 and 8 hours. It currently is the drug of choice for relief of the acute bronchospasm of an asthmatic attack. Albuterol is available in tablet, syrup, solution and aerosol formulations.

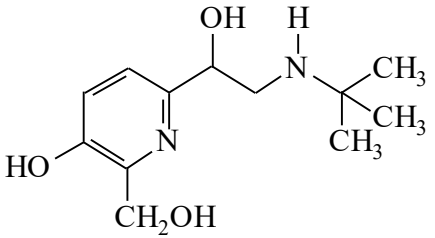
Levalbuterol is the *R*(-)-isomer of albuterol and is available only in solution to be administered via nebulizer. Because it is the active isomer, the dose is fourfold less than of albuterol.

# Short-acting $\beta_2$-selective agonists

## Albuterol, Pirbuterol, Fenoterol



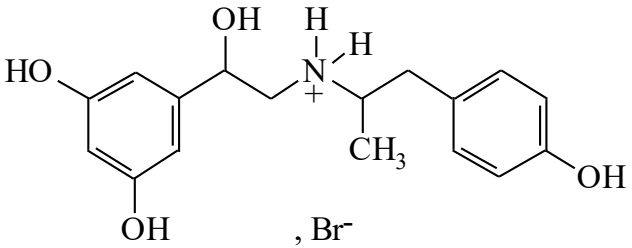

*d,l-Albuterol* (PROVENTIL, VENTOLIN
*Levalbuterol* (XOPENEX)




*Pirbuterol* (MAXAIR)

Pirbuterol is the pyridine isostere of albuterol.
It has pharmacokinetics similar to albuterol but is half as potent at the $\beta_2$-receptor.

Pirbuterol is only available as an inhaler. whereas in solution to be administered via nebulizer.




*Fenoterol hydrobromide*

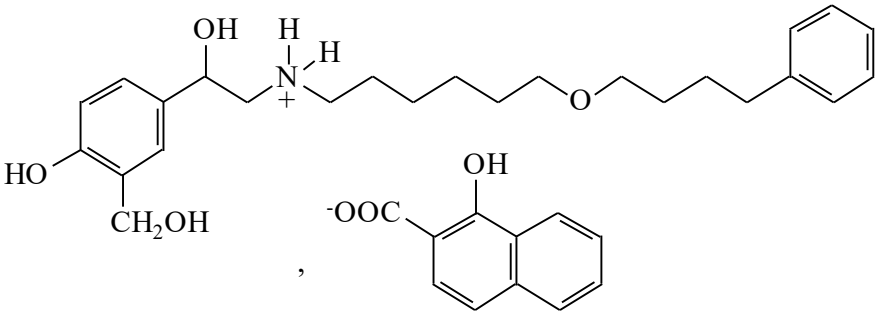
BEROTEC

Fenoterol is the p-hydroxyphenyl derivative of metaproterenorol, and the combination of the resorcinol ring and the bulky p-hydroxyphenyl isopropyl group on the nitrogen gives fenoterol significant $\beta_2$-receptor selectivity. It has approximately half the affinity for the $\beta_2$-receptor as compared to albuterol.

The resorcinol ring is resistant to COMT metabolism, and the bulky nitrogen substituent greatly retards MAO metabolism as well giving fenoterol a reasonable oral bioiavailability with pharmacokinetics similar to albuterol (rapid onset and a 4- to 6-hour duration of action after oral inhalation).

# Long-acting $\beta_2$-selective agonists

## Salmeterol, Formoterol

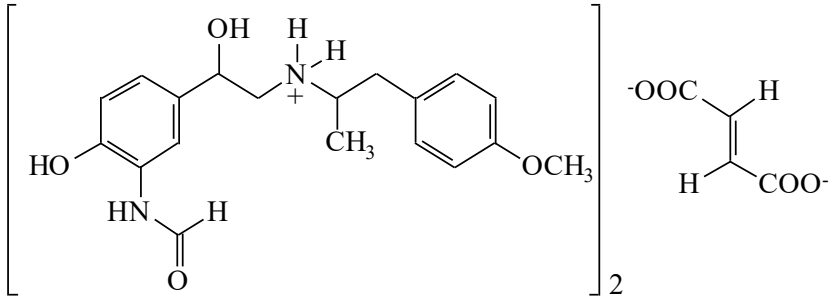



*Salmeterol xinafoate*
SEREVENT DISKUS

Salmeterol has an N-phenylbutoxyhexyl substituent in combination with a β-hydroxyl group and a salicyl phenyl ring for optimal direct-acting $\beta_2$-receptor selectivity and potency. Salmeterol has the greatest receptor affinity of all the adrenergic agonists. It is resistant to both MAO and COMT and that, together with its increased lipophilicity, gives salmeterol a long duration of action.

It is available only as a powder for inhalation, with a 20-min onset of action, which lasts for 12 hours. It is used as a controller for the long-term treatment of asthma and is not recommended for quick relief of an acute attack.

It also is available in combination with the steroid fluticasone propionate (ADVAIR DISKUS).




***Formoterol fumarate***

FORADIL aerosolizer

Formoterol has a β-directing N-isopropyl-p-methoxyphenyl and a unique *m*-formamide and *p*-hydroxyphenyl ring, which provides selectivity for $\beta_2$-receptors.

**It is resistant** to MAO and COMT, making it a long-acting agonist.

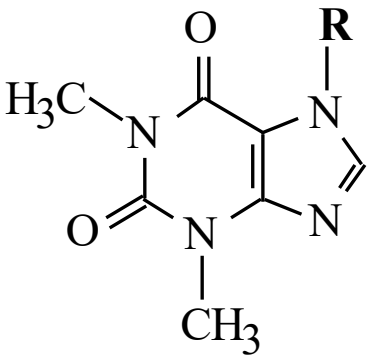
Formoterol has a more rapid onset as compared to salmeterol while maintaining the same long duration of action.

**It is indicated** for the long-term maintenance treatment of asthma for patients with symptoms of nocturnal asthma who require regular treatment with inhaled, short-acting, $\beta_2$-agonists.

**It is not indicated** for patients whose asthma can be managed by occasional use of inhaled, short-acting, $\beta_2$-agonists.

**Formoterol is available** only as a powder in a capsule for administration via the aerosolizer.

# Xanthine drugs




*Theophylline*, R = H;
3,7-Dihydro-1,3-dimetylo-1*H*-puryno-2,6-dion = 1,3-dimetyloksantyna

MONOSPAM, THEOPHYLLINE, THEOPHYLLINUM PROLONGATUM, THEOSPIREX RETARD

*Diprophylline*, *Dyphylline* R = $-CH_2-CH(OH)-CH_2-OH$
DIPROPHYLLINUM

# Xanthine drugs

- Xanthine derivatives differ in three aspects: the power of action as bronchodilators, stimulating action on the CNS and antagonistic action on adenosine receptors.
- Theophylline, apart from acting as a bronchodilator, has a stimulating effect on the CNS and the heart and is an antagonist at adenosine receptors. Theophylline is used as oral preparations (capsules, tablets) with a short or prolonged time of action and as slow-release preparations.
- Theophylline is well absorbed from the gastrointestinal tract (90 – 100 per cent). The maximal concentration of theophylline in the blood is achieved after 3 – 8 hours. The average time of absorption for short-acting preparations is 10-15 minutes, but for preparations with prolonged time of action approx. 4 h. Slow-release preparations are especially desirable because after their administration a constant drug concentration in the blood is ensured and they can be used twice or even once daily. They also increase drug tolerance. Drug absorption is influenced not only by the form of the drug but by other factors too. The rate of absorption of theophylline is lower at night. A high-fat diet prolongs drug absorption. Individual differences in the assimilation of theophylline also play a very important role.

# Xanthine drugs

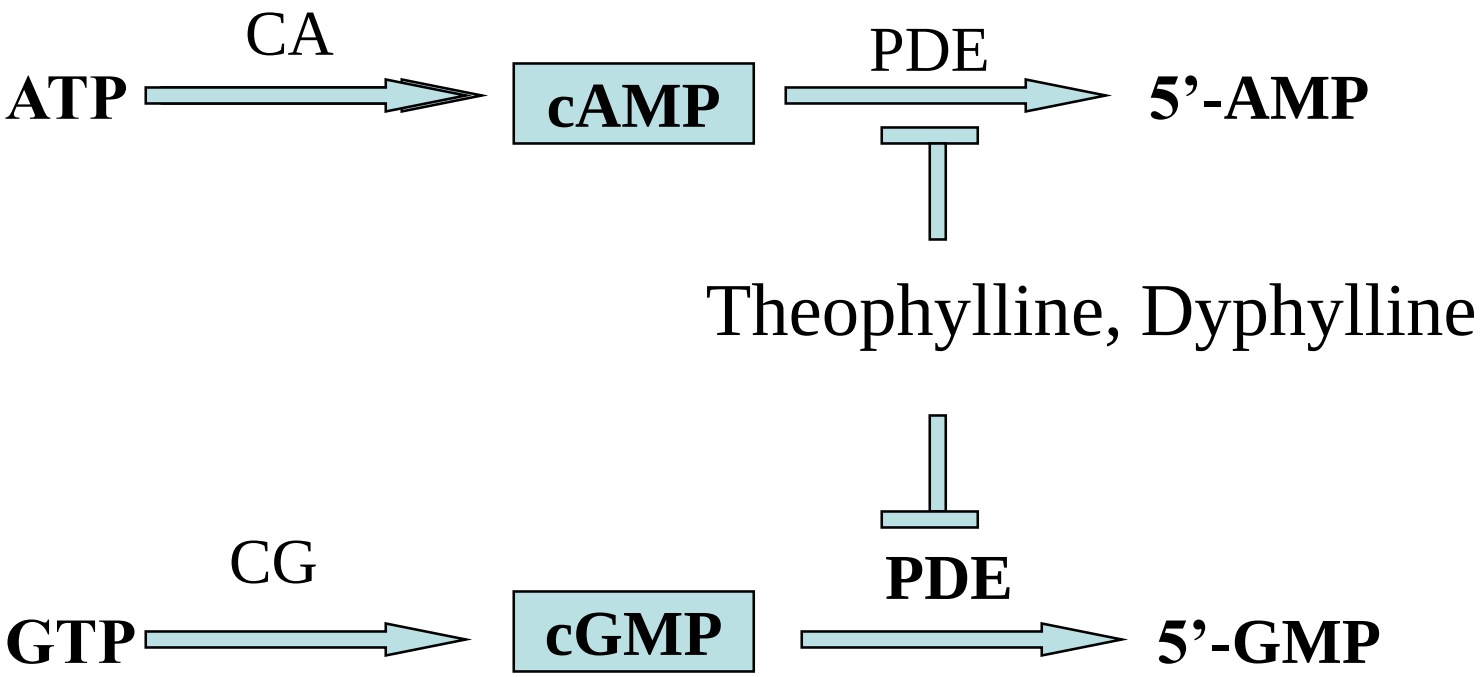
- Theophylline is used in acute bronchial attacks as it relaxes the smooth muscles of the bronchial tract.
- The therapeutic concentration of theophylline is 10-20 μg/ml of plasma. Dosage should be reduced when theophylline is administered to older or obeise patients, and when drugs inhibiting microsomal enzymes are used (macrolides, contraceptives).
- The half-life of theophylline increases in liver diseases, cardiac failure and viral infections because of changes in the liver blood flow and the oxygenation of blood.
- The half-life of theophylline decreases in heavy cigarette smokers and drinkers.

# Xanthine drugs

- Overdose of theophylline  can result in a quick onset of ventricular arrhythmias, convulsions, or even death without any previous warning.
- Monitoring plasma concentration is  necessary because of a small difference between a therapeutic dose and one which causes a toxic effect.
  It has a narrow therapeutic window.
- Dyphylline has a diminished bronchodilator effect compared to theophylline, but it may have lover and less serious side effects. Dosage forms available are an elixir and tablets.

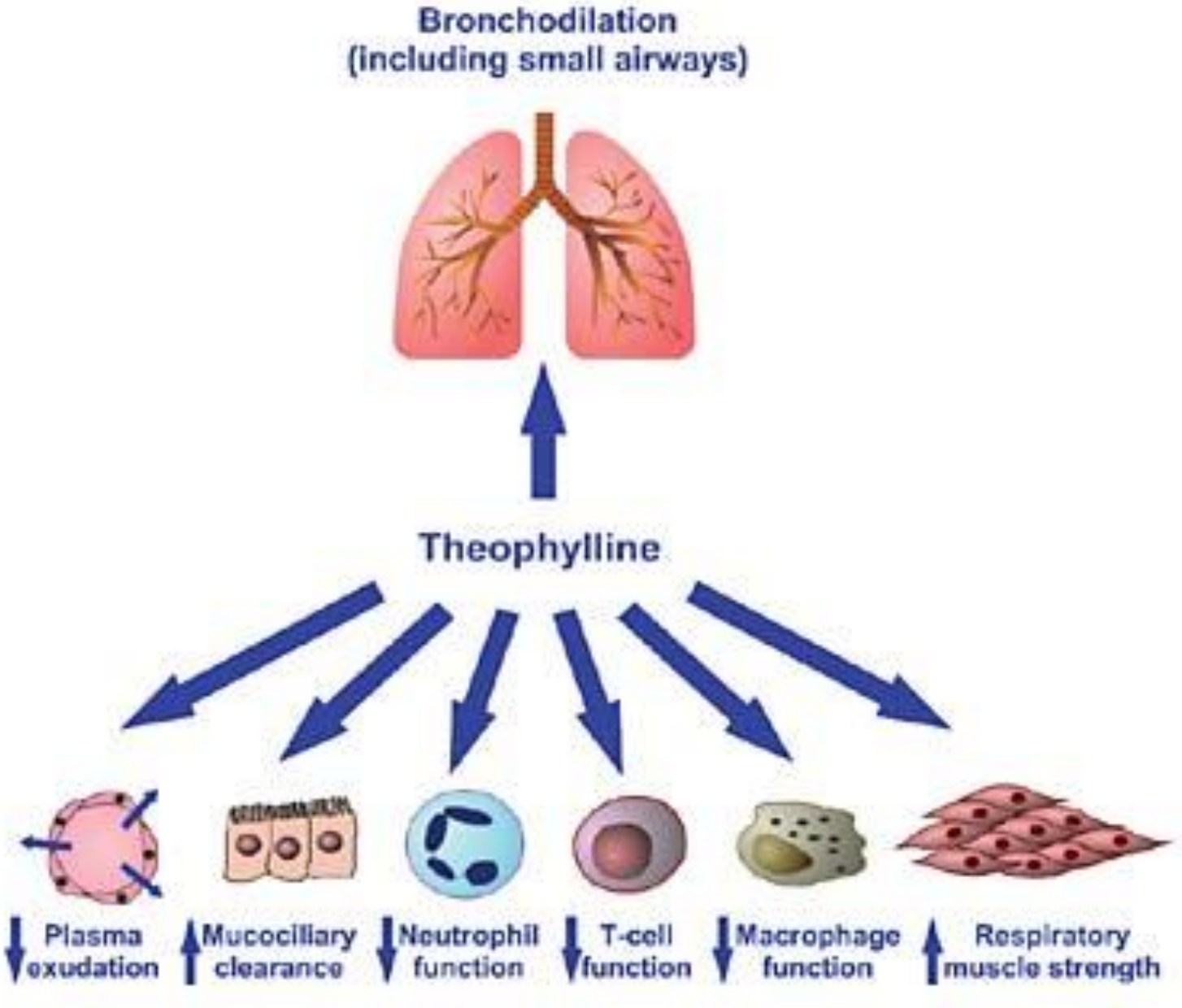
# The mechanism of the bronchodilatory action of methylxanthines

- **Methylxanthines are inhibitors of the phosphodiesterase (PDE) enzyme, which is responsible for decomposition of cyclic nucleotides (cAMP and cGMP) to the non-active monophosphates AMP and GMP.**
- **The inactivation of phosphodiesterase leads to an increase in intracellural cAMP and cGMP.**
- **The next stages of the mechanism of action of xanthines are similar to those of β-adrenergic drugs, which explains why the synergism of action of methylxanthines and $\beta_2$-agonists on the smooth muscles of the bronchi is observed.**
- **By using methylxanthines and $\beta_2$-agonists together it is possible to decrease their dosage and to reduce side effects.**


CA
ATP
cAMP
PDE
5’-AMP
Theophylline, Dyphylline
CG
GTP
cGMP
PDE
5’-GMP

# The mechanism of the bronchodilatory action of methylxanthines

- **Other forms of action of xanthines that are considered possible include:**
  - **positive inotropic effect**
  - **indirect stimulation of the respiratory center**
  - **inhibition of histamine release from leucocytes induced by an antigen**
  - **decrease in cholinolytic tension which prevents next attacks of asthma.**
- **Methylxanthines block adenosine receptors to a different degree. Theophylline inhibits more strongly A2-receptors than A1-receptors (A2/A1 = 1.7-1.9). Methylxanthines have a stimulanting effect on the CNS by neutralizing the inhibiting influence of adenosine on the CNS. Enprofylline does not directly inhibit adenosine receptors.**


Bronchodilation
(including small airways)
Theophylline
Plasma exudation
Mucociliary clearance
Neutrophil function
T-cell function
Macrophage function
Respiratory muscle strength

# The metabolism of theophylline

- The metabolism of theophylline depends on the patient's age.

- In newborns and children in the first month of life, biotransformation of theophylline is caused by methylation to caffeine. In older children and in adults 1,3-demethylation and 8-hydroxylation are observed.

- As a result of these reactions, 1-methylxanthine, 3- methylxanthine, 1-methyluric acid and 1,3-dimethyluric acid are created.

# New phosphodiesterase inhibitors for treatment of asthma and COPD

***Selective PDE4 inhibitors***

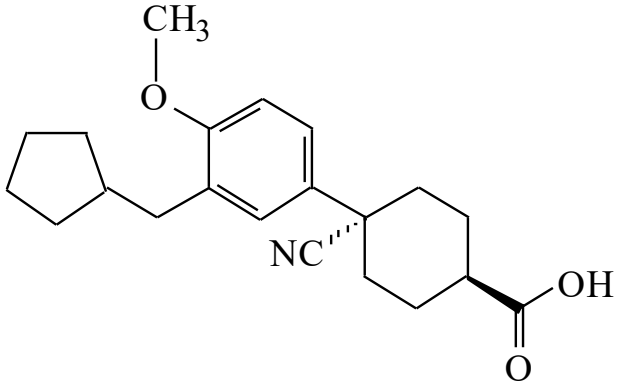
Specifically, three $PDE_4$ subtypes ($PDE_{4A}$, $PDE_{4B}$ and $PDE_{4D}$) are found in inflammatory cells (with $PDE_{4D}$ being predominant).

Therefore, recent efforts in this area have been directed toward the development and synthesis of selective $PDE_4$ inhibitors.

Two $PDE_4$ inhibitors are being investigated for their possible use in treating asthma and COPD.

In the USA, cilomilast is being investigated for the treatment of COPD, and in Europe, roflumilast is being investigated for the treatment of both asthma and COPD.

# Cilomilast, ARIFLO

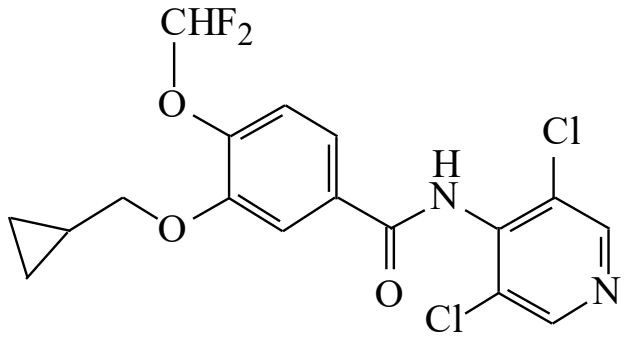



Bioavailability: 90% after orally administration

Cilomilast is 99% bound to albumin in the plasma and is metabolized in the liver by CYP2C8 (oxidation, carboxyl group glucuronidation and dealkylation of the cyclopentyl group, followed by glucuronidation or sulfation.

A major difficulty with cilomilast is that in therapeutic doses, patients during clinical trials have experienced significant diarrhea and nausea. These effects appear to be tolerable and, theoretically, result from its inhibition of the $PDE_{4D}$ receptor subtype.

# Roflumilast, DAXAS




Roflumilast is a more potent inhibitor than cilomilast toward $PDE_{4B}$.

Roflumilast is well absorbed on oral administration and has a half-life of 10 hours.
Roflumilast is metabolized in the liver to its N-oxide derivative, which also is a $PDE_4$ inhibitor, and it has a plasma half-life of 20 hours.

# Cholinolytic drugs

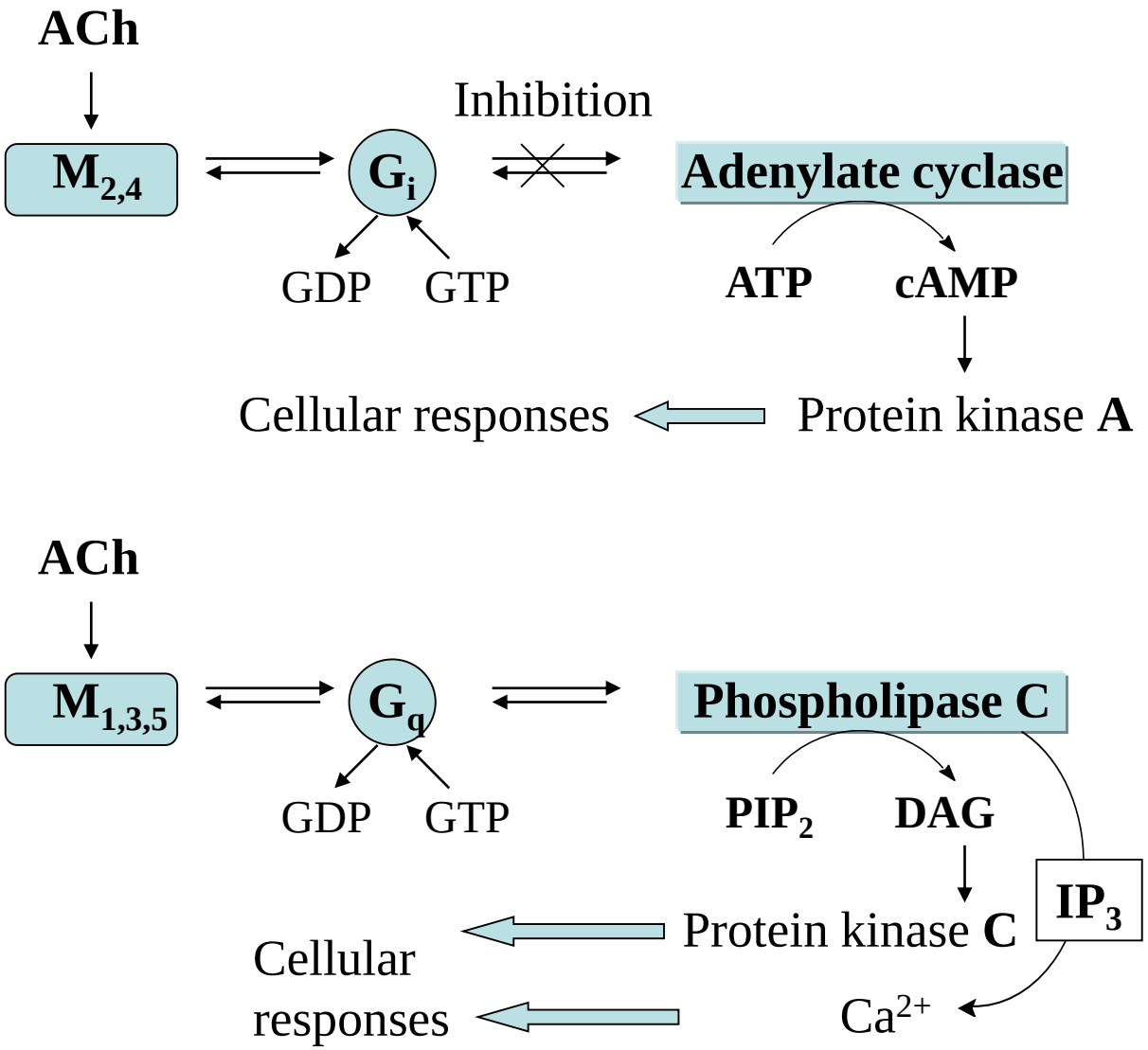
- Cholinolytic drugs relax the smooth muscles of the bronchi in asthmatics and patients with chronic bronchi-pulmonary disease, whose bronchospasm is caused by stimulation of muscarinic receptors and the afferent sensor endings of the vagus nerve and C fibrils.
- In comparison with β-adrenergic drugs, the action of cholinolytic drugs is characterized by:
  - weaker relaxation of the bronchi in asthmatics
  - the same degree or stronger relaxation of the smooth muscles in chronic bronchitis
  - later but longer effect.
- These differences are caused by the varied degree of tension of the vagus nerve. β-Adrenergic drugs relax smooth muscles irrespective of a spastic stimulus. The degree of relaxation after using cholinolytic depends on the degree of tension of the vagus nerve. An increased tension of the vagus nerve occurs in approx. 50 per cent of patients, especially at night.

# Cholinolytic drugs

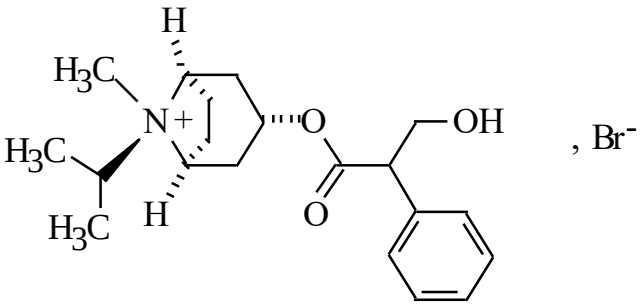
- Cholinolytics used at present are non-selective drugs. They inhibit to the same degree $M_1$, $M_2$ and $M_3$ receptors.
  **A selective inhibitor of $M_3$ receptors** would be ideal as a bronchi-relaxing drug. **Postsynaptic $M_3$ receptors** are located on the cells of the smooth muscles of the respiratory tract. Their inhibition determines the relaxation of these muscles. **Presynaptic $M_2$ receptors** are located on the nerve endings in the respiratory tract.
  The inhibition of $M_2$ receptors decreases the effect of relaxation, which is determined by the inhibition of $M_3$ receptors. In chronic inflammation, the decreased sensitivity of $M_2$ receptors, which control the release of ACh, is observed. That leads to an increased release of ACh.

- At present ipratropium bromide and oxitropium bromide are used in the treatment of asthma and in chronic bronchitis. These drugs, as quaternary ammonium salts, do not permeate the blood-brain barrier, so they do not act centrally but only peripherally.

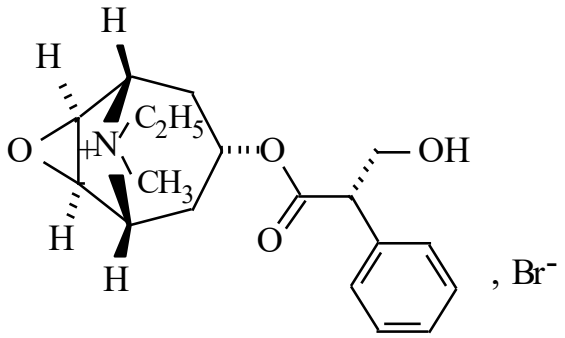
# Comparison of the role of G protein in odd- and even-numbered muscarinic receptors



# Cholinolytic drugs




*Ipratropium bromide*, ATROVENT




*Oxitropium bromide*, OXEVENT, PULSIGAN, TERSIGAN, VENTILAT

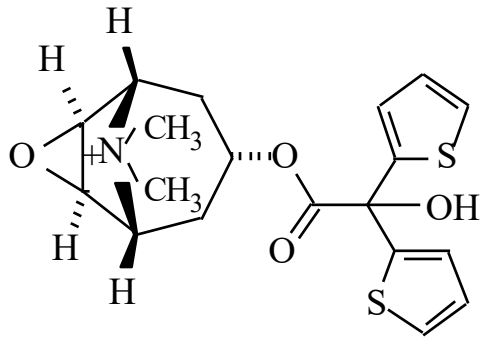
Ipratropium relaxes the bronchi and decreases the capacity of the bronchi secretion without changing its viscosity. Ipratropium decreases the post-effort spasm of the bronchi but it does not eliminate the post-histamine spasm of this organ.

# Cholinolytic drugs

- Its action develops slowly and lasts longer. It is administered as aerosol inhalation. It is not well absorbed into the circulation and thus does not have much action at muscarinic receptors other than those in the bronchi. A maximum effect occurs 30 minutes after administration and lasts for 3-4 hours. This preparation is indicated in chronic bronchospasm but it is contraindicated in proximal spasm.
- The maximum effect of ipratropium bromide is observed after 20-120 min and lasts for 6-10 hours.
- Ipratropium is used alone (ATROVENT) as an inhalant or together with β-agonists. When ipratropium is used with β-agonists, it is possible to reduce the dosage of both drugs and rapid, prolonged action is obtained. Such action is provided by BERODUAL (ipratropium bromide and fenoterol). Fenoterol starts its action after 2 minutes and ipratropium causes long-term relaxing action.
- Ipratropium bromide (ITROP) is also used in cardiology (orally and intravenously).

# Cholinolytic drugs

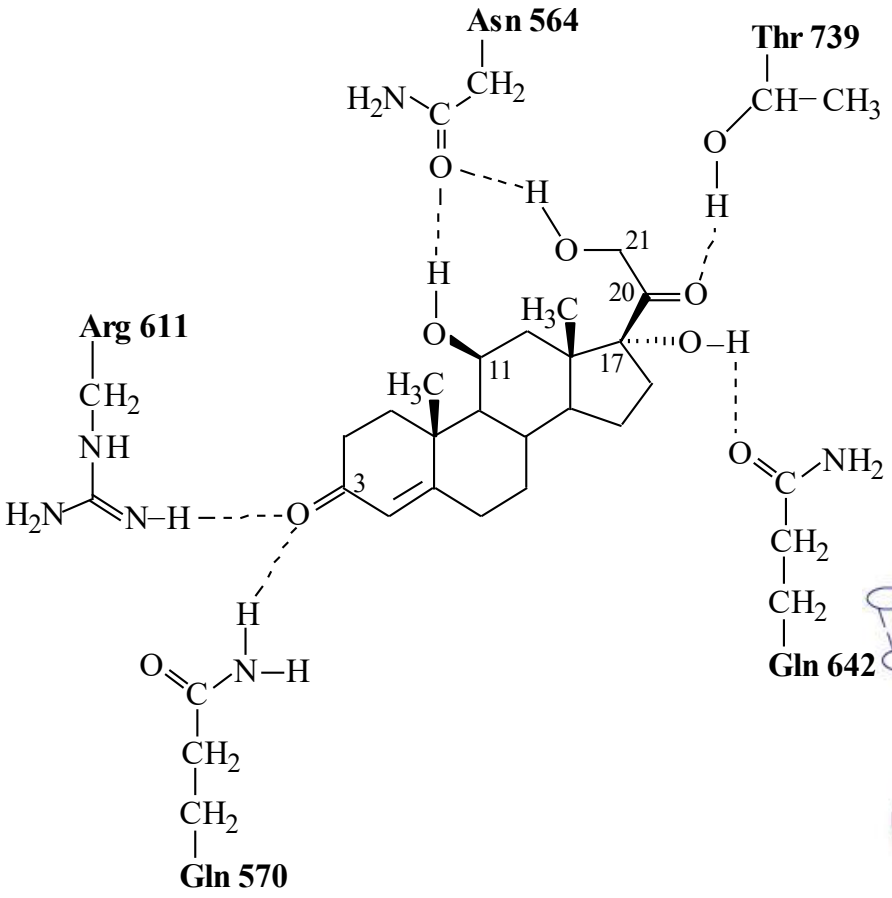
- Tiotropium inhibits the $M_3$- muscarinic receptors of the smooth muscles of the bronchi and has long-term action. It is indicated in the treatment of COPD (chronic obstructive pulmonary disease).
- Tiotropium is administered once daily as an inhalant.

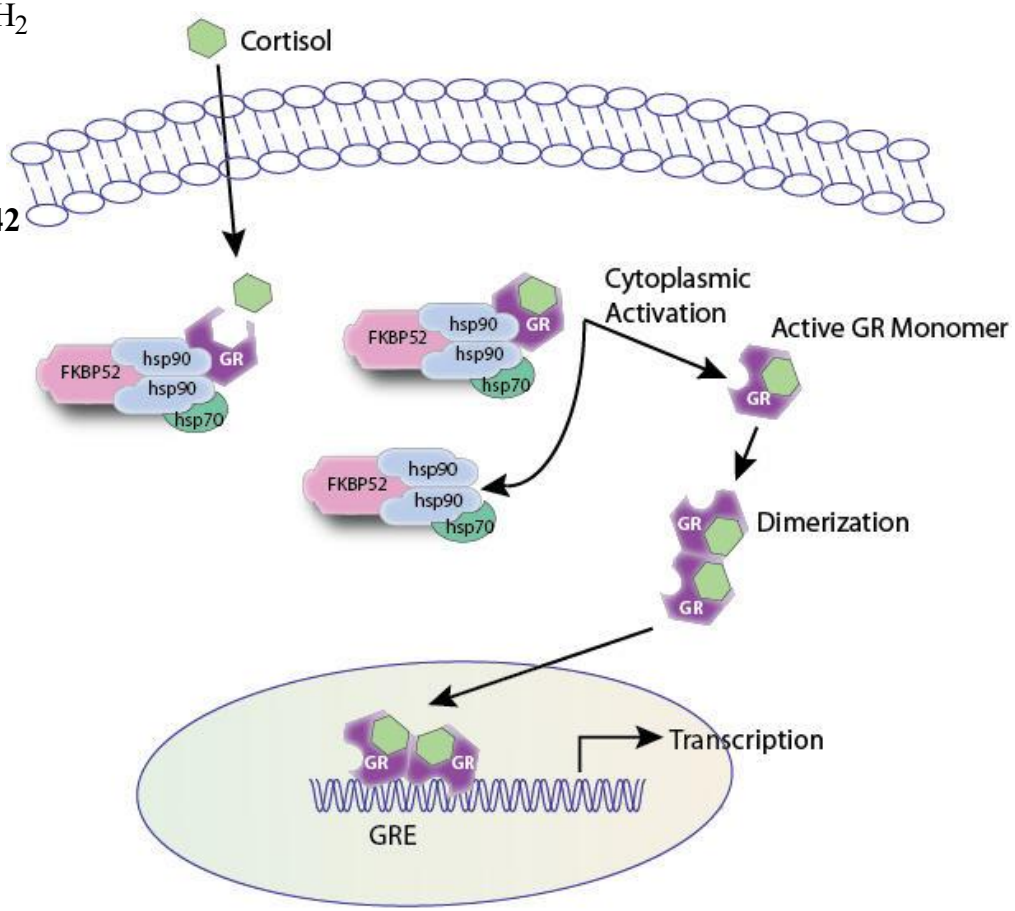



*Tiotropium*, SPIRIVA

# Glucocorticoids

- Glucocorticoids interact with steroids intercellular receptors that belong to the superfamily of receptors that control gene transcription. This superfamily also includes the receptors for mineralocortcoids, the sex steroids, thyroid hormones, vitamin $D_3$ and retinoic acid.
- Glucocorticoids, after entering cells, bind to specific receptors in the cytoplasm. After interaction with the steroid, the receptor becomes ‘activated’ i.e. it undergoes a conformational change that exposes a DNA-binding domain.
- The steroid-receptor complexes form dimmers (pairs), then move to the nucleus and bind to steroid-response elements in the DNA.


Asn 564
Thr 739
Arg 611
Gln 642
Gln 570


Cortisol
FKBP52
hsp90
GR
hsp70
Cytoplasmic Activation
Active GR Monomer
Dimerization
Transcription
GRE

# Glucocorticoids

- Lipocortin is a protein which inhibits the activity of phospholipase $A_2$ and inhibits the release of arachidonic acid and liso-PAF from membrane phospholipides, thus inhibiting creation of such lipid mediators as:
  - PAF, created from liso-PAF and acetyl-CoA under the influence of acetyltransferase
  - Metabolites of arachidonic acid formed under the influence of lipooxygenases
  - Metabolites of arachidonic acid formed under the influence of cyclooxygenases.

# Glucocorticoids

- Lipid mediators not only directly participate in the late phase of allergic reaction but also activate other inflammatory cells and stimulate the release and production of cytokines. These reactions can be interrupted by glucocorticoids, which demonstrate strong antiallergic action.
- Their action is delayed as a result of the next stages of biosynthesis of lipocortin (transcription and translation). Not all effects of the action of glucoroticoids are caused by induction of lipocortin.
- The influence of the corticoid-receptor complex on the synthesis of a gene which is necessary for the synthesis of β-adrenoreceptors during transcription is also possible. It leads to an increased density of β-adrenoreceptors and an increased response to β-sympathomimetics.

# Glucocorticoids

- Glucocorticoids can cause the expression of the gene of N-methyltransferase phenyletanolamine, which catalyses the transformation of noradrenaline to adrenaline. Adrenaline has greater affinity for β-adrenoreceptors. Glucocorticoids also increase the synthesis of endonuclease, which causes programmed cell death (apoptose).

- The anti-inflammatory action of glucocorticoids may involve the influence of the receptor-hormone complex on the transcription of the genes of induced cyclooxygenase (iCOX-2) and induced nitric oxide synthase (iNOS). As a result, a decrease in the synthesis of iCOX-2 and NO is observed. The role of nitric oxide in inflammation has not been explained yet.

# Glucocorticoids

- Steroid-receptor complexes inhibit the transcription of many cytokines, such as IL-1 or TNFα, which are involved in chronic inflammation. The inhibition of synthesis of cytokine receptors by steroids, eg. IL-2 receptors, increases the generation of these cytokines.

- Glucocorticoids may have a direct inhibiting influence on many cells which induce bronchial asthma, such as macrophages, T lymphocytes, eosinophiles and respiratory epithelium cells. Glucocorticoids do not inhibit the release of mediators of allergic reaction from mast cells, but decrease the number of these cells in the respiratory tract.

# Glucocorticoids

Glucocorticoids

- have a suppressive influence on cells in inflammation
- decrease mucus secretion in the respiratory tract, in which inflammatory changes occur
- have an anti-inflammatory effect on the mucosa of the bronchi by decreasing the oversensitivity of the cells of the respiratory tract, both in adults and children with asthma
- inhibit the hyperplasia of the cells of the epithelium of the bronchi
- inhibit the reactivity of cells to histamine, agonists of the cholinergic system and allergens
- decrease cell response to cold, humidity, bradykinine, adenosine and other irritative factors, such as sulfur dioxide and nitrogen oxide.

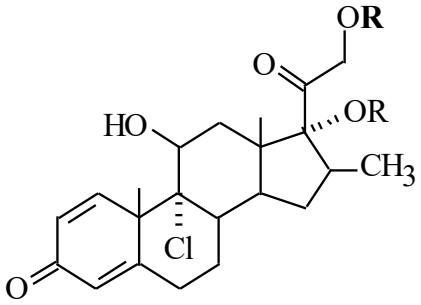
# Glucocorticoids

- In the treatment of asthma glucocorticoids are used orally, parenterally or as inhalants. Inhalatory therapy plays an important role because it reduces side effects, even when it is used for a long time.
- Unwanted effects are observed mainly when systemic therapy is administered. Using glucocorticoids as inhalants permits an effective concentration in the place of action without increasing the concentration of glucocorticoids in the systemic circulatory system.
- An ideal glucocorticoid used as an inhalant should stay in the lungs for a long time, should not be resorbed and should be slowly transported to the systemic system. When it reaches the systemic system, it should be rapidly metabolized in the liver, if possible, to non-reactive metabolites. These requirements are very well satisfied by lipophilic glucocorticoids. Such drugs should be administered as inhalants to all patients with asthma who must inhale β-mimetics more often than once daily.

# Glucocorticoids

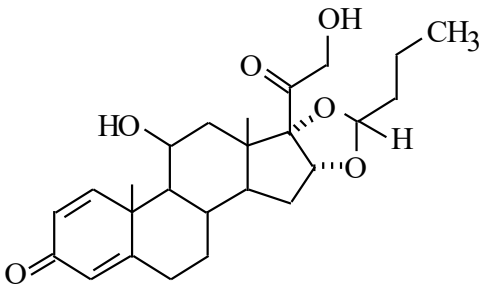
The following are used as inhalants:

- preparations of beclomethasone – Beclomethasone dipropioniate (BECLOCORT, BECLOFORTE, BECONASE, BECOTIDE)
- preparations of budesonide (BUDESONID)
- preparations of flunisolide (BRONILIDE)
- preparations of fluticasone (fluticasone propionate, FLIXOTIDE)
- preparations of mometasone furoate (ASMANEX)
- preparations of triamcinolone acetonide (AZMACORT)



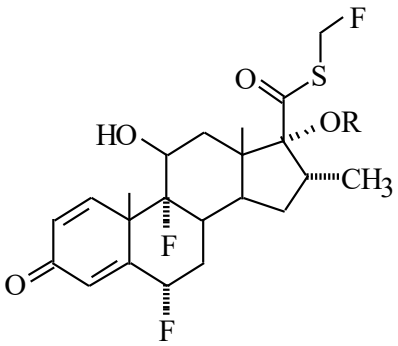

***Beclometasone dipropionate*, R = $R_1$ = -CO-$CH_2$-$CH_3$**

**BECLOFORTE, BECLOMET, BECOTIDE, BECONASE, BETNESOL, PROPADERM**




***Budesonide***, BUDECORT, BUDESONID, HORACORT, PULMICORT, RHINOCORT

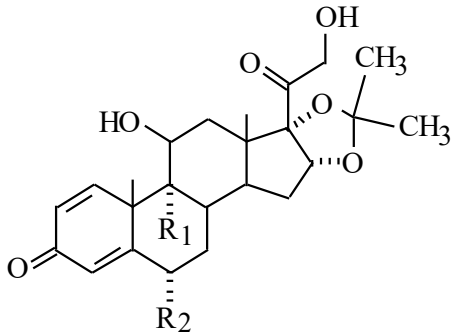
(11,16)-16,17[Butylidenobis(oksy)]-11,21-dihydroksy-pregna-1,4-dieno-3,20-dion




***Fluticasone***, R = H

*Fluticasone propionate*, R = -CO-$CH_2$-$CH_3$

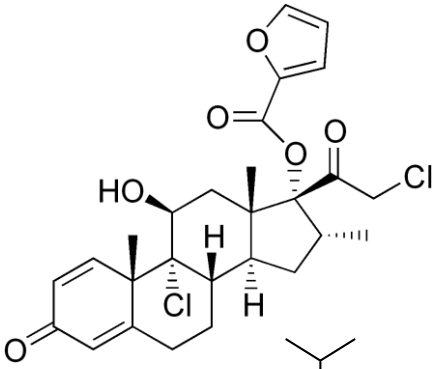
FLUTICASONE, FLIXOTIDE, FLIXONASE, FLUTIDE, FLUTINASE



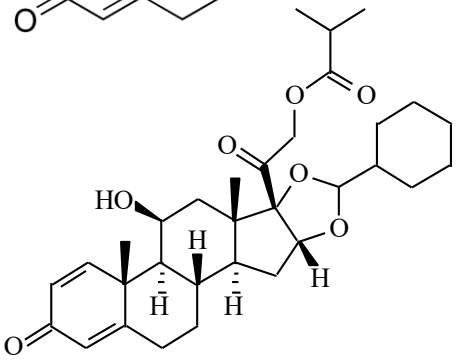

***Flunisolide***, $R_1$ = H, $R_2$ = F; BRONILIDE, SYNTARIS

***Triamcinolone acetonide***, $R_1$ = F; $R_2$ = H

POLCORTOLON, MONACORT




*Mometasone furoate*
ASMANEX Twisthaler




*Ciclesonide*, ALVESCO

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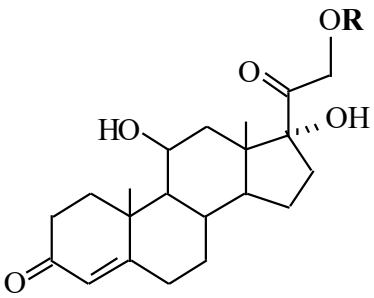



***Hydrocortisone sodium succinate***
HYDROCORTISONUM HEMISUCCINATUM
It is used parenterally

# Glucocorticoids

- Beclomethasone dipropioniate has anti-inflammatory, antiallergic and antiproliferative action 40-times stronger than hydrocortisone. Beclomethasone dipropionate is administerd as an inhalant as well as micronised powder together with lactose (BECODISK).
- This preparation is recommended for patients who have never or rarely been treated with steroids. Improved respiratory efficiency usually occurs within one week.
- Preparations of beclomethasone dipropioniate are indicated especially in the treatment of acute atopic bronchi asthma in children.
- The minimal systemic action of this drug does not inhibit growth and makes it possible to effectively control pathological processes.

# Glucocorticoids

- Flunisolide shows very strong anti-inflammatory action, high selectivity and slight adverse effects. It acts twice as strongly as beclomethasone and its time of action is 12 hours.
- Fluticasone, as it is a tioester, rapidly metabolizes to non-active metabolites in the systemic system. These derivatives do not suppress the axis hypophysis – hypothalamus – adrenal gland. Fluticasone propionate is used in bronchial asthma and in chronic spastic bronchial inflammation as a powder for inhalation (FLIXOTIDE ROTADISK, FLOVENT ROTADISK).
- With respect to affinity for hGR (human glucocorticosteroid receptor) in the case of fluticasone it is 10 times greater that in the case of dexamethasone, twice greater than that of beclomethasone 17-monopropionate and 3 times greater than that of budesonide. The preparation SERETIDE was developed recently. It is a union of the long-acting β-adrenergic drug salmeterol with a glucoroticoid – fluticasone. This union is more desirable than administering both active substances separately and more comfortable for patients. The cost of therapy is also reduced.

# Glucocorticoids

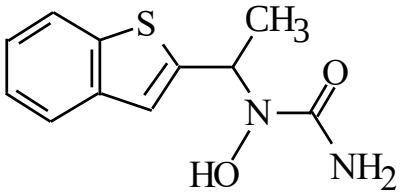
- The main adverse effects of using glucocorticoids are dysphonia, cough and mycosis of the oral cavity. Mycosis, mainly candidiasis is treated by using fungicidal drugs.
- In chronic bronchial asthma glucocorticoids such as betamethasone dipropionate (DIPROPHOS) and triamcinolone acetonide (POLCORTOLON) with long-time action are used intramuscularly.
- In acute attacks of bronchial asthma hydrocortisone hemisuccinate is administered intravenously. The blockade of secretion of leukotrienes after intravenous administration is observed after 2 hours.
- A mast cell regenerates after degranulation and after approx. 4 hours it is ready for next degranulation, which is the release of different mediators of anaphylactic reaction. For that reason glucocorticoids should be administered at least every 4 hours.

# Lipooxygenase inhibitors and antagonists at LT-receptors

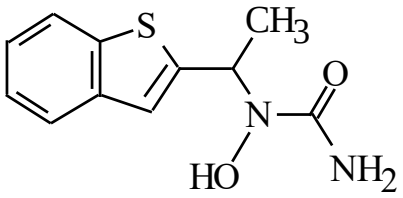
- Leukotrienes are an important group of mediators released from the inflammatory cells. Peptideleukotrienes LTC4, LTD4 and LTE4 act extremely bronchospastically, even 100-1000 times more strongly than histamine. This action develops far more slowly than in the case of other mediators.
- A mixture of leukotrienes LTC4-LTE4 is referred to as a slow-acting anaphylactic factor. LTC4 and LTD4 also increase the release of mucosa and cause epithelium edema. LTB4 does not act bronchospastically but is the strongest chemotactic factor.
- LTB4 increases the synthesis and release of IL-1 and stimulates the replication of keratocytes. LTB4 influences the overreactivity of the bronchi together with other mediators which are derived from inflammatory cells.

# Lipooxygenase inhibitors and antagonists at LT-receptors

- There are several ways of suppressing reactions caused by LTs, eg. inhibiting the activity of 5-LOX, inhibiting LT synthase, blocking LT-receptors. LOX inhibitors are divided into two groups: inhibitors of enzyme translation (FLAP) and direct inhibitors of enzyme activity.
- 5-LOX inhibitors may be very important in the treatment of asthma, hay fever, psoraisis, intestinal ulceration and arthritis.
- Many compounds which inhibit 5-LOX have been obtained. Some of them are in clinical trials. Zileuton is one of those drugs which have been introduced into therapy.




*Zileuton*




## *Zileuton*, ZYFLO

Zileuton is the ethylbezothienyl derivative of *N*-hydroxyurea and occurs as the racemic mixture of *R*-(+) and *S*-(–)-enantiomers, both of which are pharmacologically active. The hydroxyl group is essential for inhibitory activity, with the benzothienyl group contributing to its overall lipophilicity.

Zileuton is metabolized in the liver to inactive O-glucuronide (major metabolite). The glucuronidation is stereoselective; *S*-isomer is metabolized and eliminated more quickly.

The most serious side effects of zileuton is elevetion of liver enzymes.

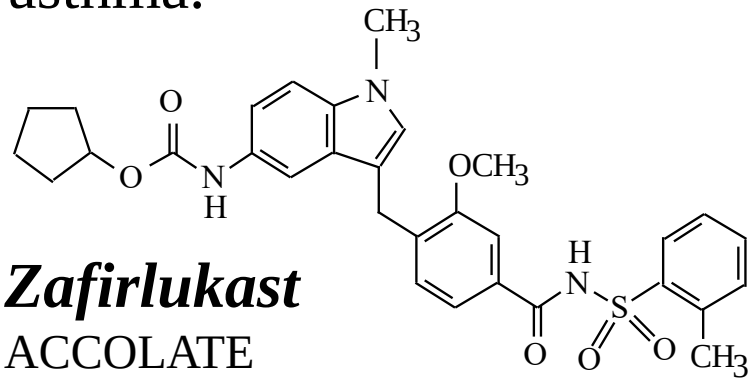
If symptoms of liver dysfunction (e.g., nausea, fatigue, pruritis, jaundice, or flu-like symptoms) occur, the drug should be discontinued.

# Antagonists at LT-receptors

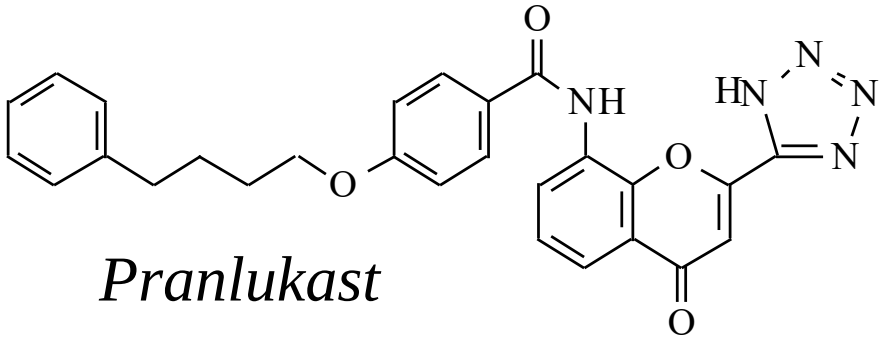
- Three types of LT receptors have been discovered in the lungs. Their stimulation leads to the spasm of the smooth muscles of the bronchi.
  It is believed that in the treatment of asthma $LTD_4$-antagonists may be crucial.
- Antagonists at LT-receptors inhibit the spasm of the bronchi and inflammatory reactions. They also suppress the migration of lymphocytes in the respiratory tract and inhibit the activity of macrophages.

# Antagonists at LT-receptors

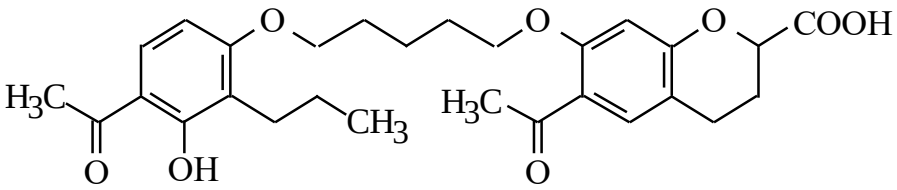
- Zafirlukast, Pranlukast, Montelukast, Ablukast and Tomelukast are classified as T-receptor antagonists. Zafirlucast and Ablucast are indicated in the treatment of acute seasonal rhinitis and bronchial asthma.



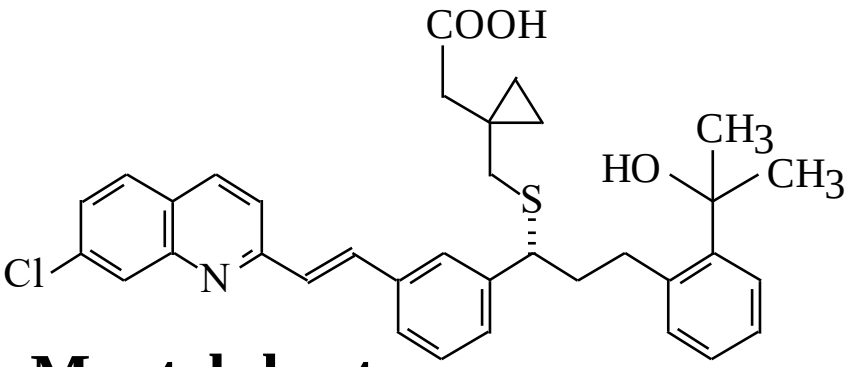
***Zafirlukast***
ACCOLATE



*Pranlukast*



*Ablukast*



**Montelukast**
SINGULAIR

**Montelukast** is a high-affinity, selective antagonist of the cysLT$_1$ receptor.

It is available in tablet, chewable tablet, and granules for administration mixed with food.

**Zafirlukast**, like montelukast, is a selective antagonist for the cysLT$_1$ receptor and antagonize the bronchoconstructive effects of all leukotrienes (LTC$_4$, LTD$_4$ and LTE$_4$).

Zafirlukast can produce an idiosyncratic hepatotoxicity in susceptible patients, because under the influence of glutathione S-transferase it forms an adduct with glutathione.

Zafirlukast is also metabolized by CYP2C9 and CYP3A4 to hydroxylated metabolites.

Zafirlukast is only available in tablet formulations.

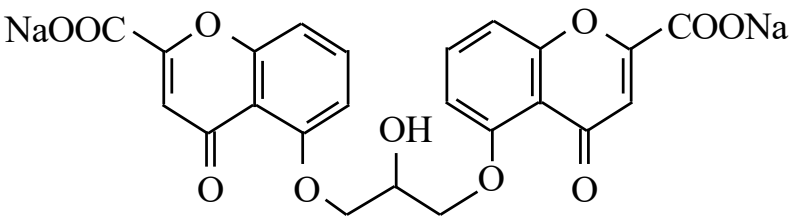
# Drugs stabilizing mast cells

- The development of the late phase of allergic reaction is caused by the release of inflammatory mediators. The inhibition of this process is called prevention. In the prevention of asthma drugs stabilizing mast cells, such as cromoglycate disodium, nedocromil disodium and ketotifen are used.
- They are administered to prevent attacks of bronchospasm. When they are used during bronchospasm they do not act.
- These drugs prevent releasing inflammatory mediators from mast cells, but they do not inhibit the binding of IgE with these cells, or the interaction of IgE with an antigen.
- When preventive drugs are used for a long time, they decrease the reactivity of the smooth muscles of the bronchi, the number and severity of bronchospasm attacks. Their use is necessary when bouts of bronchospasm occur more often than 1 or 2 times a week.

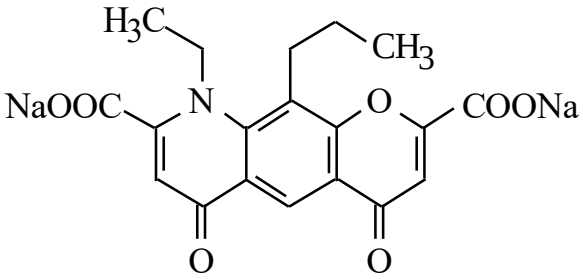
# Drugs stabilizing mast cells

- Cromoglicate disodium and nedocromil disodium are administered as micronised powder for inhalation.

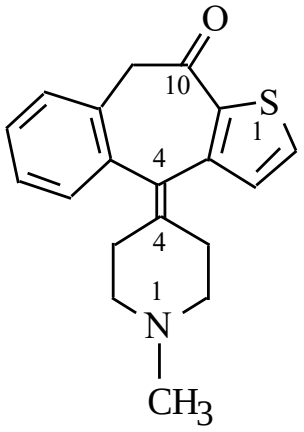
- Nedocromil acts many times more strongly than cromoglicate.
- Ketotifen is well absorbed from the gastrointestinal tract and it is used orally as tablets, capsules or syrup. Ketotifen has depressive action on the CNS.




*Cromoglicate disodium*
CROPOZ PLUS, INTAL, LOMUSOL




*Nedocromil sodium*,
HALAMID, TILADE, TILARIN




*Ketotifen*, POZITAN, KETOTIFEN, ZADITEN

# Monoclonal anti-IgE antibody

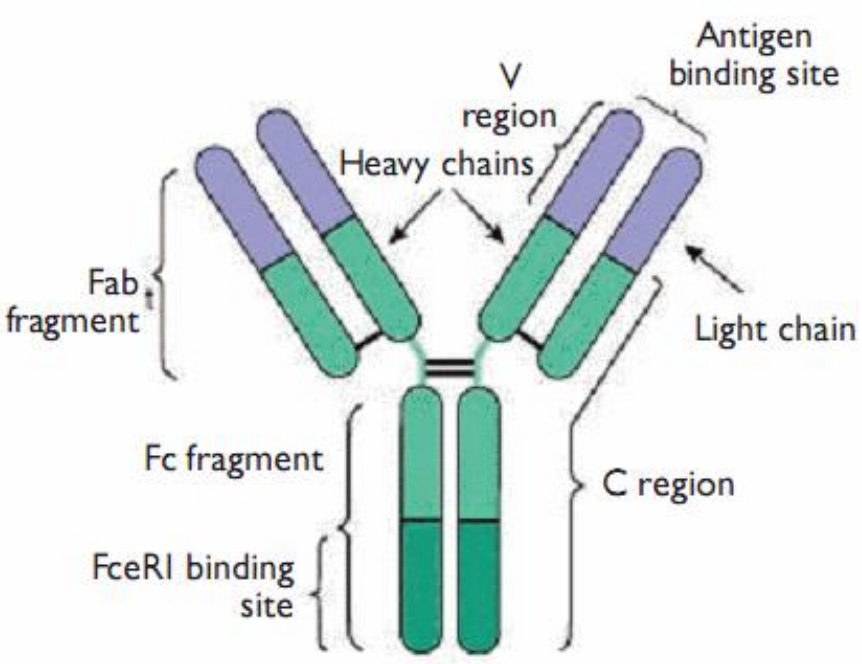
**Omalizumab** is a monoclonal antibody developed through somatic cell hybridization techniques and was identified as a murine anti-human IgE antibody, originally called MAE11.

It is designed to interact with the site that binds to FcεRI on mast cells.

Additional amino acid sequences have been incorporated into the antibody so that a humanized product resulted that only differs by 5% nonhuman amino acid residues.

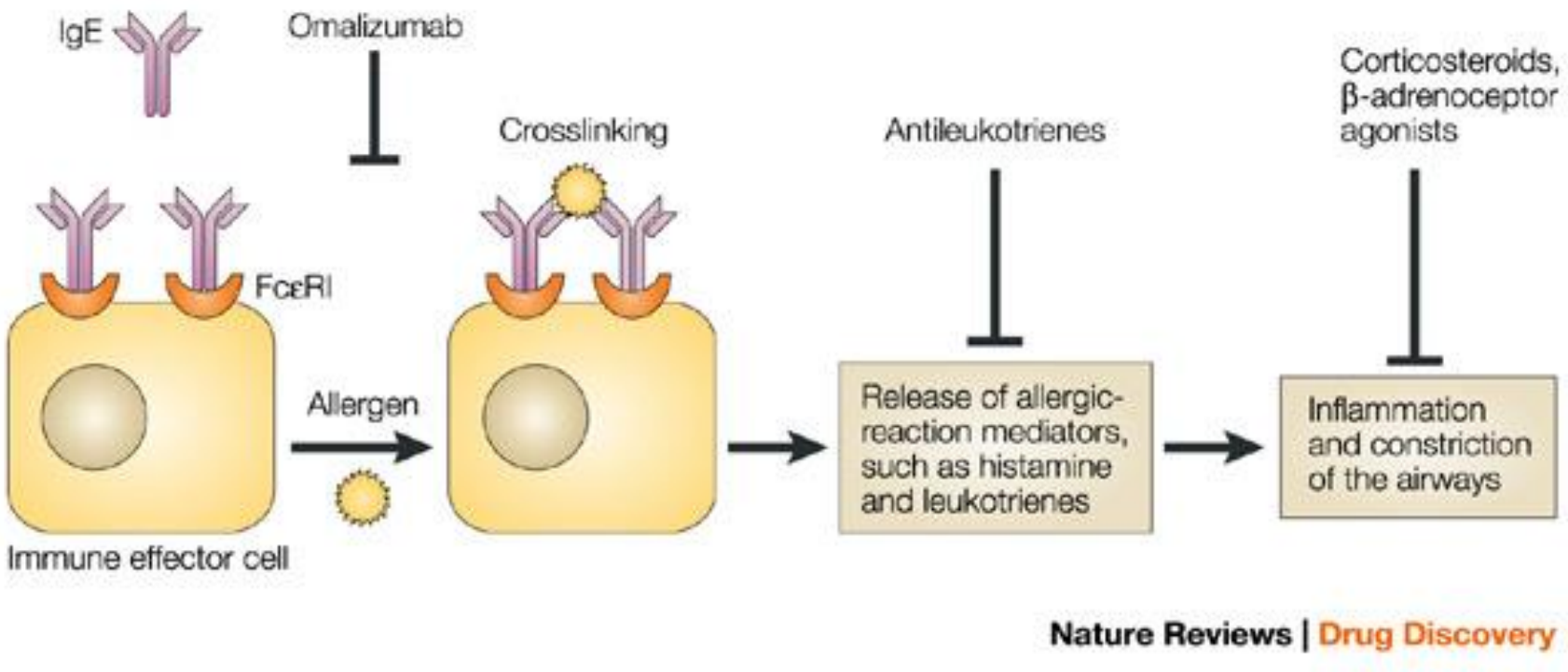
# Omalizumab, XOLAIRE

In vitro, omalizumab has been shown to complex with free IgE, forming trimers consisting of a 2:1 complex of IgE to omalizumab or a 1:2 complex of IgE to omalizumab




In addition, larger complexes also are formed, consisting of a 3:3 ratio of each. Omalizumab does not bind to IgE already bound to mast cells and, therefore, does not cause the degranulation that might be expected from such interaction.

Thus, omalizumab effectively neutralizes free IgE and, aside from the obvious decrease of available IgE, also causes the down-regulation of FcεRI receptors on the mast cell surface, resulting in decrease of IgE bound to the mast cell.




Omalizumab

Stephen A. Ames, Carole D. Gleeson & Peter Kirkpatrick

***Nature Reviews Drug Discovery* 3, 199-200 (March 2004)**

# Omalizumab, XOLAIRE

The clinical role for omalizumab is in the treatment of allergic asthma. It is approved for the treatment of adults and adolescents 12 years of age and older whose symptoms are not controlled with inhaled glucocorticoids and who have a positive skin test for airborne allergens.

The bioavailability after subcutaneous administration is 62%, with slow absorption resulting in peak serum levels in 7 to 8 days from a single dose.

Steady-state plasma concentration is reached in 14 to 29 days with multiple dosing regiments.

Omalizumab is available as a lyophilized powder for injection in single-use, 5 ml vials.

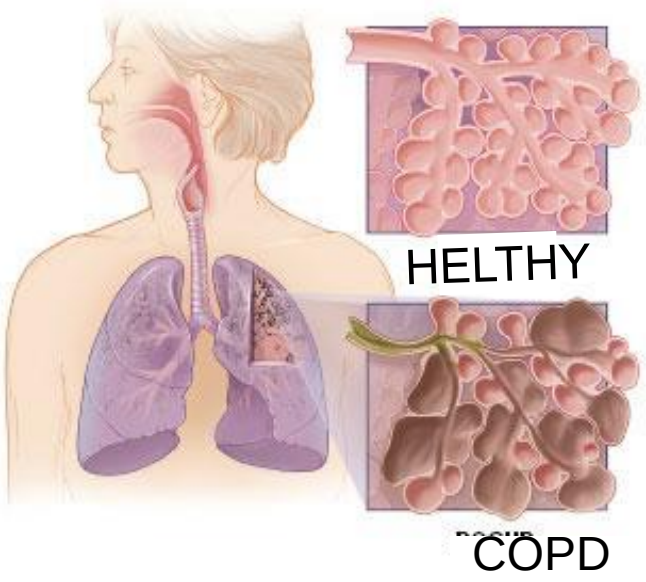
# Chronic obstructive lung disease (COPD)

**Morbus obturativus pulmonum chronicum**

Chronic obstructive lung disease is characterized by persistent breathing difficulty that is not completely reversible and is progressive over time.

It usually is the result of an abnormal inflammatory response to airborne toxic chemicals.

Thus, COPD is a general term and most commonly refers to chronic bronchitis and emphysema.



# Epidemiology

In the USA COPD is the fourth leading cause of death, being responsible for more than 100,000 deaths per year.

It has been estimated that between 16 and 24 million people in the USA have COPD and that those with chronic bronchitis outnumber those with emphysema.

Rates of COPD-related death among women have tripled over the last 30 years, and this is being attributed to their increase in smoking.

# Pathogenesis

**The single most important risk factor for the development of COPD is smoking. It is estimated that 85% of COPD cases are attributable to cigarette smoking. Not all people who smoke, however, develop the disease, which means other factors are involved.**

**It seems that genetics, environmental pollutants, and infection along with bronchial hyperreactivity all play an important role.**

# Smoking

**Cigarette smoke attracts inflammatory cells into the lungs and stimulates the release of the proteolytic enzyme elastase.**

**Elastaze breaks down elastin, which is a needed structural component of lung tissue.**

**Normally, the lung is protected from elastase by an inhibitor, $\alpha$1-antitrypsin (ATT).**

**Cigarette smoke, however, causes an abnormal amount of elastase to be produced that ATT cannot counter, leading to lung damage.**

**Smokers with an inherited deficiency of ATT have a greatly increased risk of developing emphysema, especially at an early age.**

# Pharmacotherapy

**The GOLD guidelines = The Global Initiative for Chronic Lung Disease**

**Stages O is defined as „at risk”**

The patient has normal lung function, with chronic cough and sputum production.

Treatment at this stage is to counsel the patient to reduce risk and, especially, to stop smoking.

# Pharmacotherapy

**Stage I (mild COPD)**

In stage I, there is minor airway limitation, characterized as $FEV_1$/FVC <70% but FEV1 ≥ 80% of the predicted value.

Stage I treatment is to use a short-acting bronchodilatator, usually as needed, but regular use is effective in patients with concurrent asthma. The most frequently used short-acting bronchodilatator is the $\beta_2$-agonist albuterol. Although pirbuterol and the anticholinergic ipratropium can be just as effective, but with a slightly longer onset of action.

The patient also should take precautions to avoid bacterial or viral infections by receiving vaccinations against influenza and pneumococcal pneumonia.

**Stage II (moderate disease)**

The patient demonstrates shortness of breath on exertion and spirometry reveals FEV1/FVC <70% and FEV1between 50 and 80% of the predicted value.

Stage II drug treatment requires the addition of a long-acting bronchodilatator along with a short-acting bronchodilatator. Salmeterol and formoterol are long-acting β2-agonists, and tiotropium is the long-acting anticholinergic most often used. Alternatively, the addition of ipratropium along with the short-acting β2-agonist also can be effective at this stage.

Extended-release theophylline is an option for patients who do not receive adequate relief of symptoms or who cannot tolerate other bronchodilatators.

**Stage III (a severe form of COPD, with FEV1/FVC <70% and FEV1between 30 and 50% of the predicted value)**

The patient experiences increasing dyspnea that affects his or her ability to perform routine tasks (i.e., climbing stairs).

A course of oral glucocorticoids (i.e., prednisone) may be used to control a severe attack.

**Stage IV (the most severe form of COPD with airflow restriction FEV1/FVC <70% and FEV1between < 30% of the predicted value along with chronic respiratory failure)**

At this stage, the patient is experiencing debilitating exacerbations that are not controlled by medication and requires daily oxygen for respiratory failure.

Surgery also is an option, but it is not without serious risks. Surgical options include bullectomy (removal of large blebs in the lungs), lung transplant (uncommon), and lung volume reduction surgery (removal of lung sections affected by emphysema).

Patients with emphysema that is associated with ATT deficiences can receive weekly IV infusions of to maintain acceptable antiprotease activity that can minimize their disease progression.

The three approved ATT products are **ARALAST, PROLASTIN, ZEMAIRA.**

Because these protein products are derived from human plasma, there is the risk of transmission of viral infection and Creutzfeldt-Jakob disease.