Adrenoceptor Agonists & Sympathomimetic Drugs

Relative Receptor Affinities

Alpha agonists

Phenylephrine, methoxamine	α 1 >α 2 >>>>> β
Clonidine, methylnorepinephrine	α 2 > α 1 >>>>> β

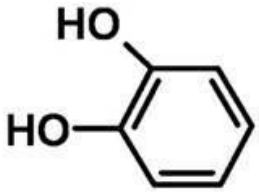
Mixed alpha and beta agonists

Norepinephrine	α 1 = α 2; β1 >> β2
Epinephrine	α 1 = α 2; β1 = β 2

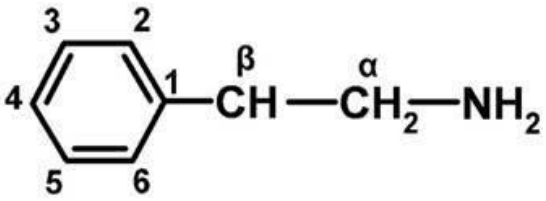
Beta agonists

Dobutamine	β 1 > β 2 >>>> α
Isoproterenol	β1 = β 2 >>>> α
Albuterol (Salbutamol), terbutaline,, ritodrine	β 2 >> β 1>>>> α

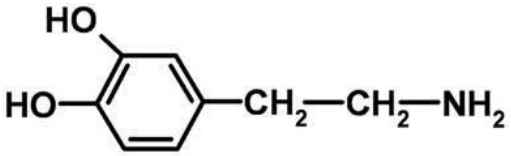
Medicinal Chemistry of Sympathomimetic Drugs



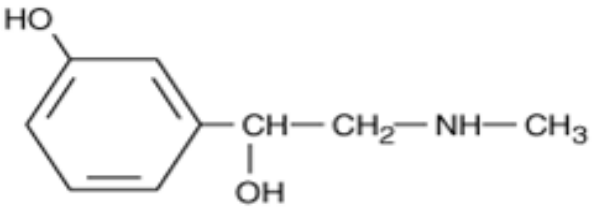
CATECHOL



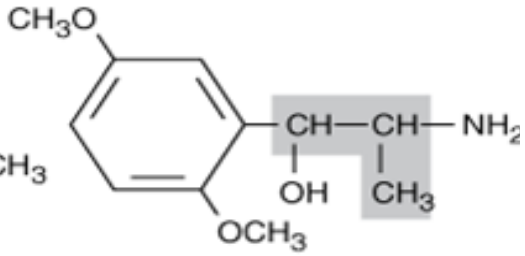
PHENYLETHYLAMINE



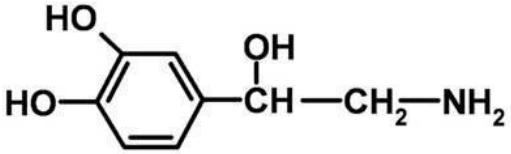
DOPAMINE
(3-Hydroxytyramine)



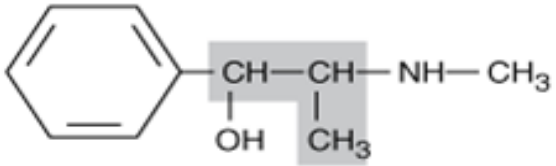
Phenylephrine



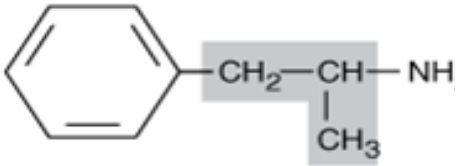
Methoxamine



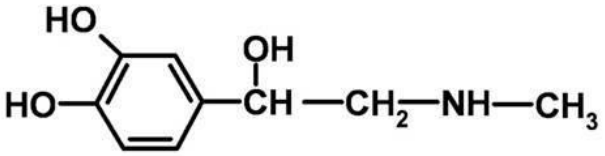
NORADRENALINE
NOREPINEPHRINE



Ephedrine



Amphetamine



ADRENALINE
EPINEPHRINE

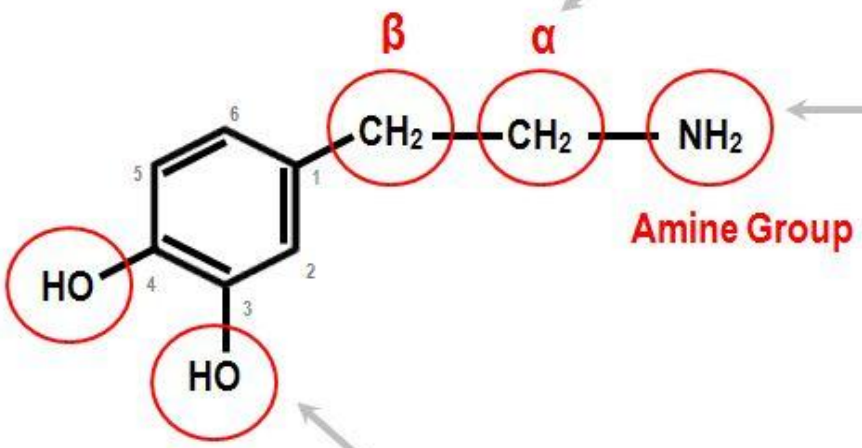
None catecholamines

catecholamines

Beta- carbon atom
ANY additional group here GREATLY increases alpha and beta receptor agonist activity.

extra hydroxyl group decrease lipid solubility, & decrease CNS penetration

Alpha- carbon atom
Any additional groups here increase the half life by inhibiting MAO, and also allow the drug to act as an indirect sympathomimetic



Amine group
A methyl group here confers alpha selectivity.
The smaller the group, the more alpha effect there is.

Increase of the alkyl substituent on the amine group increases the molecules preference or beta receptors instead of alpha.

The Aromatic Ring and Catechol hydroxyl groups
It all depends where you substitute the extra groups.
You need two to have the maximum receptor affinity.

two polar hydroxyl groups decreases lipid solubility and keeps out of the brain. Having no groups results in good CNS penetration. Positions 3 and 5 confer a beta-2 selectivity in compounds with large amino substituents.

Organ System Effects of Sympathomimetics.

Cardiovascular System.

The net effect **of a Sympathomimetic drug** depends on:

- its **relative selectivity for α or β** adrenoceptors
- 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 leading to a rise in blood pressure (BP)
- decreases venous capacitance.
- 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 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 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 (in sk muscles).

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 increases 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

At LOW DOSES (1-2 ug /kg/min)

- **DA** IV 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.**
- **DA** is used to improve perfusion to the kidney in situations of oliguria (abnormally low urinary output).

Noncardiac Effects of Sympathomimetics

- Activation of **β 2** receptors leads to **bronchodilation**, & β 2 agonists are important in treatment of **asthma.**
- In the **eye, α** receptors activation by phenylephrine causes **mydriasis** .
- **Epinephrine & Alpha 2 agonists** also increase the outflow of aqueous humor & used 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.

- 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

- CA are almost completely excluded by **BBB.**
- Peripheral effects of β agonists. e.g. tachycardia and tremor are similar to the **somatic manifestations of anxiety.**
- Noncatecholamines with indirect actions, such as **amphetamines** 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 in the CNS.

Metabolism.

- **β 3** receptors in fat cells **increases lipolysis** & release of free fatty acids & 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)

Epinephrine **stimulates both α** and **β** receptors.

– When given i.v. it is a very potent vasoconstrictor and cardiac stimulant.

The rise in systolic BP results from a β1 mediated increase in heart rate & ventricular contractility

The rise in diastolic pressure results from stimulation of α1 and α2 receptor mediated vasoconstriction in many vascular beds

EP also stimulates β2 receptors present in skeletal muscle blood vessels, resulting in their dilation

Activation of β 2 receptors in skeletal muscle increases blood flow during exercise.

– **At low doses, at which β2 receptor stimulation predominates** over α receptor stimulation, **total peripheral resistance and diastolic pressure may fall**

Under physiological conditions, epinephrine released from the adrenal gland functions as a hormone and, via activation of β2 receptors, contributes to increased blood flow during exercise.

- β2 stimulation will cause bronchodilation in the lung and activate glycogenolysis in the liver

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 but the positive inotropic effects on the heart are maintained.

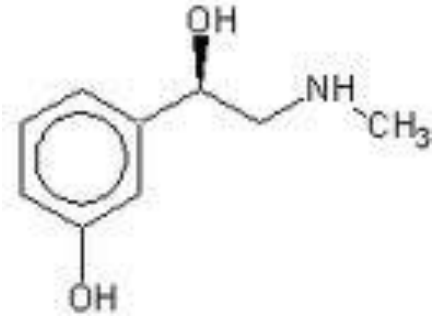
Dopamine

- 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**.

- **At LOW DOSES (1-2 ug/kg/min) it selectively activates D1 receptors** in several vascular beds (e.g. kidney) resulting in vasodilation.

  The D1 mediated effect to increase renal blood flow may be of clinical significance (e.g. in the treatment of shock).
- Activation of presynaptic D2 receptors may suppress norepinephrine release.
- **At INTERMEDIATE DOSES (5-10 ug/kg/min) dopamine activates β1 receptors in the heart.**
- **At HIGH DOSES (>10 ug/kg/min) dopamine activates α receptors leading to vasoconstriction, including the renal vascular bed.**
- High doses of dopamine may mimic the actions of epinephrine.

Direct-Acting Sympathomimetics



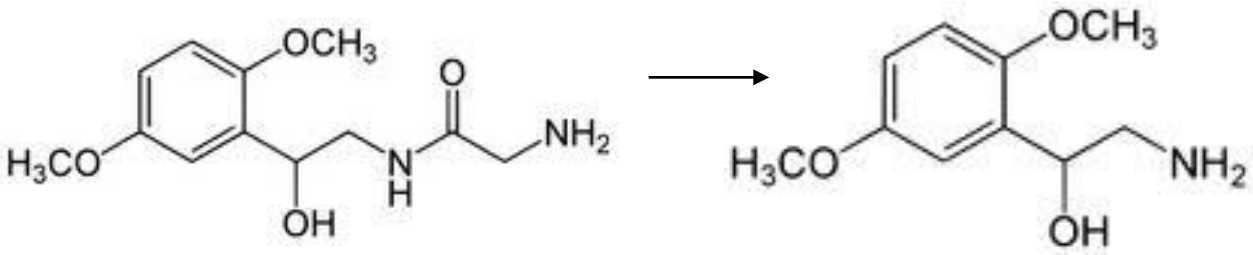
Phenylephrine

- 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.
- 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.

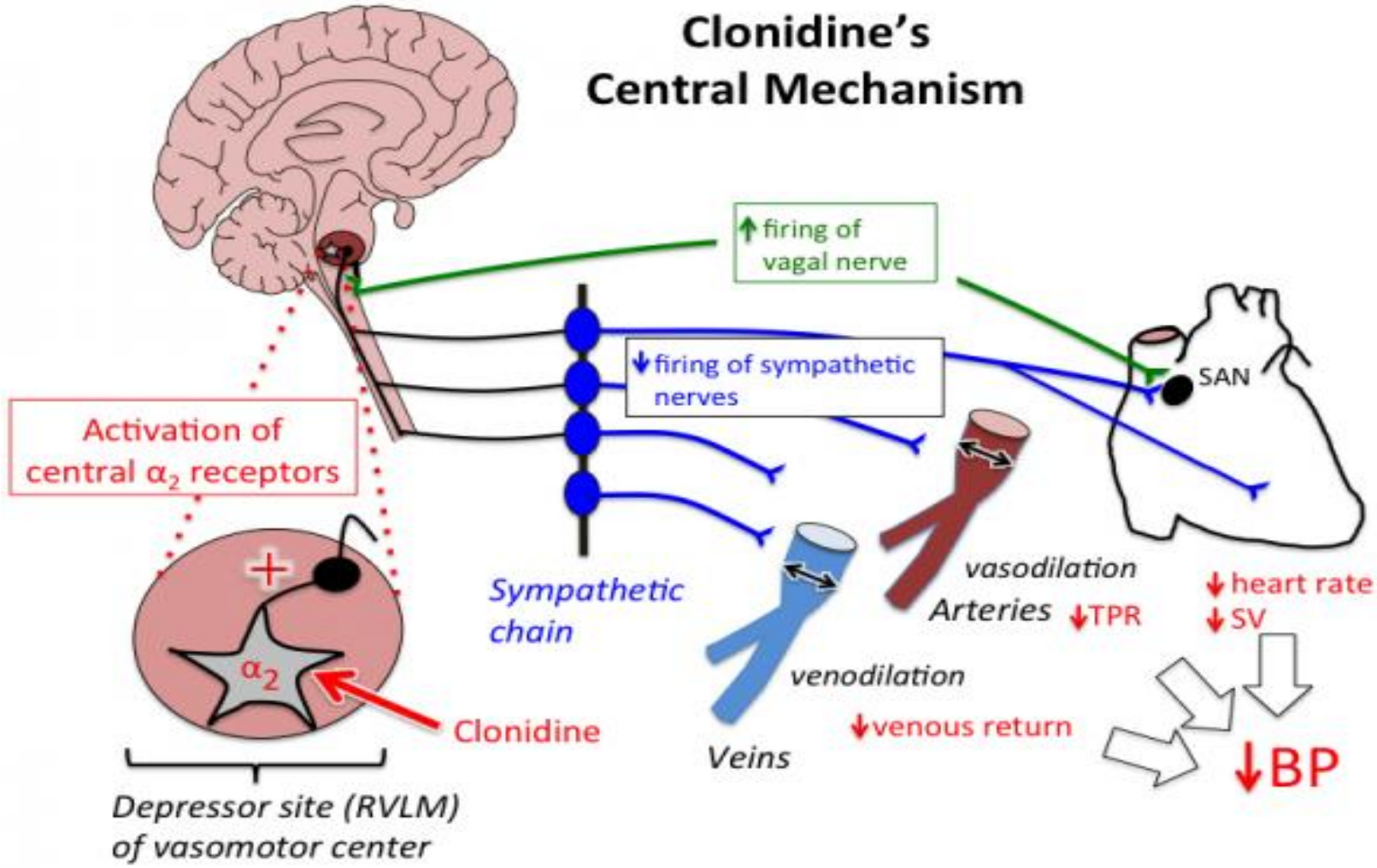
Midodrine

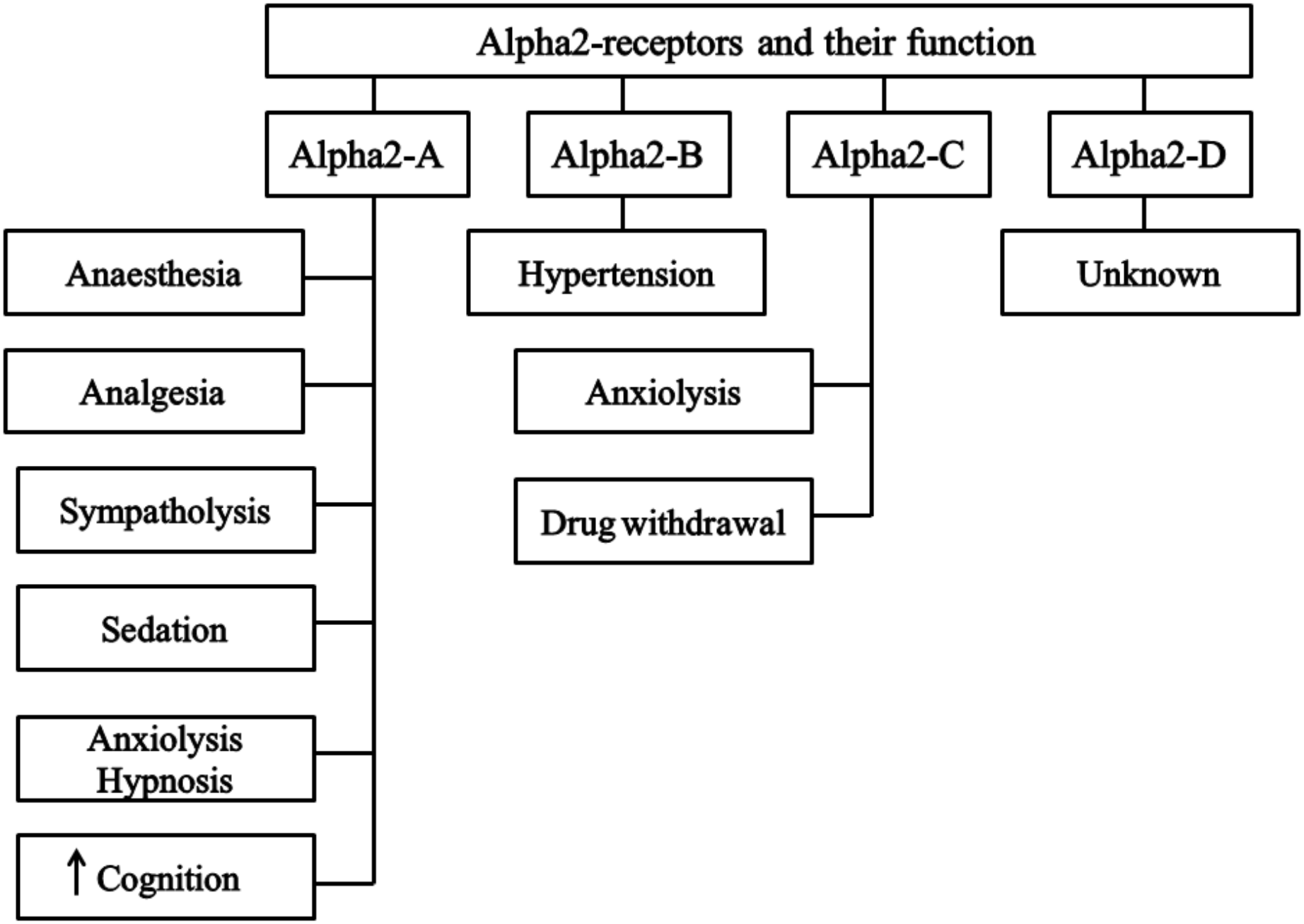


- A **prodrug** that is enzymatically hydrolyzed to **desglymidodrine**, a selective **α 1-receptor** agonist.
- The primary indication for midodrine is the **treatment of orthostatic hypotension**, due to impaired autonomic nervous system function.
- Prevents the fall of blood pressure when the patient 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.




Alpha2-receptors and their function
Alpha2-A
Alpha2-B
Alpha2-C
Alpha2-D
Anaesthesia
Analgesia
Sympatholysis
Sedation
Anxiolysis
Hypnosis
↑ Cognition
Hypertension
Anxiolysis
Drug withdrawal
Unknown

Clonidine

- Stimulates α2A adrenoceptors in the vasomotor centre in brainstem causing a decrease in BP and cardiac output.
- High dose activates peripheral presynaptic autoreceptors on adrenergic nerve ending mediating negative feedback suppression of noradrenaline release
- Overdose stimulates peripheral postsynaptic α1 adrenoceptors & cause hypertension by vasoconstriction.
- Clonide has a sedative, analgesic, antishivering and diuretic actions
- The site for the sedative action is in the locus ceruleus of the brain stem. The site for the analgesic action is in the spinal cord.

- In the heart, the dominant action of α^2agonists is a decrease in tachycardia (through decreasing NE release) and bradycardia (through a vagomimetic action).
- The mechanism for the antishivering and diuretic actions have yet to be established.
- Uses:
- ADHD in children, opioid withdrawal, restless legs, hypertension, alcohol withdrawal
- Low dose of Clonidine is used in migraine prophylaxis, menopausal flushing and chorea
- **Abrupt withdrawal** causes **rebound hypertension**
- Side effects: Sedation, dry mouth, dizziness and constipation

Methyldopa

Metabolized to **α-methyl norepinephrine**, which then lowers arterial pressure by **activation of presynaptic α2 receptors in the brainstem which reduce sympathetic outflow**, lowering blood pressure (similar to clonidine) & a reduction of plasma renin activity.

Used for treatment of hypertension during pregnancy as a replacement for ACE inhibitors & angiotensin II receptor blockers (which are more efficacious, but are strongly contraindicated in pregnancy).

Guanfacine

Centrally acting α 2-selective agonist.

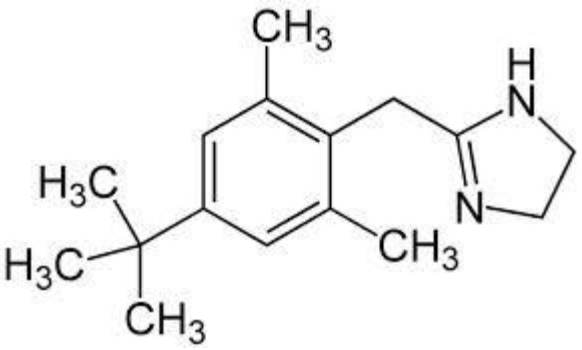
used in the treatment of hypertension

Dexmedetomidine

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



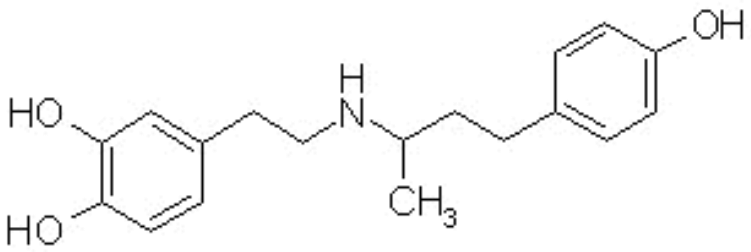
- Direct-acting α agonists.
- Used as **topical decongestants** because of promoting constriction of the nasal mucosa.
- When taken in large doses, oxymetazoline may cause **hypotension**, presumably because of a **central clonidine -like effect**
- Oxymetazoline has significant affinity for **α 2A**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

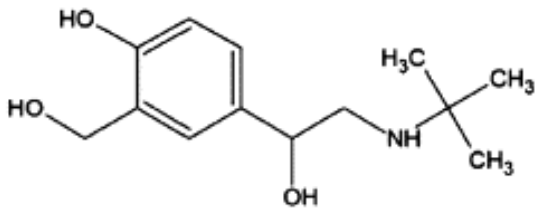
Dobutamine



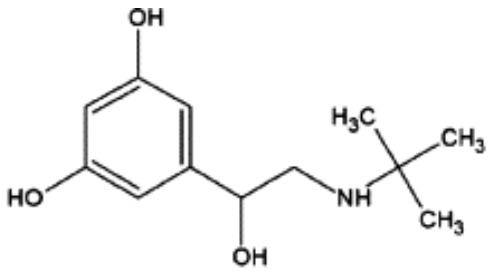
- It resembles dopamine, but its actions are mediated by activation of **α** and **β** receptors.
- Dobutamine is a racemic mixture of (–) & (+) isomers.
- The (**+**) isomer is a **potent β 1 agonist** and an **α 1 receptor antagonist.**
- The (**–**) isomer is a potent **α 1 agonist**
- The resultant 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.



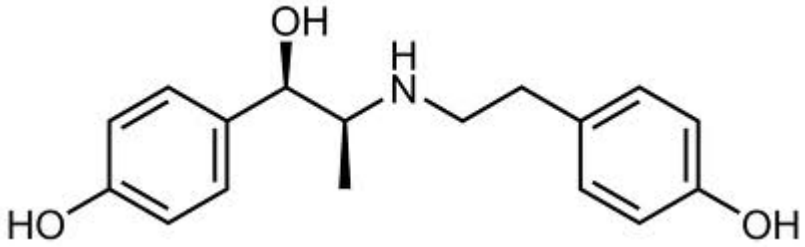
Salbutamol



Terbutaline

- **Ritodrine**

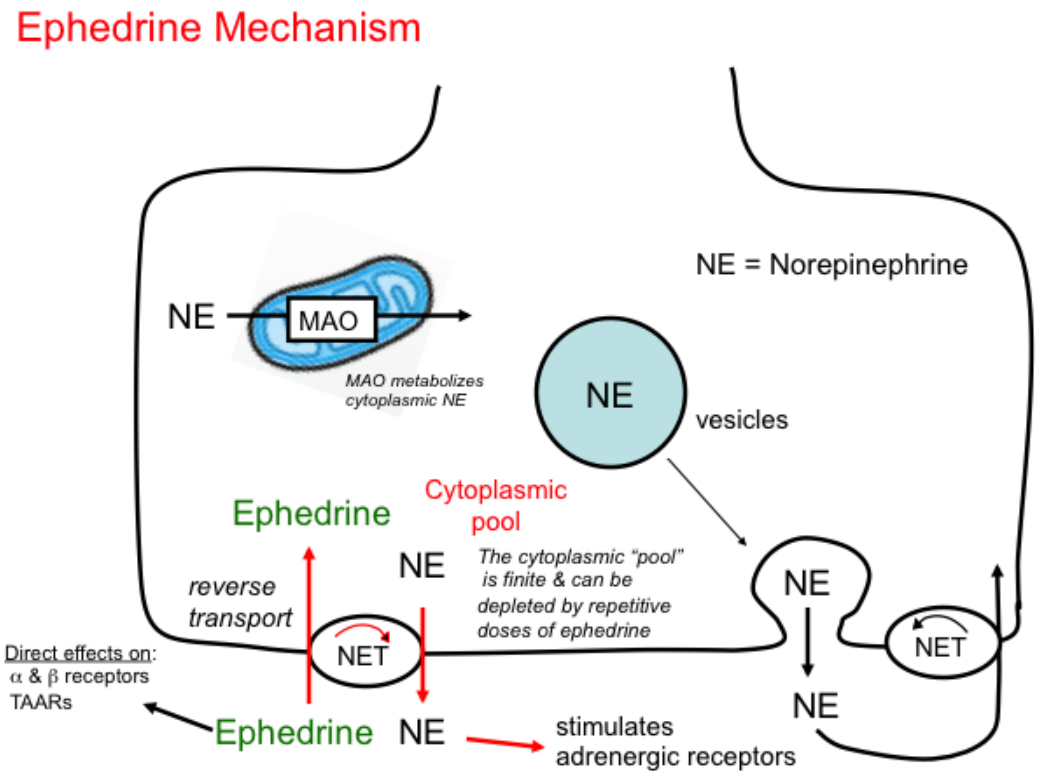
Used to achieve uterine relaxation in premature labor.



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.



Indications:

Bronchodilator,

Decongestant,

Used as a pressor agent during spinal anesthesia when hypotension frequently occurs (produces a longer pressor response compared to most other directly acting agonists)

Contraindications: Cardiovascular disease

Side Effects: Higher than normal incidence of myocardial infarction, stroke and sudden death (e.g. associated with chronic use of ephedrine-containing herbal supplements)

Hypertension, insomnia

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.

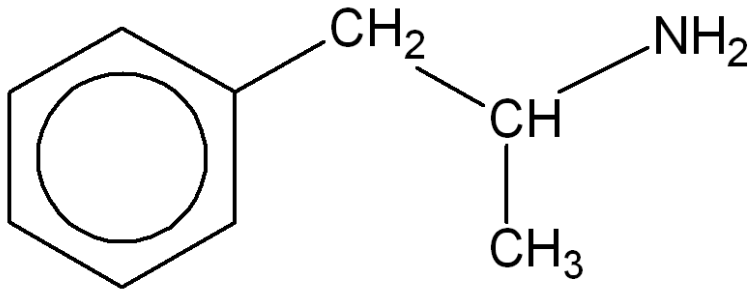
The mechanism of this potential adverse effect is unknown.

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** .

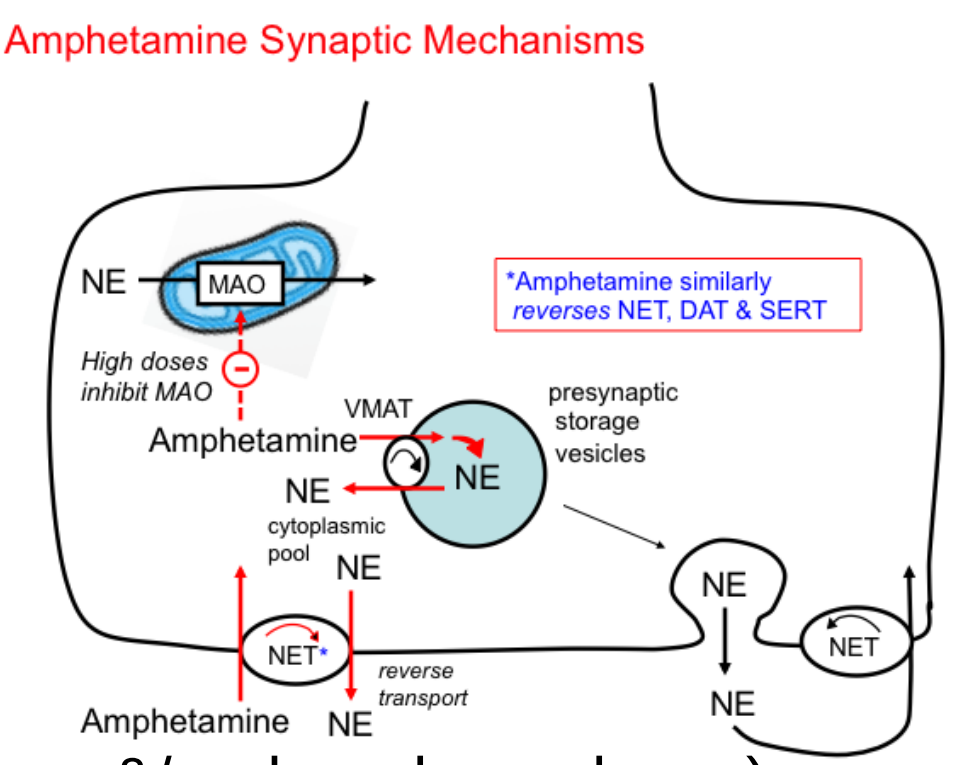
Readily enters the CNS, where it has marked stimulant effects on **mood and alertness and a depressant effect on appetite.**

Its **D-isomer** is more potent than the **L-isome**r.

Amphetamine's actions are mediated through the release of **NE DA & serotonin** from nerve terminals.

Compete with monoamines for reuptake

MAO inhibition - high doses of amphetamines inhibit MAO.



Indications:

attention-deficit disorders and narcolepsy

Contraindications:

Lactation,

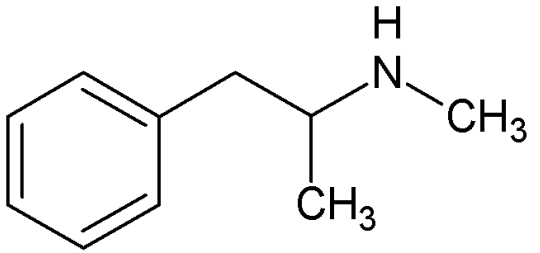
Contraindicated for long-term use for treating obesity (due to development of tolerance &/or drug dependence)

Side Effects:

nervousness, insomnia, palpitations, hypertension, hyperpyrexia, headaches, dizziness, anorexia, weight loss, dryness of the mouth

Black Box Warnings: HIGH POTENTIAL FOR ABUSE

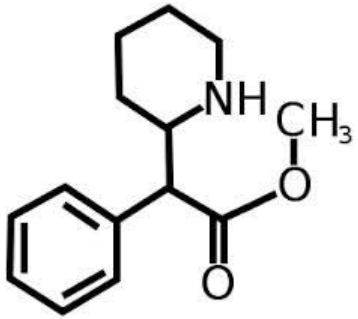
Administration for prolonged periods of time may result in drug dependence. Misuse may cause sudden death and cardiovascular adverse events.



Methamphetamine

(*N*- methylamphetamine)

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

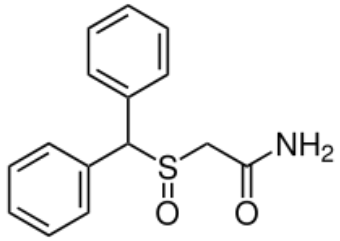


Methylphenidate

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 α 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.