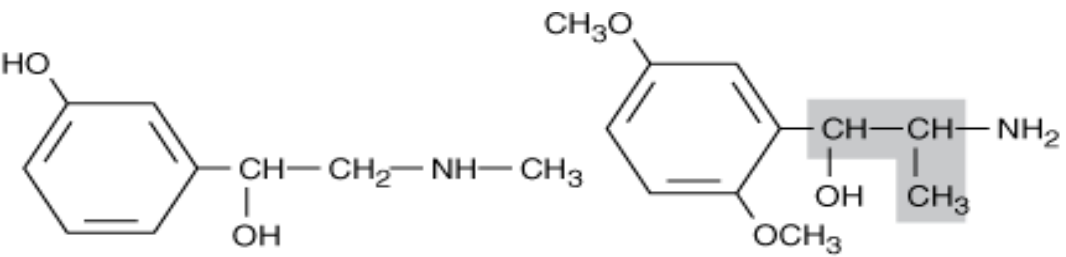
Adrenoceptor Agonists & Sympathomimetic Drugs

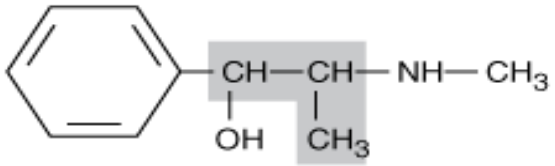
	Relative Receptor Affinities
Alpha agonists	
Phenylephrine, methoxamine	α 1 >α 2 >>>>> β
Clonidine, methylnorepinephrine	α 2 > α 1 >>>>> β
Mixed alpha and beta agonists	
Norepinephrine	α 1 = α 2; β1 >> β2
Epinephrine	α 1 = α 2; β1 = β 2
Beta agonists	
Dobutamine	β 1 > β 2 >>>> α
Isoproterenol	β1 = β 2 >>>> α
Albuterol (Salbutamol), terbutaline,, ritodrine	β 2 >> β 1 >>>> α

Medicinal Chemistry of Sympathomimetic Drugs

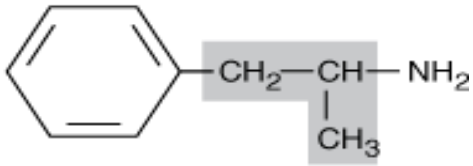


Phenylephrine

Methoxamine

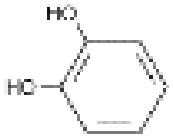


Ephedrine

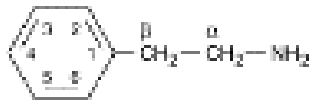


Amphetamine

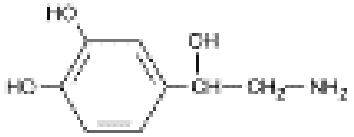
None catecholamines



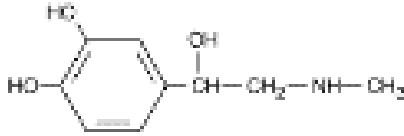
Catechol



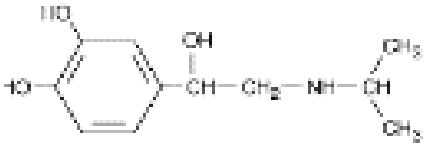
Phenylethylamine



Norepinephrine



Epinephrine



Isoproterenol

Dopamine

catecholamines

Organ System Effects of Sympathomimetics.

Cardiovascular System.

- The net effect **of a Sympathomimetic drug** depends on:
- its **relative selectivity for α or β** adrenoceptors
- and the compensatory **baroreflex** mechanisms aimed at restoring homeostasis.

- **Effects of Alpha1-Receptor Activation**
- A pure **α** agonist such as **phenylephrine** causes **arterial and venoconstriction, increases peripheral arterial resistance and decreases venous capacitance**.
- The enhanced arterial resistance leads to a rise in blood pressure (BP).
- The rise in BP elicits a baroreceptor - mediated increase in vagal tone with slowing of the heart rate.
- If baroreflex function is removed by pretreatment with the ganglionic blocker **trimethaphan**, the pressor effect of phenylephrine is increased approximately tenfold, and bradycardia is no longer observed.

- The **skin vessels** & the **splanchnic vessels** have predominantly **alpha** receptors and constrict in response to epinephrine and norepinephrine.

- Vessels in **skeletal muscle** may constrict or dilate depending on whether alpha or **beta 2** receptors are activated.

- The blood vessels of the **nasal mucosa** have **alpha** receptors, and local vasoconstriction induced by sympathomimetics produces a **decongestant** action

- **Effects of Alpha2-Receptor Activation**
- Alpha2 adrenoceptors are present in the vasculature, and their activation leads to vasoconstriction.
- This effect, however, is observed only when α 2 agonists are given by **rapid IV** injection or in **very high oral doses**.
- When given systemically, these vascular effects are obscured by the **central effects of α 2 receptors**, which lead to **inhibition of sympathetic tone** and a decrease in BP.
- Hence, α 2 agonists are used in the treatment of hypertension .

- **Effects of Beta-Receptor Activation**

- Stimulation of β receptors in the **heart** increases cardiac output by stimulating contractility and by increasing the heart rate.
- Beta agonists also **decrease peripheral resistance** by activating **β 2** receptors, leading to vasodilation in certain vascular beds.
- **Isoproterenol** activates both **β 1** and **β 2** receptors.
- The net effect is to maintain or **slightly increase systolic pressure** and to **lower diastolic pressure**, so that mean blood pressure is decreased

- **Beta-receptor** activation results in increased calcium influx in cardiac cells.
- Pacemaker activity is increased (**positive chronotropic** effect).
- Conduction velocity in the AV node is increased (**positive dromotropic** effect), and the **refractory period is decreased**.
- Intrinsic contractility is increased (**positive inotropic** effect).
- The direct effects on heart rate may be dominated by a **reflex** response to BP changes.
- Physiologic stimulation of the heart by catecholamines tends to increase coronary blood flow.

- **Effects of Dopamine-Receptor Activation**
- IV administration of dopamine promotes vasodilation of renal, splanchnic, coronary, and cerebral vessels, via activation of **D1** receptors.
- Activation of the **D1** receptors in the renal vasculature may also induce **natriuresis.**
- The renal effects of dopamine have been used clinically to improve perfusion to the kidney in situations of oliguria (abnormally low urinary output).

- Dopamine activates **β 1** receptors in the heart.
- At low doses, peripheral resistance may decrease.
- At higher rates of infusion, dopamine activates vascular α receptors, leading to vasoconstriction, including in the renal vascular bed (alpha receptor)
- Consequently, high rates of infusion of dopamine may mimic the actions of epinephrine.

Noncardiac Effects of Sympathomimetics

- Activation of **β 2** receptors in **bronchial smooth muscle** leads to **bronchodilation**, and β 2 agonists are important in the treatment of **asthma.**
- In the **eye, α** receptors; activation by drugs such as phenylephrine causes **mydriasis** .
- **Alpha agonists** also increase the outflow of aqueous humor from the eye and can be used clinically to **reduce intraocular pressure.**
- In contrast, beta agonists have little effect, **but beta *antagonists* decrease the production of aqueous humor**. These effects are important in the treatment of glaucoma.

- In **genitourinary** organs, the bladder base, urethral sphincter, and prostate contain **alpha receptors** that mediate contraction and therefore promote urinary continence (control urination).

- The specific subtype of α 1 receptor involved in mediating constriction of the bladder base and prostate is uncertain, but **α 1A** receptors probably play an important role.

- Alpha-receptor activation in the ductus deferens, seminal vesicles, and prostate plays a role in normal ejaculation.

- **Hormone secretion**
- Insulin secretion is stimulated by β receptors and inhibited by α 2 receptors.

- Renin secretion is stimulated by β 1 and inhibited by α 2 receptors.

- **CNS**
- The catecholamines are almost completely excluded by **blood-brain barrier.**
- Peripheral effects of β -adrenoceptor agonists such as tachycardia and tremor are similar to the **somatic manifestations of anxiety.**
- Noncatecholamines with indirect actions, such as **amphetamines**, which readily enter the CNS produce CNS effects.
- These actions vary from mild alerting, with improved attention to boring tasks; through **elevation of mood, insomnia, euphoria, and anorexia; to full-blown psychotic behavior**.
- These effects may represent **enhancement of dopamine-mediated** processes or other effects of these drugs in the CNS.

- **Metabolism.**
- Activation of **β 3** receptors in fat cells **increases lipolysis** with enhanced release of free fatty acids and glycerol into the blood.
- Activation of **β** receptors enhance **glycogenolysis** in the liver, increasing glucose release into the blood.
- Activation of **β 2** receptors promotes the uptake of **K** into cells, leading to a fall in extracellular **potassium**.
- This may lead to a fall in the plasma potassium concentration during stress or protect against a rise in plasma potassium during exercise.
- In pancreatic islets, **β receptors** increase and **α 2 receptors** decrease **insulin** secretion, but the major regulator of insulin release is the plasma concentration of glucose.

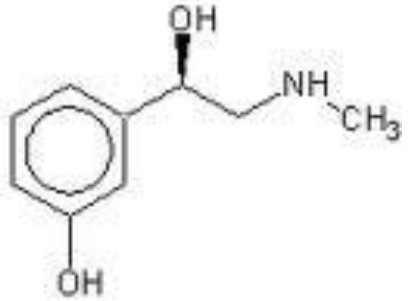
Specific Sympathomimetic Drugs

- **Endogenous Catecholamines**
- **Epinephrine (adrenaline)**
- Agonist at both **α** and **β** receptors.
- Very potent vasoconstrictor and cardiac stimulant.
- Causes a **rise in systolic BP** by its **positive inotropic and chronotropic** actions on the heart (β1) and the vasoconstriction induced in many vascular beds (α).
- Epinephrine also activates **β 2** receptors in skeletal muscle blood vessels, leading to their dilation. Consequently, total **peripheral resistance may fall**.
- Activation of β 2 receptors in skeletal muscle contributes to increased blood flow during exercise.

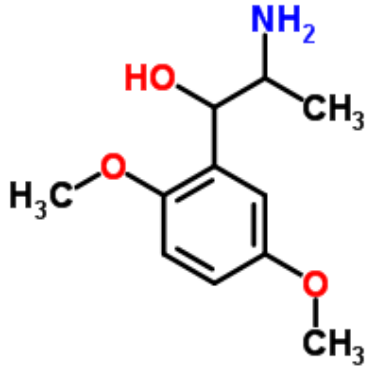
- **Norepinephrine** (noradrenaline)
- Agonist at **α1, α 2** and **β 1** receptors with similar potency as epinephrine, but has relatively little effect on β 2 receptors.
- Consequently, norepinephrine **increases peripheral resistance and both diastolic and systolic blood pressure.**
- Compensatory **baroreflex** activation tends to overcome the direct positive chronotropic effects of norepinephrine; however, the positive inotropic effects on the heart are maintained.

- **Dopamine**
- is the immediate precursor in the synthesis of norepinephrine
- Endogenous dopamine may have more important effects in regulating **sodium excretion** and renal function.
- Its deficiency in the basal ganglia leads to **Parkinson's disease**, which is treated with its precursor **levodopa.**
- Dopamine antagonists are **antipsychotic drugs**.

- **Direct-Acting Sympathomimetics**
- **Phenylephrine**

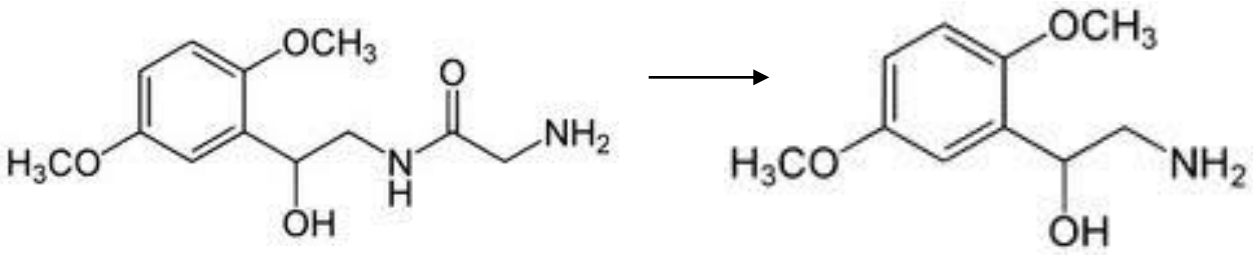


- A relatively **pure α 1** agonist.
- Not a catechol derivative ,it is not inactivated by COMT and has a longer duration of action than the catecholamines.
- It is an effective **mydriatic** and **decongestant** and can be **used to raise the blood pressure**.



- **Methoxamine**
- A direct-acting **α 1** receptor agonist.
- Causes a prolonged increase in BP due to vasoconstriction & a **vagally mediated bradycardia**.
- Clinical uses are rare and limited to hypotensive states.

- **Midodrine**



- A **prodrug** that is enzymatically hydrolyzed to **desglymidodrine**, a selective **α 1-receptor** agonist.
- The primary indication for midodrine is the **treatment of orthostatic hypotension**, due to impaired autonomic nervous system function.
- Although the drug has efficacy in diminishing the fall of blood pressure when the patient is standing, **it may cause hypertension when the subject is supine.**

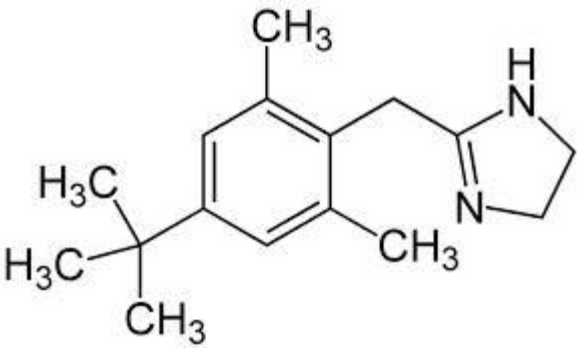
- **Alpha2-selective agonists**
- Decrease BP through actions in the CNS even though direct application to a blood vessel may cause vasoconstriction.
- **Clonidine**, **methyldopa**, **guanfacine**

  are useful in the treatment of hypertension
- **Dexmedetomidine**

  is a centrally acting α 2-selective agonist that is indicated for **sedation** of initially intubated and mechanically ventilated patients during treatment in an intensive care setting.

  It also reduces the requirements for opioids in pain control.

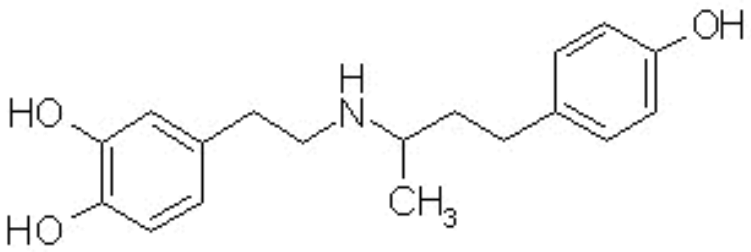
- **Oxymetazoline**
- Direct-acting α agonists.



- Used as **topical decongestants** because of promoting constriction of the nasal mucosa.
- When taken in large doses, oxymetazoline may cause **hypotension**, presumably because of a **central clonidine -like effect**
- Oxymetazoline has significant affinity for **α 2A** receptors.

- **Isoproterenol (isoprenaline)**
- Very potent **β** -receptor agonist and has little effect on α receptors.
- Has **positive chronotropic and inotropic actions.**
- Activates **β** receptors almost exclusively, it is a potent vasodilator.
- These actions lead to a marked increase in cardiac output and a fall in diastolic and mean arterial pressure and a lesser decrease or a slight increase in systolic pressure.

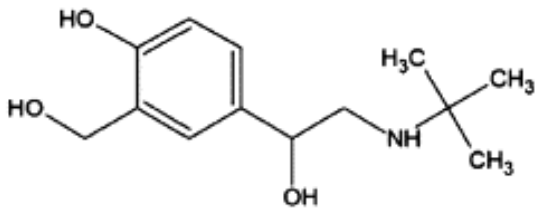
Beta1-selective agents



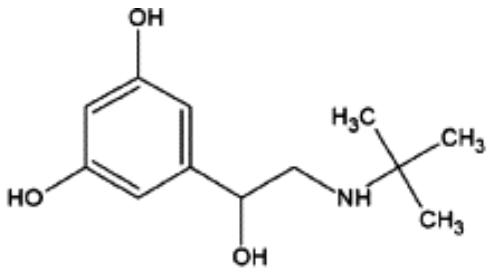
- **Dobutamine**
- It resembles dopamine, but its actions are mediated by activation of **α** and **β** receptors.
- Dobutamine is a racemic mixture of (–) and (+) isomers.
- The (**+**) isomer is a **potent β 1 agonist** and an **α 1 receptor antagonist.**
- The (**–**) isomer is a potent **α 1 agonist**
- The resultant effects of dobutamine is **β 1** stimulation.
- Dobutamine has a **positive inotropic** action caused by the isomer with predominantly **β1** receptor activity. It has relatively **greater inotropic than chronotropic** effect compared with isoproterenol.

- Beta2-selective agents
- **Salbutamol, terbutaline**

Important in the treatment of asthma.



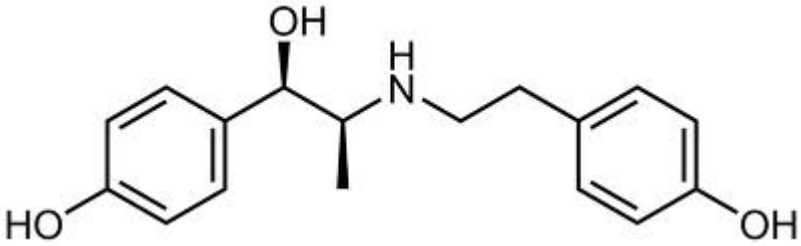
Salbutamol



Terbutaline

- **Ritodrine**

Used to achieve uterine relaxation in premature labor.



- **Mixed-Acting Sympathomimetics**
- **Ephedrine**
- The plant *Ephedra sinica*, has been used in traditional Chinese medicine for 5,000 years for the treatment of asthma and hay fever, as well as for the common cold
- Ephedrine is a noncatechol ,it has high bioavailability and a relatively long duration.
- **It releases NE** and **activates β2** receptors directly.
- Because it gains access to the CNS, it is a mild stimulant.

- **Pseudoephedrine**

  One of four ephedrine enantiomers.

  Available over the counter as a component of many **decongestant** mixtures.

- **Phenylpropanolamine**

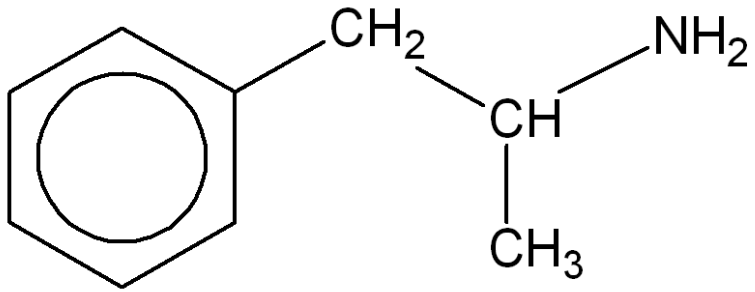
  Was a common component in over-the-counter **appetite suppressants.**

  It was removed from the market because its use was associated with hemorrhagic strokes in young women.

  The mechanism of this potential adverse effect is unknown.

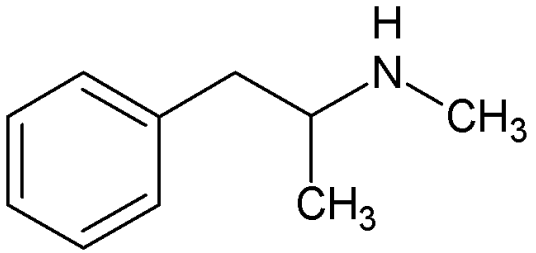
- **Indirect-Acting Sympathomimetics**

- Indirect-acting sympathomimetics can have one of two different mechanisms
- First, they may enter the sympathetic nerve ending and **displace stored catecholamine** transmitter.
- Such drugs have been called **amphetamine-like or "displacers.**
- " Second, they may **inhibit the reuptake** of released transmitter by interfering with the action of the NE transporter, NET.



- **Amphetamine-Like**
- **Amphetamine**
- A racemic mixture that is important because of its use and misuse as a **CNS stimulant** .
- Readily enters the CNS, where it has marked stimulant effects on **mood and alertness and a depressant effect on appetite.**
- Its **D-isomer** is more potent than the **L-isome**r. Amphetamine's actions are mediated through the release of **NE** and, to some extent, **dopamine.**

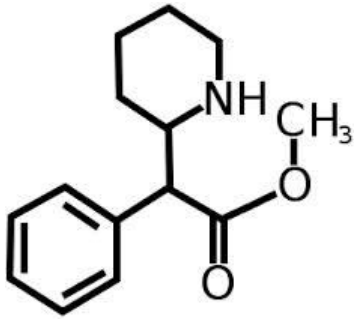
- **Methamphetamine**



(*N*- methylamphetamine)

Very similar to amphetamine with an even higher ratio of central to peripheral actions.

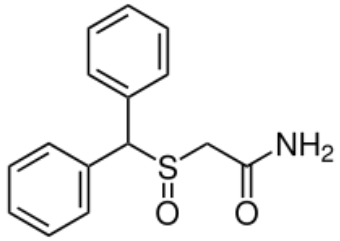
- **Methylphenidate**



Amphetamine variant whose major pharmacologic effects and abuse potential are similar to those of amphetamine.

Methylphenidate may be effective in some children with **attention deficit hyperactivity disorder**.

- **Modafinil**



A **psychostimulant.**

Inhibits both NE and DA transporters, and it increases interstitial concentrations of NE, DA , serotonin and glutamate while decreasing GABA levels.

It is used primarily to improve wakefulness in **narcolepsy**.

It is often associated with increases in BP and heart rate, though these are usually mild.

- **Tyramine**

Found in high concentrations in some fermented foods such as **cheese**.

Readily metabolized by MAO in the liver and is normally inactive when taken orally because of a very high first-pass effect,

If administered parenterally, it has an indirect sympathomimetic action caused by the release of stored catecholamines.

In patients treated with **MAO inhibitors** , tyramine may cause **marked increases in blood pressure.**

Patients taking MAO inhibitors must be very careful to avoid tyramine -containing foods.

- **Catecholamine Reuptake Inhibitors**
- Many antidepressants, particularly **tricyclic antidepressants** can inhibit norepinephrine and serotonin reuptake to different degrees leading to orthostatic tachycardia as a side effect.
- **Atomoxetine**

A selective inhibitor of the NE reuptake transporter used in the **treatment of attention deficit disorders**

Sibutramine

A **serotonin** and **NE** reuptake inhibitor and was used as **appetite suppressant for long-term treatment of obesity.**

Cocaine

A local anesthetic with a peripheral sympathomimetic action that results from inhibition of NE reuptake .

It readily enters the central nervous system and produces an **amphetamine-like psychological** effect that is **shorter** lasting and **more intense** than amphetamine.

Its major action in the CNS is to **inhibit dopamine reuptake** into neurons in the "**pleasure centers**" of the brain.

These properties and the fact that it can be smoked, snorted into the nose, or injected for rapid onset of effect have made it a **heavily abused drug**

- **Dopamine Agonists**
- **Levodopa**
- Converted to dopamine in the body, and of considerable value in the treatment of Parkinson's disease.
- **Fenoldopam**

  A D1-receptor agonist that selectively leads to peripheral vasodilation in some vascular beds.

The primary indication for fenoldopam is in the **IV treatment of severe hypertension**

Therapeutic Uses of Sympathomimetics

- **Cardiovascular Applications**
- **Treatment of Acute Hypotension**

  Used in a hypotensive emergency to preserve cerebral and coronary blood flow.
- The treatment is usually of short duration while the appropriate intravenous fluid or blood is being administered.
- Direct-acting agonists such as **NE, phenylephrine,** and **methoxamine** have been used when vasoconstriction is desired.

- **Cardiogenic shock and acute heart failure**
  Usually due to massive myocardial infarction.

  Positive inotropic agents such as **dopamine** or **dobutamine** may provide short-term relief of heart failure symptoms in patients with advanced ventricular dysfunction.

  In low to moderate doses, these drugs may increase cardiac output and cause relatively little peripheral vasoconstriction.

- **Chronic Orthostatic Hypotension**.
- Impairment of autonomic reflexes that regulate BP can lead to chronic orthostatic hypotension.
- Due to medications that can interfere with autonomic function, diabetes and other diseases causing peripheral autonomic neuropathies.
- **Midodrine**
- orally active **α 1 agonist,** is frequently used for this indication.
- Other sympathomimetics, such as oral ephedrine or phenylephrine, can be tried.
- **Cardiac Applications**
- **Isoproterenol** and **epinephrine** have been used in the temporary emergency management of complete **heart block and cardiac arrest**.

Inducing Local Vasoconstriction

Epinephrine applied topically in nasal packs (for epistaxis) or in a gingival string for gingivectomy (a surgery that removes diseased gum tissue).

Cocaine is used for nasopharyngeal surgery because it combines a hemostatic effect with local anesthesia.

Combining α agonists with **local anesthetics** greatly prolongs the duration of local anesthesia & the total dose of local anesthetic & the probability of toxicity can therefore be reduced.

Epinephrine

1:200,000, is the favored agent for this application, but **norepinephrine**, **phenylephrine**, & other α agonists have also been used.

Systemic effects on the heart and peripheral vasculature may occur even with local drug administration but are usually minimal.

- Mucous membrane **decongestants** are alpha agonists.
- Rebound congestion may follow the use of these agents.
- **Phenylephrine,** used in nasal decongestant sprays.
- A longer duration of action at the cost of greater potential for cardiac and CNS effects can be achieved by the **oral** administration of **ephedrine** or **pseudoephedrine**.
- Long-acting topical decongestants include **xylometazoline** and **oxymetazoline**.
- Most of these decongestants are available as over-the-counter products.

- **Pulmonary Applications**

  One of the most important uses of sympathomimetic drugs is in the therapy of **bronchial asthma**.

β 2-selective agents:

Albuterol (Salbutamol), metaproterenol, terbutaline all are available for this indication.

Sympathomimetics other than the β 2–selective drugs are now rarely used because they are likely to have more adverse effects than the selective drugs.

- **Anaphylaxis**
- The syndrome of bronchospasm, mucous membrane congestion, angioedema, and severe hypotension usually responds rapidly to the parenteral administration of **epinephrine.**

  Epinephrine is effective because:

  1- β1 increases cardiac output.

  2- β2 relaxes constricted bronchioles.

  3- α1 constricts capillaries.
- **Glucocorticoids** and **antihistamine**s may be useful as secondary therapy in anaphylaxis; however, epinephrine is the initial treatment.

- **Ophthalmic Applications**
- **Phenylephrine** is an effective **mydriatic** agent used to facilitate examination of the retina.

  It is also a useful decongestant for minor allergic hyperemia and itching of the conjunctival membranes.

- **Glaucoma** responds to a variety of sympathomimetic and sympathoplegic drugs.
- **Epinephrine** is now rarely used, but β -blocking agents are among the most important therapies.

Apraclonidine

Alpha 2-selective agonist that also lower intraocular pressure is used in glaucoma.

The mechanism of action of these drugs in treating glaucoma is still uncertain.

- **Genitourinary Applications**
- **β 2** selective agents relax the pregnant uterus. **Ritodrine, terbutaline,** and similar drugs have been used to suppress premature labor.
- Oral sympathomimetic therapy is useful in the treatment of **stress incontinence** (loss of small amounts of urine associated with coughing, laughing, sneezing, exercising or other movements that increase intra-abdominal pressure and thus increase pressure on the bladder.).
- **Ephedrine** or **pseudoephedrine** may be tried.

- **CNS Applications**
- **Treatment of narcolepsy.**
- **Modafinil**

A new amphetamine substitute, is claimed to have fewer disadvantages (excessive mood changes, insomnia and abuse potential) than amphetamine in this condition. .

- **Attention-deficit hyperactivity disorder (ADHD)**

A behavioral syndrome of short attention span, hyperkinetic physical behavior, and learning problems. Some patients respond well to low doses of **methylphenidate** and related agents or to **clonidine. Modafinil** may also be useful in ADHD.