MSc Pharmaceutical Chemistry
Semester 4
16P4CPHT15EL DRUG DESIGN
UNIT 6
Topic : DRUGS ACTING ON CNS

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The motor (efferent) portion of the nervous system can be divided into two major subdivisions: autonomic and somatic.

The autonomic nervous system (ANS) is largely independent in that its activities are not under direct conscious control. It is concerned primarily with visceral functions such as cardiac output, blood flow to various organs, and digestion, which are necessary for life.

The somatic division is largely concerned with consciously controlled functions such as movement, respiration, and posture.

Nerve impulses elicit responses in smooth, cardiac, and skeletal muscles, exocrine glands, and postsynaptic neurons by liberating specific chemical neurotransmitters.

By using drugs that mimic or block the actions of chemical

transmitters, we can selectively modify many autonomic

functions. These functions involve a variety of effector

tissues, including cardiac muscle, smooth muscle,

vascular endothelium, exocrine glands, and

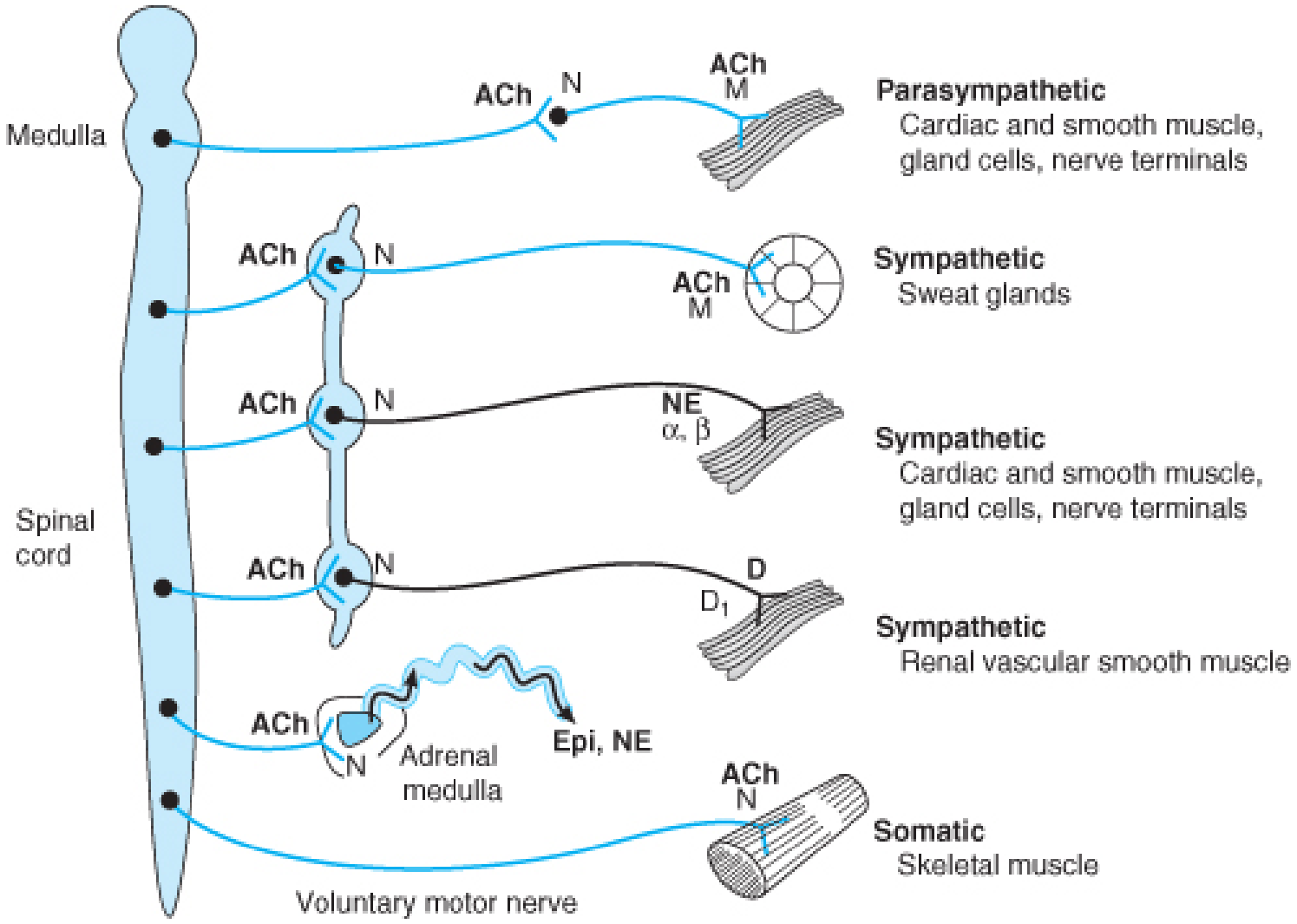
presynaptic nerve terminals.

Autonomic drugs are useful in many clinical conditions

The ANS has two major portions:

the sympathetic division and

the parasympathetic division.


Medulla
Spinal cord
ACh
N
ACh
M
Parasympathetic
Cardiac and smooth muscle, gland cells, nerve terminals
ACh
N
ACh
M
Sympathetic
Sweat glands
ACh
N
NE
α, β
Sympathetic
Cardiac and smooth muscle, gland cells, nerve terminals
ACh
N
D
D1
Sympathetic
Renal vascular smooth muscle
ACh
N
Adrenal medulla
Epi, NE
ACh
N
Somatic
Skeletal muscle
Voluntary motor nerve

- Parasympathetic nerves regulate processes
- connected with *energy assimilation* (food intake,
- digestion, absorption) *and storage*.

- These processes operate when the body
- is at rest, allowing increased bronchomotor tone (state of contraction or relaxation of the smooth muscles in the bronchial wall) and decreased cardiac activity.

- Secretion of saliva and intestinal fluids promotes the
- digestion of foodstuffs; transport of intestinal contents
- is speeded up because of enhanced peristaltic activity

Definitions

- Sympathetic and parasympathetic divisions typically function in opposition to each other. But this opposition is better termed complementary in nature rather than antagonistic. For an analogy, one may think of the sympathetic division as the accelerator and the parasympathetic division as the brake.

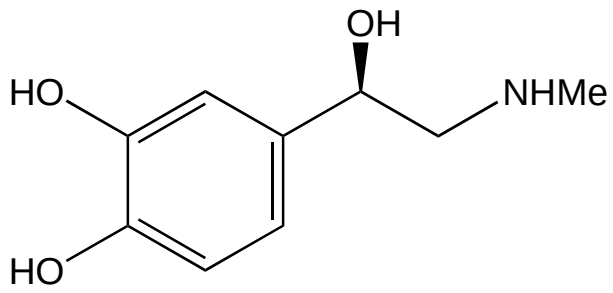
- The sympathetic division typically functions in actions requiring quick responses.

- The parasympathetic division functions with actions that do not require immediate reaction.

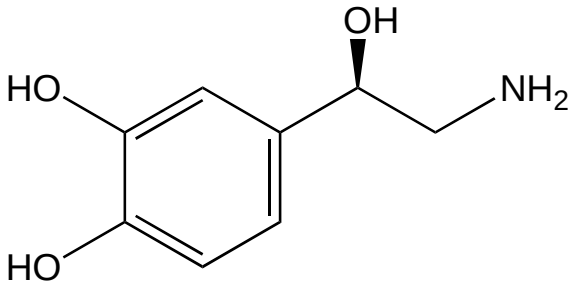
- Consider sympathetic as "fight or flight" and parasympathetic as "rest and digest".

I. Adrenergic Nervous System (Sympathetic System)

Uses adrenaline (epinephrine) and noradrenaline (norepinephrine) as neurotransmitters



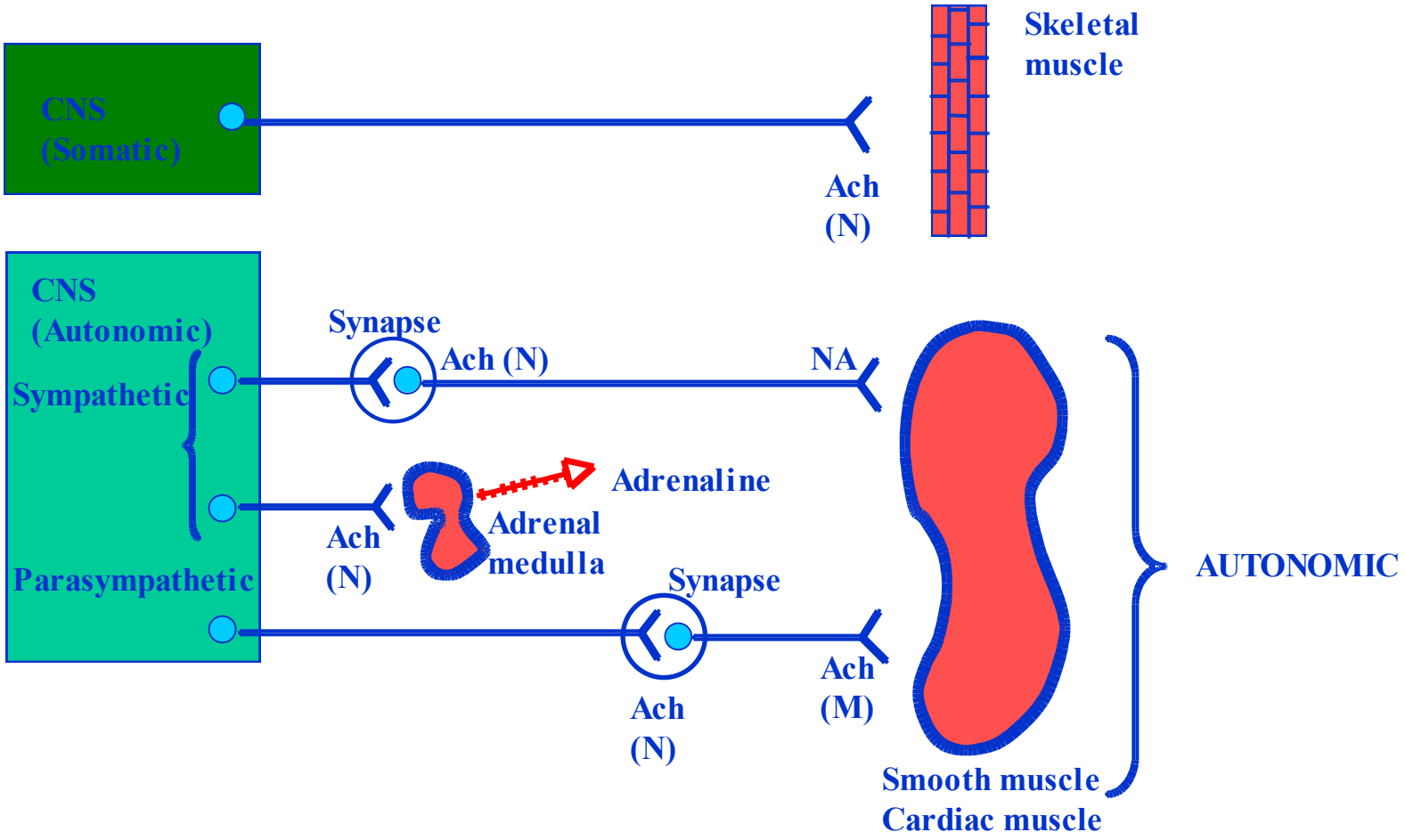
Epinephrine
(Adrenaline)



Norepinephrine
(Noradrenaline)

1. Nerve Transmission

Peripheral nervous system



Fight or Flight?

- The **fight-or-flight** response, also called the acute stress response, was first described by Walter Cannon in 1929. His theory states that animals react to threats with a general discharge of the sympathetic nervous system, priming the animal for fighting or fleeing. This response was later recognized as the first stage of a general adaptation syndrome that regulates stress responses among vertebrates and other organisms.

- Normally, when a person is in a serene, unstimulated state, the "firing" of neurons in the locus ceruleus is minimal. A novel stimulus (which could include a perception of danger or an environmental stressor signal such as elevated sound levels or over-illumination), once perceived, is relayed from the sensory cortex of the brain through the thalamus to the brain stem. That route of signaling increases the rate of noradrenergic activity in the locus ceruleus, and the person becomes alert and attentive to the environment. Similarly, an abundance of catecholamines at neuroreceptor sites facilitates reliance on spontaneous or intuitive behaviors often related to combat or escape.If a stimulus is perceived as a threat, a more intense and prolonged discharge of the locus ceruleus activates the sympathetic division of the autonomic nervous system (Thase & Howland, 1995). This activation is associated with specific physiological actions in the system, both directly and indirectly through the release of epinephrine (adrenaline) and to a lesser extent norepinephrine from the medulla of the adrenal glands. The release is triggered by acetylcholine released from preganglionic sympathetic nerves. The other major player in the acute stress response is the hypothalamic-pituitary-adrenal axis.

Fight or Flight Response:

- These catecholamine hormones facilitate immediate physical reactions associated with a preparation for violent muscular action. (Gleitman, et al, 2004). These include the following:

- ・Acceleration of heart and lung action・Inhibition of stomach and intestinal action
- ・Constriction of blood vessels in many parts of the body
- ・Liberation of nutrients for muscular action
- ・Dilation of blood vessels for muscles
- ・Inhibition of tear glands and salivation
- ・Dilation of pupil
- ・Relaxation of bladder
- ・Inhibition of erection

Adrenergic Receptors

- In 1948, adrenergic receptors were subdivided into alpha and beta by Ahlquist. The distinction was based on sensitivities of different organs to catecholamines of closely related structure. Regulation of the functions of different organs depends to a greater or lesser extent on alpha or beta receptors.

- Alpha receptors are located postsynaptically at sympathetic neuroeffector junctions of many organs. In general, alpha receptors mediate excitation or increased activity of the effector cells. Vascular smooth muscle is an important site of alpha receptors. SNS activity maintains vascular tone, and thus blood pressure, by maintaining a tone of neurotransmitter on vascular alpha receptors.

- Beta receptors are also located postsynaptically at sympathetic neuroeffector junctions of many organs. In general, beta receptors mediate relaxation or decreased activity of the effector cells. Thus, blood vessels dilate and uterine smooth muscle relaxes in response to activation of beta receptors. Heart muscle is an important exception to this rule. Activation of beta adrenoceptors in heart increases the automaticity and contractility of all parts of the heart.

Types of α-adrenergic receptor

- **α-adrenergic receptors** are adrenergic receptors that respond to norepinephrine and to such blocking agents as phenoxybenzamine.
- They are subdivided into two types:
- **α1**, found in smooth muscle, heart, and liver, with effects including vasoconstriction, intestinal relaxation, uterine contraction and pupillary dilation,
- **α2**, found in platelets, vascular smooth muscle, nerve termini, and pancreatic islets, with effects including platelet aggregation, vasoconstriction, and inhibition of norepinephrine release and of insulin secretion.

β-receptor types

- **β-adrenergic receptors** respond particularly to epinephrine and to such blocking agents as propranolol.
- There are three known types of beta receptor, designated β_1, β_2 and β_3.
- β_1-Adrenergic receptors are located mainly in the heart.
- β_2-Adrenergic receptors are located mainly in the lungs, gastrointestinal tract, liver, uterus, vascular smooth muscle, and skeletal muscle.
- β_3-receptors are located in fat cells.

What do the receptors do?

Activation of **α receptors** leads to smooth muscle contraction

Activation of **β_2 receptors** leads to smooth muscle relaxation

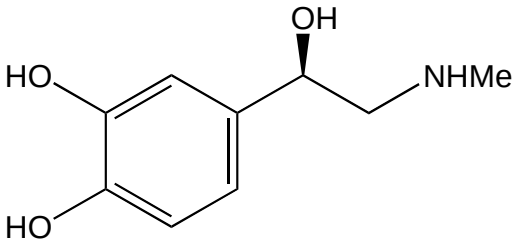
Activation of **β_1 receptors** leads to smooth muscle contraction (especially in heart)

Clinical Utility of drugs which affect the adrenergic nervous system:

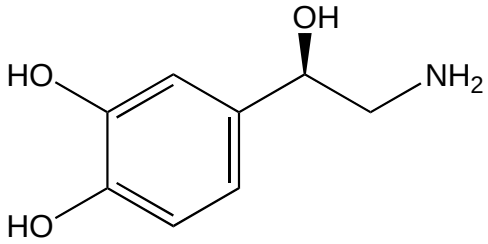
a. **Agonists** of the β_2 **receptors** are used in the treatment of asthma (relaxation of the smooth muscles of the bronchi)

b. **Antagonists** of the β_1 **receptors** are used in the treatment of hypertension and angina (slow heart and reduce force of contraction)

c. **Antagonists** of the α_1 **receptors** are known to cause lowering of the blood pressure (relaxation of smooth muscle and dilation of the blood vessels)



Epinephrine
(Adrenaline)



Norepinephrine
(Noradrenaline)

•Epinephrine (INN) (IPA: [ˌɛpɪˈnɛfrən]) or adrenaline (European Pharmacopoeia and BAN) (IPA: [əˈdrɛnələn]), sometimes spelled "epinephrin" or "adrenalin" respectively, is a hormone. It is a catecholamine, a sympathomimetic monoamine derived from the amino acids phenylalanine and tyrosine.

•The Latin roots *ad*-+*renes* and the Greek roots *epi*-+*nephros* both literally mean "on/to the kidney" (referring to the adrenal gland, which secretes epinephrine). Epinephrine is sometimes shortened to epi in medical jargon.

•Epinephrine is now also used in EpiPens and Twinjects. EpiPens are long narrow auto-injectors that administer epinephrine, Twinjects are similar but contain two doses of epinephrine. Though both *EpiPen* and *Twinject* are trademark names, common usage of the terms are drifting toward the generic context of any epinephrine autoinjector.

Ephinephrine can be injected directly into the heart to stimulate it after it as stopped beating due to drowning, suffocation, shock, electrocution, and anesthesia. The epinephrine dramatically restores the heart beat. In cases of shock, norepinephrine has been used to restore and maintain sufficient blood pressure and ensure adequate blood flow to vital organs.

When local anesthetics are used to reduce or eliminate pain in a specific area, epinephrine is frequently used in conjunction with these agents to constrict the blood vessels at the area and prevent drug diffusion from that area

Historically, what therapeutic agents have been used?

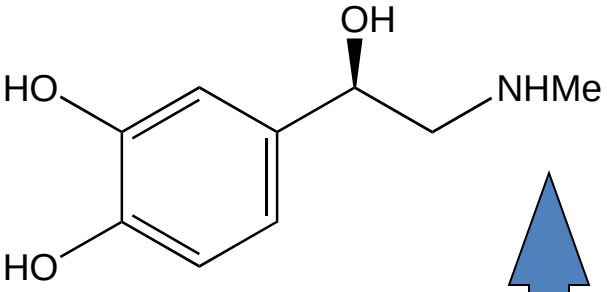
- Ephedrine, as part of the Chinese medicine Ma Huang, has been used in the treatment of respiratory diseases for over 5000 years
- Ephedrine is now known to act indirectly, by releasing endogenous catecholamines, resulting in bronchodilation
- In 1900, Solis-Cohen showed that orally administered adrenal extract was beneficial in asthma.

Historic

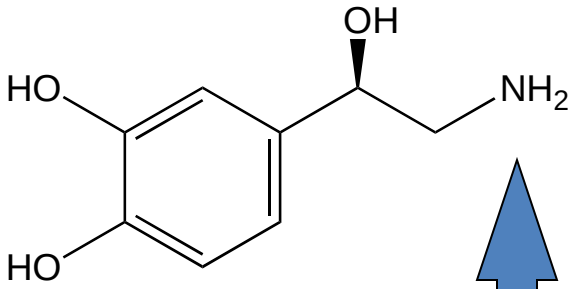
- Initially, subcutaneous injections of epinephrine were used, followed by a nebulized epinephrine solution.
- Epinephrine is one of the most potent vasopressor (i.e. causes constriction of the blood vessels and corresponding rise in blood pressure) drugs known.
- Epinephrine affects respiration primarily by relaxing the bronchial muscle.
- Epinephrine is rapidly metabolized by COMT, primarily in the liver.

Can we make an asthma drug with less side effects, and longer lasting?

- Clues:
- It is known that the β_2 receptor is the target for relaxation of bronchial smooth muscle.
- Epinephrine has approx. equal affinity for both α and β receptors
- However norepinephrine has greater affinity for the α receptors
- This indicates that placing an alkyl group on the nitrogen leads to an increase in selectivity for the β-receptors.



Epinephrine
(Adrenaline)



Norepinephrine
(Noradrenaline)

Equal selectivity for
Both α and β-receptors

Greater selectivity for
α–receptors

Perhaps, still greater selectivity for β-receptors could be
Generated by appending larger alkyl substituent on nitrogen

SAR

- For maximum sympathomimetic activity, a drug must have:
- Amine group two carbons away from an aromatic group
- A hydroxyl group at the chiral beta position in the R-configuration
- Hydroxyl groups in the meta and para position of the aromatic ring to form a catechol which is essential for receptor binding
- The structure can be modified to alter binding. If the amine is primary or secondary, it will have direct action, but if the amine is tertiary, it will have poor direct action. Also, if the amine has bulky substituents, then it will have greater beta adrenergic receptor activity, but if the substituent is not bulky, then it will favor the alpha adrenergic receptors.
- A primary or secondary aliphatic amine separated by 2 carbons from a substituted benzene ring is minimally required for high agonist activity.
- Substitution on aromatic ring-
- The presence of hydroxy group in the benzene ring at 3rd and 4th position shows maximum alpha and beta activity

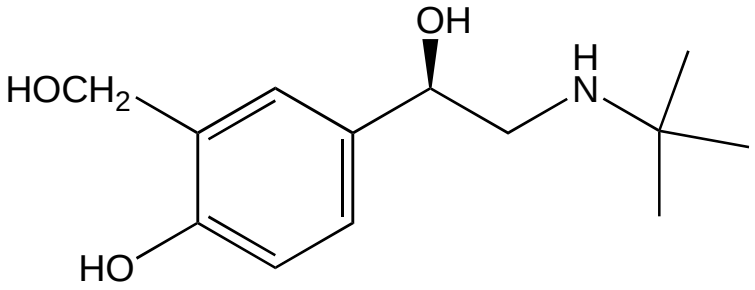
Mechanism of action

- As a hormone and neurotransmitter, epinephrine acts on nearly all body tissues. Its actions vary by tissue type and tissue expression of adrenergic receptors. For example, high levels of epinephrine causes smooth muscle relaxation in the airways but causes contraction of the smooth muscle that lines most arterioles.
- Epinephrine acts by binding to a variety of adrenergic receptors. Epinephrine is a nonselective agonist of all adrenergic receptors, including the major subtypesα_1, α_2, β_1, β_2, and β_3.[49] Epinephrine's binding to these receptors triggers a number of metabolic changes. Binding to α-adrenergic receptors inhibits insulin secretion by the pancreas, stimulates glycogenolysis in the liver and muscle, and stimulates glycolysis in muscle.[54] β-Adrenergic receptor binding triggersglucagon secretion in the pancreas, increased adrenocorticotropic hormone(ACTH) secretion by the pituitary gland, and increased lipolysis by adipose tissue. Together, these effects lead to increased blood glucose and fatty acids, providing substrates for energy production within cells throughout the body

Further improvements needed

- Needed an agent which was longer lasting, more resistant to COMT (Catechol –O-Methyl transferase)is a protein coding gene
- Needed an agent which was more selective for the β_2 receptors in the lung and less selective for the β_1 receptors of heart.

Arrives Salbutamol



Salbutamol

- Tert-butyl group renders salbutamol more selective for β_2
- Hydroxymethyl group (in place of OH) renders salbutamol resistant to COMT (catechol o-methyl transferase)
- Remains the most widely used anti-asthma drug in the world

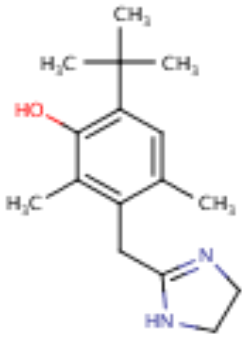
MECHANISM OF ACTION

- Salbutamol is a beta(2)-adrenergic agonist and thus it stimulates beta(2)-adrenergic receptors. Binding of albuterol to beta(2)-receptors in the lungs results in relaxation of bronchial smooth muscles. It is believed that salbutamol increases cAMP production by activating adenylate cyclase, and the actions of salbutamol are mediated by cAMP. Increased intracellular cyclic AMP increases the activity of cAMP-dependent protein kinase A, which inhibits the phosphorylation of myosin and lowers intracellular calcium concentrations. A lowered intracellular calcium concentration leads to a smooth muscle relaxation and bronchodilation. In addition to bronchodilation, salbutamol inhibits the release of bronchoconstricting agents from mast cells, inhibits microvascular leakage, and enhances mucociliary clearance.

Imidazolines and α-Adrenergic Agonists

- A second chemical class of α-agonists is the imidazolines. These imidazolines can be nonselective, or they can be selective for either α1- or α2-receptors. Structurally, most imidazolines have their heterocyclic imidazoline nucleus linked to a substituted aromatic moiety via some type of bridging unit. The optimum bridging unit (X) is usually a single methylene group or amino group.

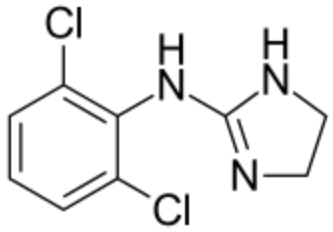
Oxymetazoline



For treatment of nasal congestion and redness associated with minor irritations of the eye

Oxymetazoline is a direct acting sympathomimetic amine, which acts on alpha-adrenergic receptors in the arterioles of the conjunctiva and nasal mucosa. It produces vasoconstriction, resulting in decreased conjunctival congestion in ophthalmic. In nasal it produces constriction, resulting in decreased blood flow and decreased nasal congestion.

Clonidine



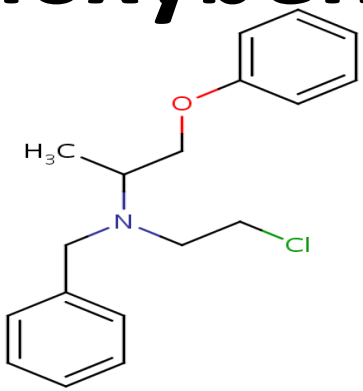
Clonidine

- Clonidine is an imidazoline derivate and centrally-acting alpha-adrenergic agonist, with antihypertensive activity. Clonidine binds to and stimulates central alpha-2 adrenergic receptors, thereby reducing the amount of norepinephrine (NE) release and thus decreasing sympathetic outflow to the heart, kidneys, and peripheral vasculature. The reduction in sympathetic outflow leads to decreased peripheral vascular resistance, decreased blood pressure, and decreased heart rate. In addition, clonidine binds to imidazoline receptor subtype 1 (I1), which may also contribute to a reduction in blood pressure.

Adrenergic Blockers (antagonists/sympatholytics)

- Block alpha & beta receptor sites (nonselective)
- direct or indirect acting on the release of norepinephrine and epinephrine
- Use - Cardiac arrthymias (an abnormal rate of muscle contractions in the heart), HTN- Abbreviation for hypertension (high blood pressure) (cardiac output), angina (O2 demand)
- CHF (Congestive heart failure), bronchospasm(spasm of bronchial smooth muscle, producing narrowing of the bronchi).
- Bradycardia (abnormally slow heart action), wheezing

Phenoxybenzamine

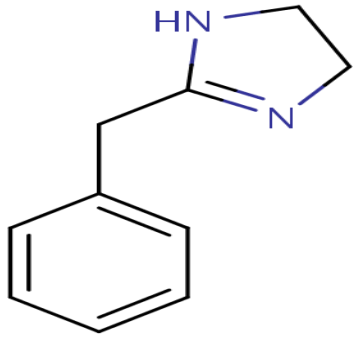


An alpha-adrenergic antagonist with long duration of action. It has been used to treat hypertension and as a peripheral vasodilator.

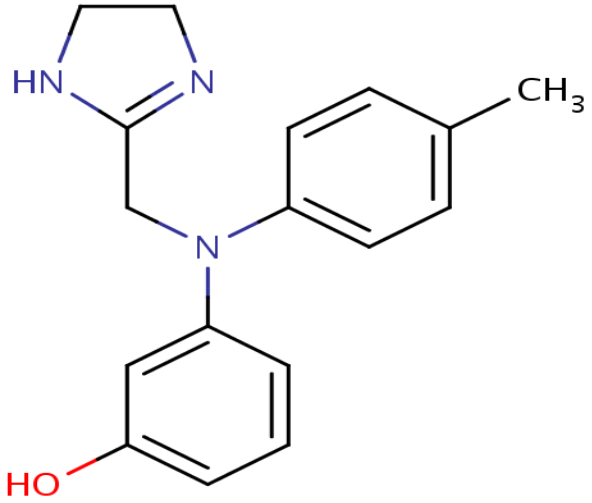
For the treatment of phaeochromocytoma (malignant), benign prostatic hypertrophy (prostrate gland enlargement)and malignant essential hypertension.

Phenoxybenzamine produces its therapeutic actions by blocking alpha receptors, leading to a muscle relaxation and a widening of the blood vessels. This widening of the blood vessels results in a lowering of blood pressure.

Tolazoline and phentolamine



Tolazoline



phentolamine

Tolazoline and phentolamine are two imidazoline nonselective α-antagonists that also have antihypertensive activity, although they have been replaced in general clinical use by far better agents.

SAR

- Tolazoline has clear structural similarities to the imidazoline α_1-agonists, such as naphazoline and xylometazoline but does not have the lipophilic substituents required for agonist activity.
- The resemblance of phentolamine is not as readily apparent, but extensive molecular modeling studies have provided a topologic scheme for α_1-antagonist SAR[19]. This pattern, however, cannot be readily visualized without computer graphics

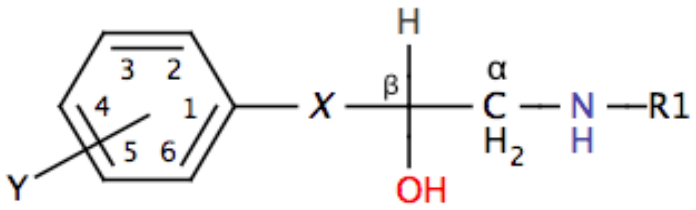
PHENTOLAMINE

- A nonselective alpha-adrenergic antagonist. It is used in the treatment of hypertension and hypertensive emergencies, pheochromocytoma, vasospasm of raynaud disease and frostbite, clonidine withdrawal syndrome, impotence, and peripheral vascular disease.

Mechanism of action

- Phentolamine produces its therapeutic actions by competitively blocking alpha-adrenergic receptors (primarily excitatory responses of smooth muscle and exocrine glands), leading to a muscle relaxation and a widening of the blood vessels. This widening of the blood vessels results in a lowering of blood pressure. The action of phentolamine on the alpha adrenergic receptors is relatively transient and the blocking effect is incomplete. Phentolamine also stimulates β-adrenergic receptors and produces a positive inotropic and chronotropic effect on the heart and increases cardiac output.

SAR



- For the function of a β-blocker it's essential for the compound to contain an aromatic ring and a β-ethanolamine. The aromatic ring can either be benzoheterocyclic (such as indol) or heterocyclic (such as thiadiazole). This is mandatory.The side chains can be variable

SAR Contn

- The X part of the side chain can either be directly linked to the aromatic ring or linked through a $-OCH_2-$ group.
- When X is $-CH_2CH_2-$, -CH=CH-, $-SCH_2-$ or $-NCH_2-$ there is little or no activity.
- The R group can only be a secondary substitution and branched is the optimal choice.
- Alkyl (CH_3) substituents on the α, β or γ carbon (if X = OCH_2) lower beta blockade, especially at the α carbon.
- The general rule for aromatic substitution is: *ortho* > *meta* > *para*. This gives non-selective β-blockers. Large para-substituents usually decrease activity but large ortho-groups retain some activity. Polysubstitution on carbon 2 and 6 makes the compound inactive but when the substitution is on carbon 3 and 5 there's some activity. For the highest cardioselectivity, the substituents should be as following: *para* > *meta* > *ortho*. All the β-blockade is in one isomer, (S)-aryloxypropylamine and (R)-ethanolamine

What are β-blockers used for?

- Numerous studies suggest that beta-blockers can reduce mortality by 25% to 40% in patients with certain kinds of heart failure, and cut sudden cardiac death up to 50% in patients with a recent heart attack.

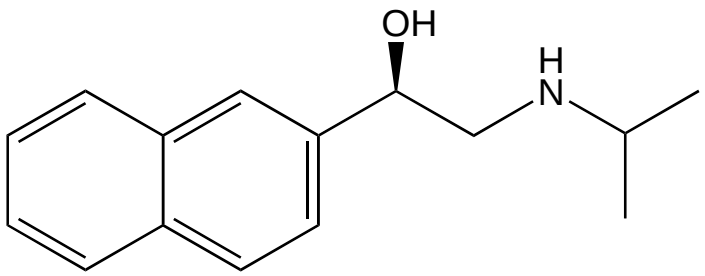
- **Current Uses**
- **Treatment**·Angina pectoris (chest pain associated with lack of oxygen to the heart)·Arrhythmias (irregular heart rhythms)·Heart attack·Heart failure·Hypertension (high blood pressure)
- **Prevention**·Protects the heart in people who have coronary artery disease·Reduces risk of stroke· Protective prior to non-cardiac surgery in persons at high risk of complications

How do β-blockers work?

- **Mechanism for How It Works**·Beta-blockers "block" the effects of adrenaline on your body's beta-receptors. This slows the nerve impulses that travel through the heart. As a result, your heart does not have to work as hard because it needs less blood and oxygen. This decreases heart rate, blood pressure, and lessens the need for nitrates. Beta-blockers also block the impulses that can cause an arrhythmia (abnormal heart beat).·
- Beta-blockers generally work by affecting the response to some nerve impulses. Your body has 2 main beta-receptors: beta 1 and beta 2. Some beta-blockers are selective, which means that they block beta 1 receptors more than they block beta 2 receptors. Beta 1 receptors are responsible for heart rate and the strength of your heartbeat. Nonselective beta-blockers block both beta 1 and beta 2 receptors. Beta 2 receptors are responsible for the function of your smooth muscles (muscles that control body functions but that you do not have control over).·
- This class of drugs may decrease the sympathetic outflow from the central nervous system and/or suppress the release of renin (**Renin** (/ˈriːnɨn/ ***REE**-nin*), also known as an **angiotensinogenase**, is an enzyme that participates in the body's renin-angiotensin system (RAS)—also known as the renin-angiotensin-aldosterone axis—that mediates extracellular volume (i.e., that of the blood plasma, lymph and interstitial fluid), and arterialvasoconstriction. Thus, it regulates the body's mean arterial blood pressure.) substance that is elevated in some patients with high blood pressure and is involved in a cascade of events leading to constriction of blood vessels. In addition, some speculate that beta-blockers may have possible antioxidant and

β-blocker design

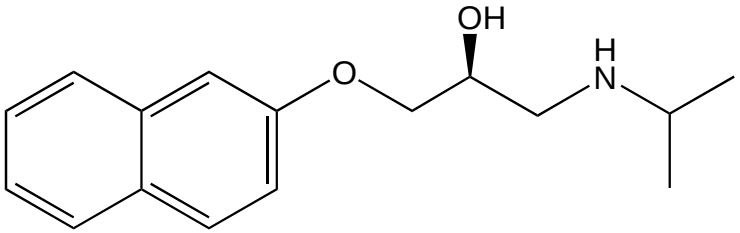
- Replace two chlorine atoms with a fused aryl ring
- Resulted in a partial agonist, which partially blocked effect of epinephrine



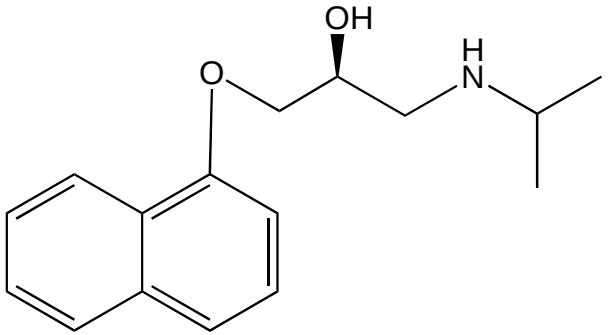
Pronethalol
(still a partial agonist)

β-blocker design

- Next extend the side chain to try and achieve “umbrella” effect
- Serendipity comes into play, as one synthetic intermediate is not available in the research lab, another is used, and a drug is discovered.



Target Structure



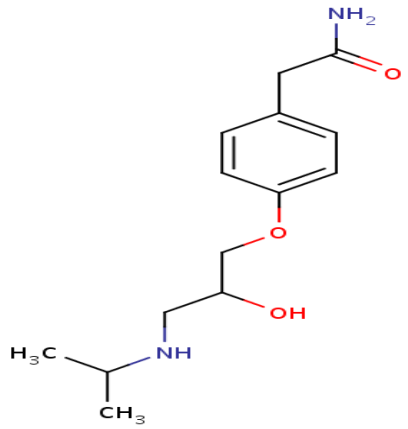
Propranolol

β-blocker design

- **Propranolol** (INN) (IPA: [proˈprɬnəloʊl]) is a non-selective beta blocker mainly used in the treatment of hypertension. It was the first successful beta blocker developed. Propranolol is commonly marketed by AstraZeneca under the trade name **Inderal**.

- Scottish scientist James W. Black successfully developed propranolol in the late 1950s. He was awarded the Nobel Prize in Medicine for this discovery in 1988.

- Propranolol, the prototype of the beta-adrenergic receptor antagonists, is a competitive, nonselective beta-blocker similar to nadolol without intrinsic sympathomimetic activity. Propanolol is a racemic compound; the l-isomer is responsible for adrenergic blocking activity.
- Propranolol competes with sympathomimetic neurotransmitters such as catecholamines for binding at beta(1)-adrenergic receptors in the heart, inhibiting sympathetic stimulation. This results in a reduction in resting heart rate, cardiac output, systolic and diastolic blood pressure, and reflex orthostatic hypotension.



Atenolol

For the management of hypertention and long-term management of patients with angina pectoris

Atenolol, a competitive beta(1)-selective adrenergic antagonist, has the lowest lipid solubility of this drug class. Atenolol does not have intrinsic sympathomimetic properties or membrane-stabilizing activity. Atenolol is used alone or with chlorthalidone in the management of hypertension and edema.

Like metoprolol, atenolol competes with sympathomimetic neurotransmitters such as catecholamines for binding at beta(1)-adrenergic receptors in the heart and vascular smooth muscle, inhibiting sympathetic stimulation. This results in a reduction in resting heart rate, cardiac output, systolic and diastolic blood pressure, and reflex orthostatic hypotension. Higher doses of atenolol also competitively block beta(2)-adrenergic responses in the bronchial and vascular smooth muscles.

Ergot alkaloids

- Ergot alkaloids are amides of the terpenoid indole derivate D-lysergic acid, and are produced by a wide range of fungi, predominantly the Clavicipitaceae, but are also present in members of the plant family Convolvulaceae, e.g. Ipomoea violacea and Turbina corymbosa (Samuelsson, 1999; Tudzynski
- et al., 2001). More than 50 ergot alkaloids have been isolated from ergot, of these those derived from isolysergic acid (with names ending with –inine) are pharmacologically inactive, but may inan aqueous solution isomerise to produce an equilibrium mixture with pharmacologically active lysergic acid derivatives

- The pharmacological effects of the various ergot alkaloids and their derivatives are due to the
- structural similarity of the tetracyclic ring system to neurotransmitters such as noradrenaline, dopamine or serotonin (Fig. 2), and interaction with multiple receptors in these systems
- (Silberstein, 1997).
- The compounds have a wide spectrum of activities, and depending on thesubstituent attached to the C-8 carboxyl group of the ergoline ring, the affinity towards the neurotransmitters receptors vary; behaving as agonists or antagonists or playing a dual role as partial-agonist and antagonist.

- Ergot alkaloids exhibit a wide spectrum of biological action

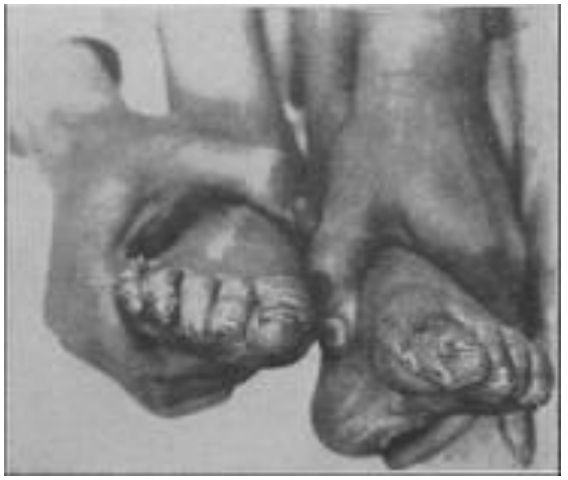
Ergot Alkaloids

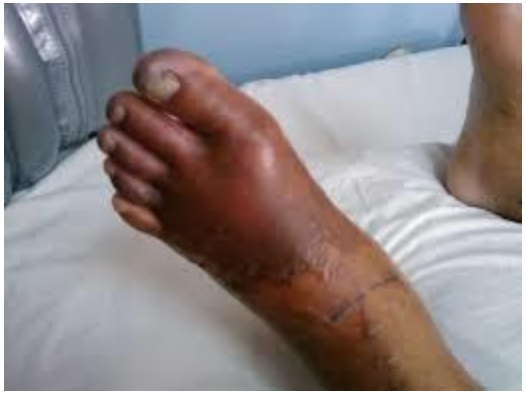
Produced by *Claviceps purpurea*, a grain (rye, especially) fungus

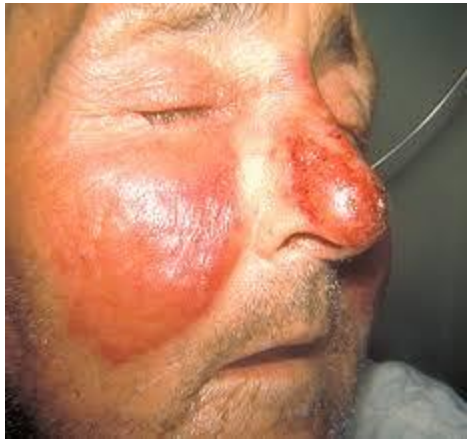
This fungus synthesizes many biologically active agents including:

acetylcholine, histamine, tyramine and many unique ergot alkaloids which effect: Alpha-adrenergic receptors, Dopamine receptors, Serotonin receptors

Ergot poisoning (Ergotism, St. Anthony's fire), dementia, florid hallucinations persistent vasospasm (gangrene may develop) uterine muscle stimulation (may cause abortion in pregnancy







On 15 August 1951 one in twenty of the 4000 inhabitants of another village in France called Pont Saint Esprit (Bridge of the Holy Spirit) went mad. They had hallucinations, writhed in agony in their beds, vomited, ran crazily in the streets and suffered terrible burning sensations in their limbs.

The madness was quickly diagnosed. They were suffering from St Anthony's Fire, a dreaded illness that was common in the Middle Ages. The cause was poisoning from a fungus (ergot) that grows on rye grass. The fungus contaminated the rye flour used in making bread.

Ergot contains a chemical that makes the sufferers go berserk and causes gangrene of the hands and feet due to constriction of blood supply to the extremities. If it is not treated (and this was not possible in the Middle Ages), victims had the sensation of being burned at the stake, before their fingers, toes, hands and feet dropped off.

Ergotamine
Ergosine
Ergocornine
Ergocristine
Ergocryptine
} Ergotoxine
And their dihydrogenated derivatives

The dihydrogenated alkaloids usually reduce BP, even though the aminoacid derivatives usually raise the BP. The exception is DHE which retains a considerable vasoconstrictor effect in addition to adrenergic blocking activity.

They block the alpha receptors and directly stimulate the vascular and uterine muscle.

They are divided into:

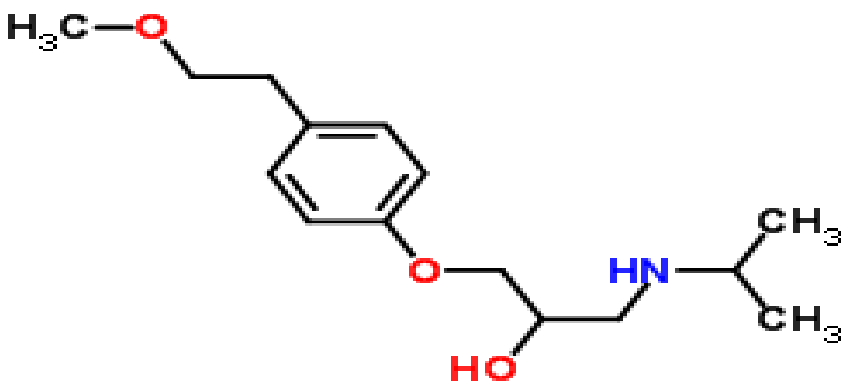
Aminoacid alkaloids Eg: Ergotamine, Ergosine and Ergotoxin

Amine alkaloid Eg: Ergometrine

Semisynthetic dihydrogenated aminoacid alkaloids :
Dihydroergotamine (DHE)

- of the grain fungus *Claviceps purpura*
- 5 Major alkaloids based on R and R’; Ergotamine the most common
- Used in the treatment of migraine
- Ergots possess strong oxytocic action

Metoprolol

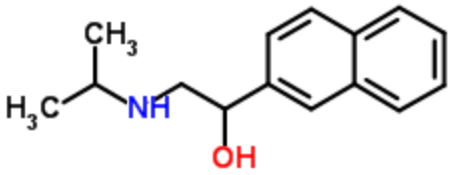


- Metoprolol, a competitive, beta1-selective (cardioselective) adrenergic antagonist, is similar to atenolol in its moderate lipid solubility, lack of intrinsic sympathomimetic activity (ISA), and weak membrane stabilizing activity (MSA)

Metoprolol

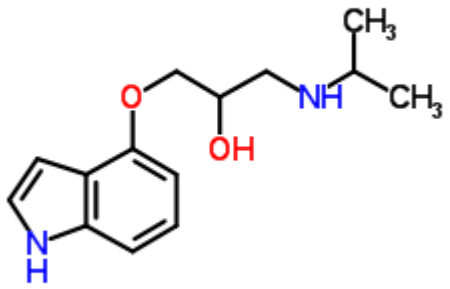
- It has antihypertensive properties and devoid of intrinsic sympathomimetic activity. Metoprolol antagonizes beta 1-adrenergic receptors in the myocardium, thereby reducing the rate and force of myocardial contraction leading to a reduction in cardiac output. This agent may also reduce the secretion of renin with subsequent reduction in levels of angiotensin II thereby preventing vasoconstriction and aldosterone secretion.

pronetalol



Pronethalol is a non-selective beta-adrenergic blocking agent, protect against and to reverse Digitalis-induced ventricular arrhythmias. These compounds would lower the heart's oxygen consumption by interfering with the effects of catecholamines

Pindolol



- A moderately lipophilic beta blocker (adrenergic beta-antagonists). It is non-cardioselective and has intrinsic sympathomimetic actions, but little membrane-stabilizing activity.

Treatment of COPD

- **Bronchodilators**There are three types of bronchodilators used clinically: β2-agonists, anticholinergics and methylxanthines.[8]These drugs relax the smooth muscles of the airway allowing for improved airflow. Many patients feel less breathless after taking bronchodilators.

Combivent®
Salbutamol / Ipratropium bromide

Presentation
Inhaler 100mcg / 20 mcg per inhalation
Combivent metered dose inhaler has an opaque shaft with a grey mouthpiece and cap. The canister contains a creamy-white homogenous suspension of micronised substances in a chlorofluorohydrocarbon propellant mixture filled in an aluminium canister with a metering valve. Each metered dose contains salbutamol 100 mcg (equivalent to 120 mcg salbutamol sulphate), and ipratropium bromide 20 mcg (equivalent to 21 mcg of ipratropium bromide monohydrate).

Respules® 2.5mg / 500mcg in 2.5ml
Combivent 2.5ml Respule contains an isotonic, clear, preservative-free solution for inhalation of 2.5mg salbutamol (equivalent to 3.01mg salbutamol sulphate) and 500 mcg ipratropium bromide anhydrous (equivalent to 520 mcg ipratropium bromide monohydrate)

Uses
Actions

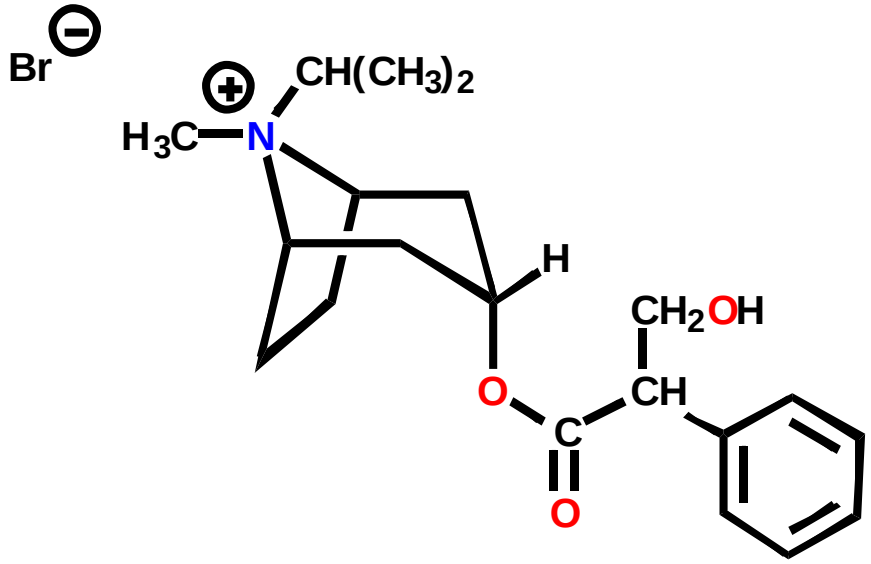
Combivent contains two active bronchodilating substances, salbutamol sulphate and ipratropium bromide.

Salbutamol sulphate is a beta2-adrenergic agent which acts on airway smooth muscle resulting in relaxation. Salbutamol relaxes all smooth muscle from the trachea to the terminal bronchioles and protects against all bronchoconstrictor challenges.

Ipratropium bromide is a quaternary ammonium compound with anticholinergic properties. In preclinical studies, it appears to inhibit vagally mediated reflexes by antagonising the action of acetylcholine, the transmitter agent released from the vagus nerve. Anticholinergics prevent the increase of intracellular concentration of cyclic guanosine monophosphate (cyclic GMP) caused by interaction of acetylcholine with muscarinic receptors on bronchial smooth muscle. The bronchodilation following inhalation of ipratropium bromide is primarily local and site specific to the lung and not systemic in nature.

Combivent provides the simultaneous release of ipratropium bromide and salbutamol allowing the synergistic efficacy on the muscarinic and beta2-adrenergic receptors in the airways to cause bronchodilation which is superior to that provided by each single agent and with no potentiation of adverse

Cholinergic Antagonists (Muscarinic receptor)



Ipratropium
(bronchodilator & anti-asthmatic)

Adrenergic Receptors in the CNS

- http://www.brainexplorer.org/video/index.shtml

α-Blockers

- **Alpha blockers** (also called alpha-adrenergic blocking agents) constitute a variety of drugs which block α_1-adrenergic receptors in arteries and smooth muscles.

- These drugs may be used to treat:・benign prostatic hyperplasia (BPH)・high blood pressure (hypertension). This is not typically the drug of choice unless the patient also has BPH.・symptoms of non inflammatory chronic pelvic pain syndrome, a type of prostatitis. As a side effect they may reduce blood pressure and result in lightheadedness.

Benign Prostatic Hyperplasia

- http://www.muschealth.com/gs/AnimationList.aspx#anim4

- http://health.howstuffworks.com/adam-200003.htm

Treatment of benign prostatic hyperplasia (BPH)

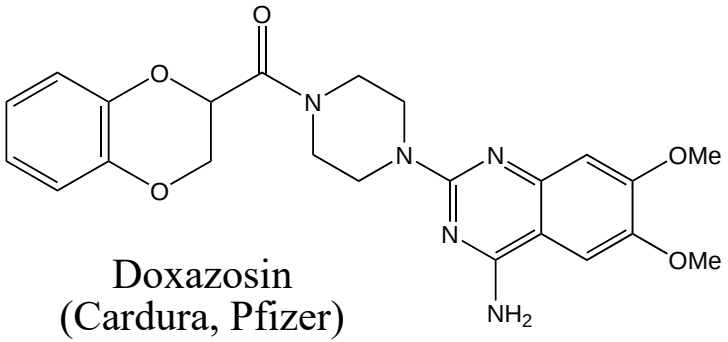
Medications

Alpha blockers (α1-adrenergic receptor antagonists) (such as doxazosin, prazosin, alfuzosin and tamsulosin) and certain antiandrogens such as the 5α-reductase inhibitors (finasteride and dutasteride) are used, often together, in suppressing the symptoms. Alpha-blockers relax smooth muscle in the prostate and bladder neck decreasing the degree of blockage of urine flow. Alpha-blockers may cause ejaculation back into the bladder (retrograde ejaculation). This is not harmful.

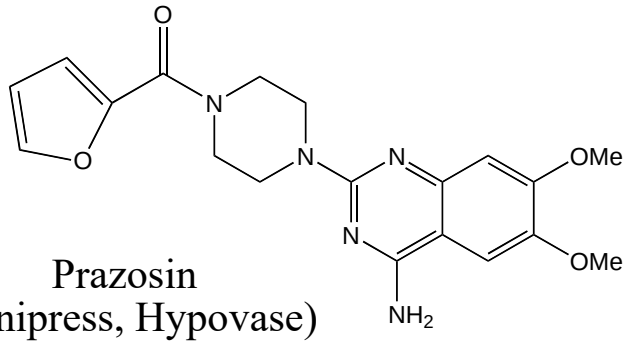
There is also extensive evidence of the efficacy of S*erenoa repens* (saw palmetto) fruit extracts in alleviating mild-to-moderate BPH symptoms. A systematic review of evidence found comparable efficacy to finasteride. (Wilt e*t al.*, 2002) Other herbal medicines that have solid research support in systematic reviews include beta-sitosterol from H*ypoxis rooperi* (African star grass) and P*runus africanum* (pygeum) bark, while there is less substantial support for the efficacy of C*ucurbita pepo* (pumpkin) seed and U*rtica dioica* (stinging nettle) root. (Wilt e*t al.*, 2000) At least one double-blind trial has also supported the efficacy of rye flower pollen. (Buck, e*t al.*, 1990)

Sildenafil shows some symptomatic relief, suggesting a possible common etiology with erectile disfunction. (Brown 2005)o

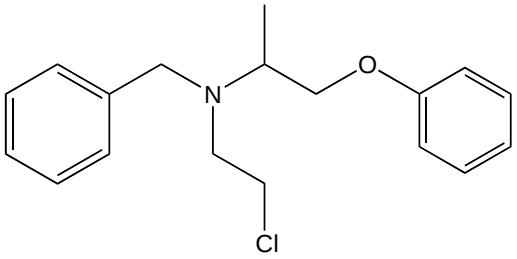
Examples of commercial α-blockers



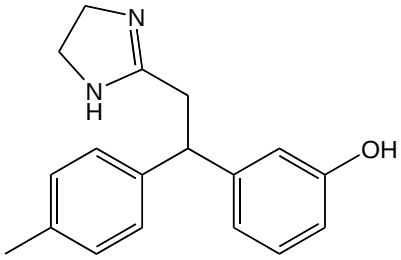
Doxazosin
(Cardura, Pfizer)



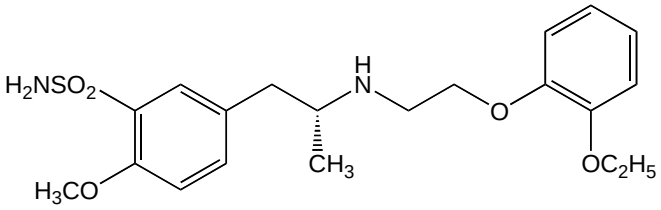
Prazosin
(Minipress, Hypovase)



Phenoxybenzamine



Phentolamine



Tamsulosin
(Flomax, Astellas Pharma)

β-Blockers

- **Beta blockers** (sometimes written as **β-blockers**) are a class of drugs used for various indications, but particularly for the management of cardiac arrhythmias and cardioprotection after myocardial infarction. Whilst once first-line treatment for hypertension, their role was downgraded in June 2006 in the United Kingdom to fourth-line as they perform less well than other drugs, particularly in the elderly, and there is increasing evidence that the most frequently used beta-blockers at usual doses carry an unacceptable risk of provoking type 2 diabetes.[1]

Hypertension

- http://www.healthscout.com/animation/68/47/main.html

Heart Failure

- http://www.healthscout.com/animation/68/13/main.html

- http://www.medindia.net/animation/heart_attack.asp

Examples of beta blockers

Dichloroisoprenaline, the first beta blocker.

Alprenolol
Carteolol
Levobunolol
Mepindolol
Metipranolol
Nadolol
Oxprenolol
Penbutolol
Pindolol
Propranolol
Sotalol
Timolol
[edit]β1-Selective agents
Acebutolol
Atenolol
Betaxolol
Bisoprolol
Esmolol
Metoprolol
Nebivolol
[edit]Mixed α1/β-adrenergic antagonists
Carvedilol
Celiprolol
Labetalolprolol
Labetalol□□□耀O汐楯ฉ凸嫋

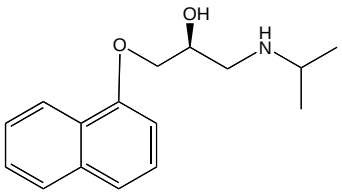
Some β-blockers are also used to treat glaucoma

http://www.goodhope.org.uk/departments/eyedept/images/glaucoma.html

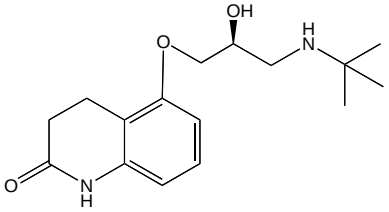
http://www.goodhope.org.uk/departments/eyedept/angleclosureetc.htm

http://www.goodhope.org.uk/departments/eyedept/dropsfor.htm

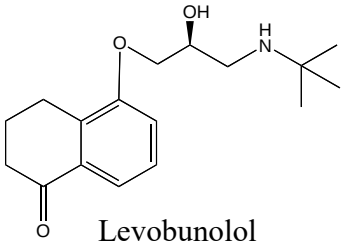
Non-specific β-blockers
(antagonize both β1 and β2 receptors)



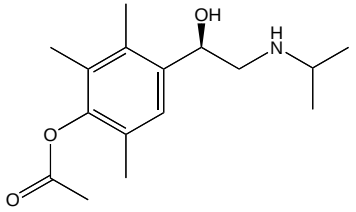
Propranolol



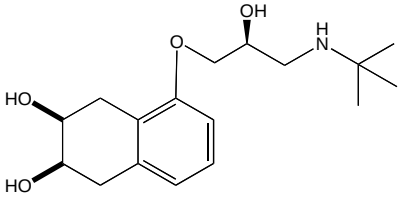
Carteolol



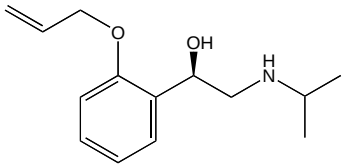
Levobunolol



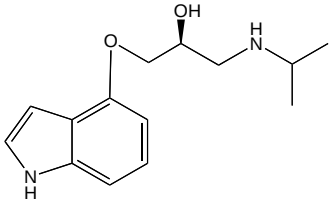
Metipranolol
(OptiPranolol, Glaucoma)



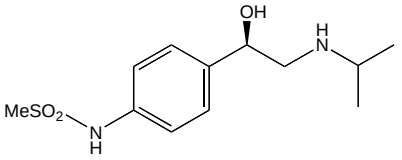
Nadolol
(Corgard, blood pressure, chest pain)



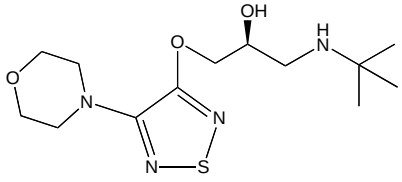
Oxprenolol



Pindolol

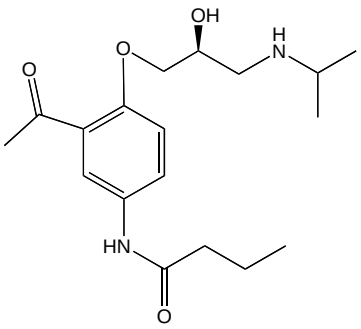


Sotalol
(also inhibits inward potassium channels in the heart)

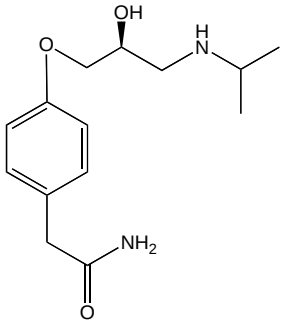


Timolol
(oral form is Blocadren)
(Opthalmic form Timoptol or Timoptic)

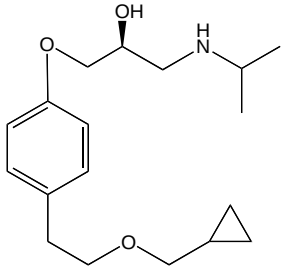
Selective (β1 selective) β-blockers



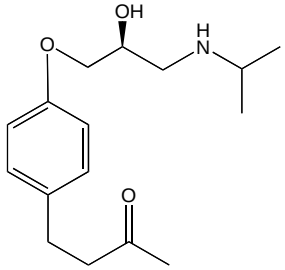
Acebutolol



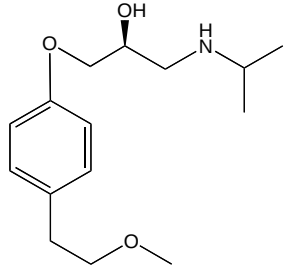
Atenolol



Betaxolol
(Betoptic, Lokren)



Esmolol
(Brevibloc)

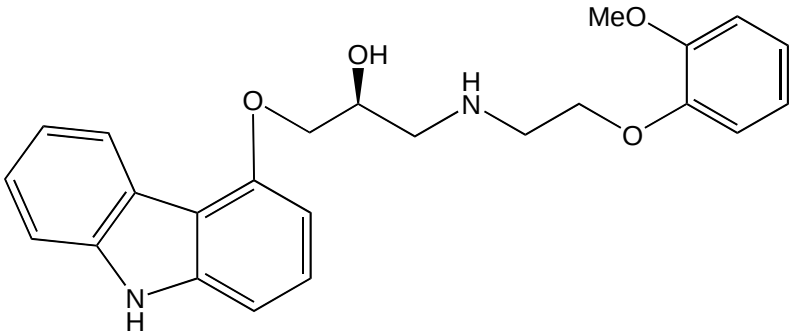


Metoprolol
(Lopressor, Novartis)
(also Toprol-XL,
Betaloc (AstraZeneca)

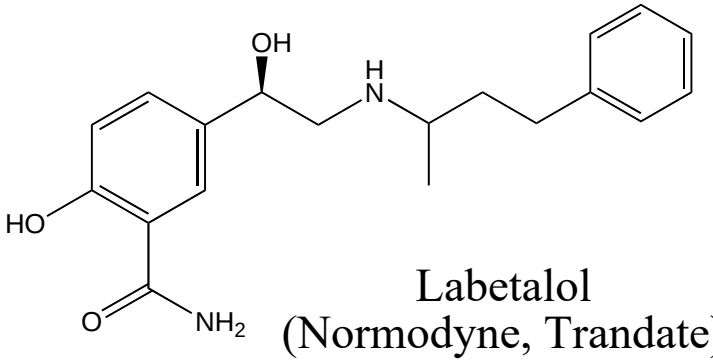
Why do you want selective antagonists?

- Acebutolol is a cardioselective beta blocker. It is more suitable than non cardioselective beta blockers, if a patient with Asthma bronchiale or chronic obstructive lung disease (COLD) needs treatment with a beta blocker.

Non-selective β-blockers which also antagonize at the α1 receptor



Carvedilol
(Coreg, GSK)
(Dilatrend, Eucardic, Roche)

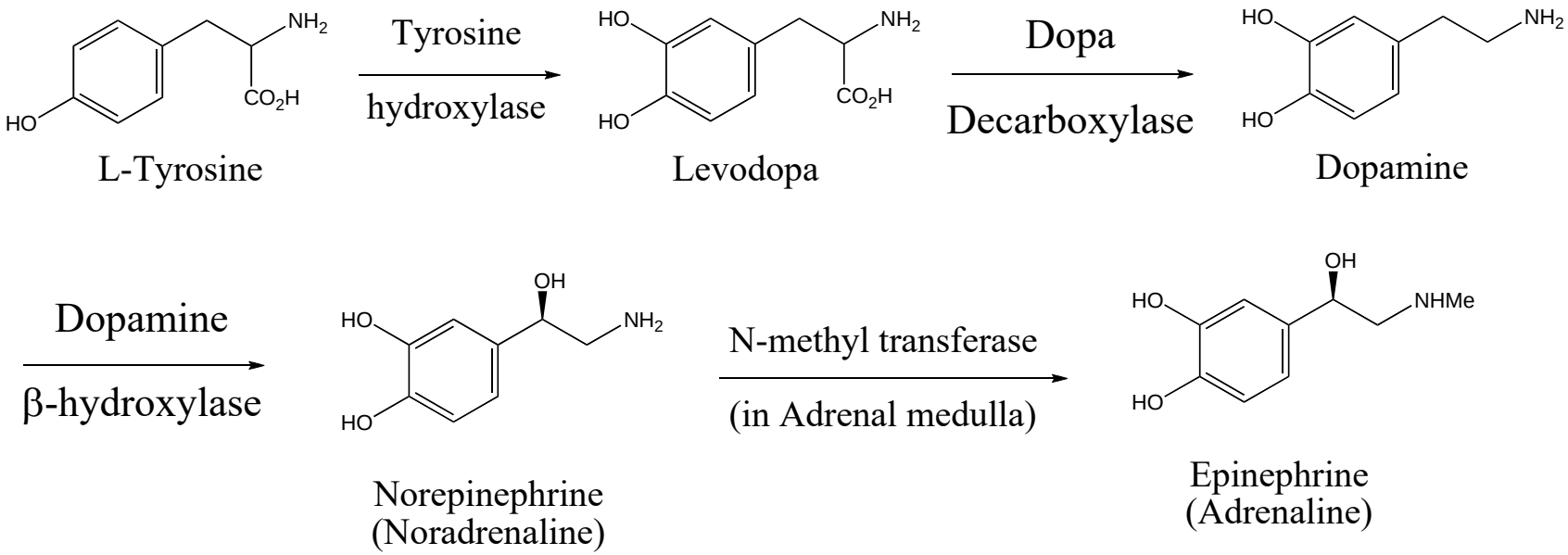


Labetalol
(Normodyne, Trandate)

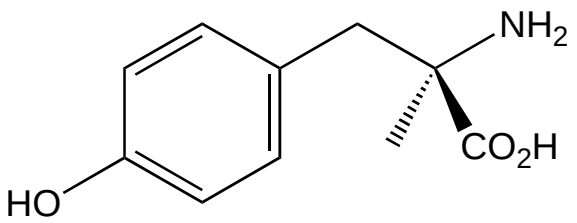
Why add α1 antagonism?

- In addition to blocking both β_1- and β_2-adrenergic receptors, carvedilol also displays α_1-adrenergic antagonism, which confers the added benefit of reducing blood pressure through vasodilation.

Biosynthesis of norepinephrine and epinephrine



A competitive inhibitor of tyrosine hydroxylase can be used to slow production of catecholamines



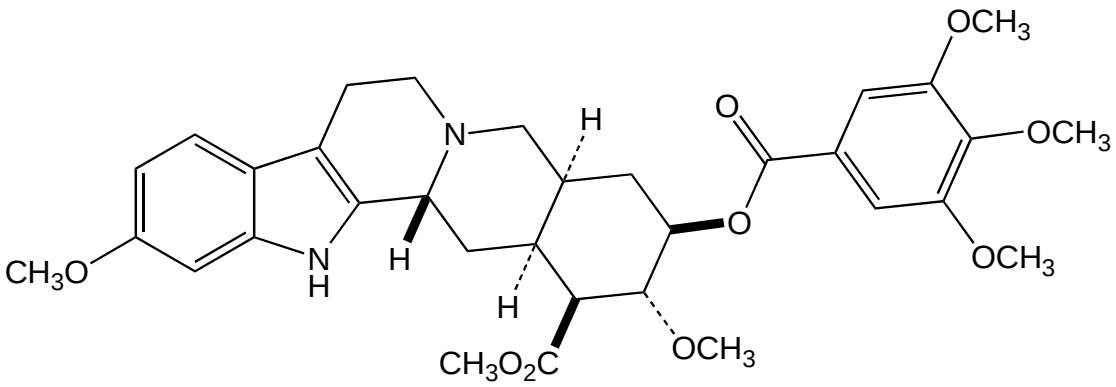
α-Methyltyrosine

Inhibition of catecholamine synthesis

- α-methyltyrosine is occasionally used to treat hypertension associated with tumors in the adrenal medulla

Reserpine

- Reserpine was isolated in 1952 from the dried root of *Rauwolfia serpentina* (Indian snakeroot),[4] and introduced in 1954, two years after chlorpromazine.[5] Reserpine almost irreversibly blocks the uptake (and storage) of noradrenaline and dopamine into synaptic vesicles by inhibiting the Vesicular Monoamine Transporters (VMAT).[6] In so doing, it leaves the noradrenaline in the cytoplasm, where it is destroyed by monamine oxidase (MAO). It was once used to treat hypertension, but has many side effects, including depression, stomach cramps, diarrhea, etc.



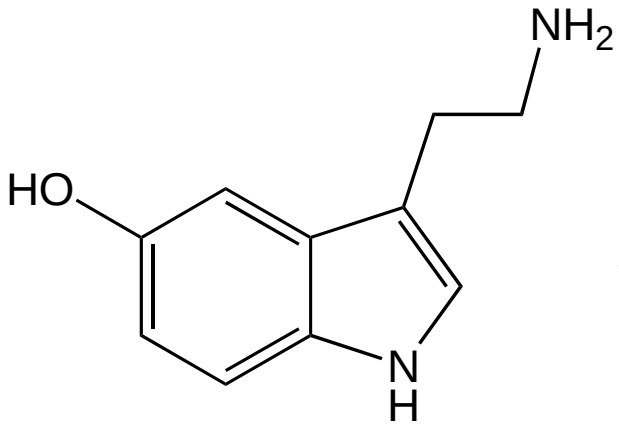
Norepinephrine Reuptake Inhibitors as Antidepressants

- **Norepinephrine reuptake inhibitors** (**NRIs**), also known as **noradrenaline reuptake inhibitors** (**NARIs**), are compounds that elevate the extracellular level of the neurotransmitter norepinephrine in the central nervous system by inhibiting its reuptake from the synaptic cleft into the presynaptic neuronal terminal. The drugs inhibit the class of neurotransmitter transporters known as norepinephrine transporters. They have virtually no action at other monoamine transporters.

Depression

- http://www.healthcentral.com/depression/introduction-5003-109.html
- http://www.healthcentral.com/depression/introduction-5003-109.html
- http://www.healthscout.com/animation/68/10/main.html

What is serotonin?



5-Hydroxytryptamine, or 5-HT

In the central nervous system, serotonin is believed to play an important role in the regulation of body temperature, mood, sleep, vomiting, sexuality, and appetite. Low levels of serotonin have been associated with several disorders, namely clinical depression, obsessive-compulsive disorder (OCD), migraine, irritable bowel syndrome, tinnitus, fibromyalgia, bipolar disorder, and anxiety disorders.[*citation needed*] If neurons of the brainstem that make serotonin—serotonergic neurons—are abnormal, there is a risk of sudden infant death syndrome (SIDS) in an infant.[1]

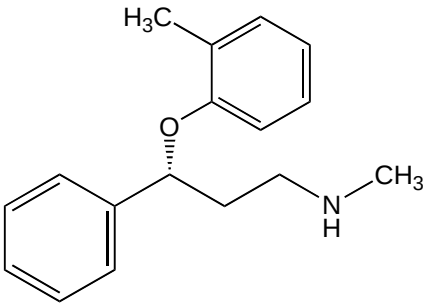
Understanding Serotonin

- The pharmacology of 5-HT is extremely complex, with its actions being mediated by a large and diverse range of 5-HT receptors. At least seven different receptor "families" are known to exist, each located in different parts of the body and triggering different responses. As with all neurotransmitters, the effects of 5-HT on the human mood and state of mind, and its role in consciousness, are very difficult to ascertain.

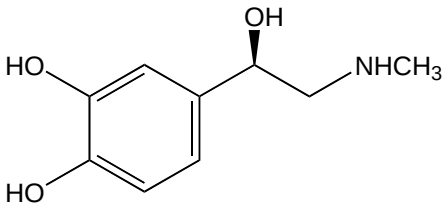
Understanding Serotonin

- Serotonergic action is terminated primarily via uptake of 5-HT from the synapse. This is through the specific monoamine transporter for 5-HT, 5-HT reuptake transporter, on the presynaptic neuron. Various agents can inhibit 5-HT reuptake including MDMA (ecstasy), cocaine, tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs).Recent research suggests that serotonin plays an important role in liver regeneration and acts as a mitogen (induces cell division) throughout the body.[6]

Norepinephrin Reuptake Inhibitors for Depression



Atomoxetine
(Strattera, Eli Lilly & Co.)



Epinephrine

- Atomoxetine is classified as a norepinephrine reuptake inhibitor, and is approved for use in children, adolescents, and adults.

- **Atomoxetine** is the first non-stimulant drug approved for the treatment of attention-deficit hyperactivity disorder (ADHD). It is sold in the form of the hydrochloride salt of atomoxetine. It is manufactured and marketed under the brand name **Strattera**[1] by Eli Lilly and Company as a generic **Attentin** by Torrent Pharmaceuticals. There is currently no generic available within the United States due to patent restrictions.