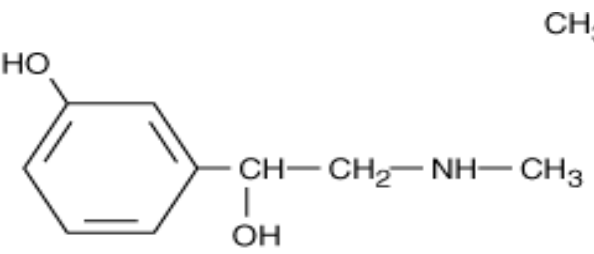
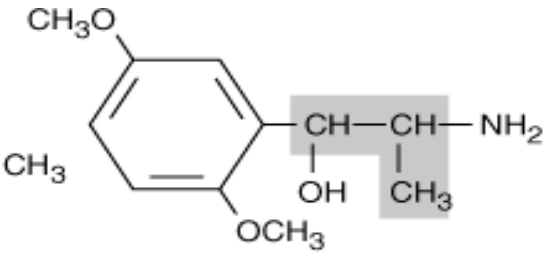
Adrenoceptor Agonists & Sympathomimetic Drugs 2018-2019

	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

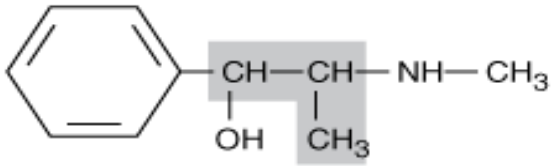
Medicinal Chemistry of Sympathomimetic Drugs



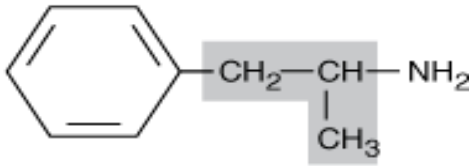
Phenylephrine



Methoxamine

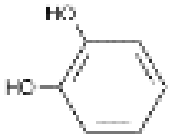


Ephedrine

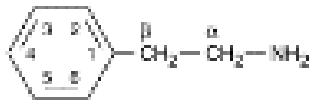


Amphetamine

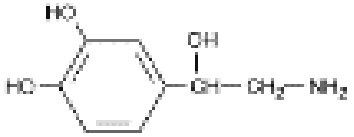
None catecholamines



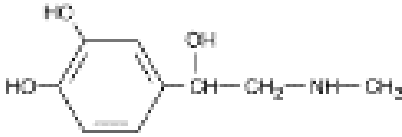
Catechol



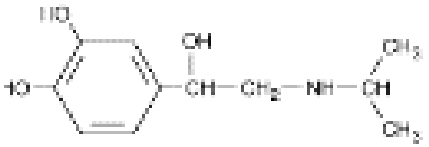
Phenylethylamine



Norepinephrine



Epinephrine



Isoproterenol

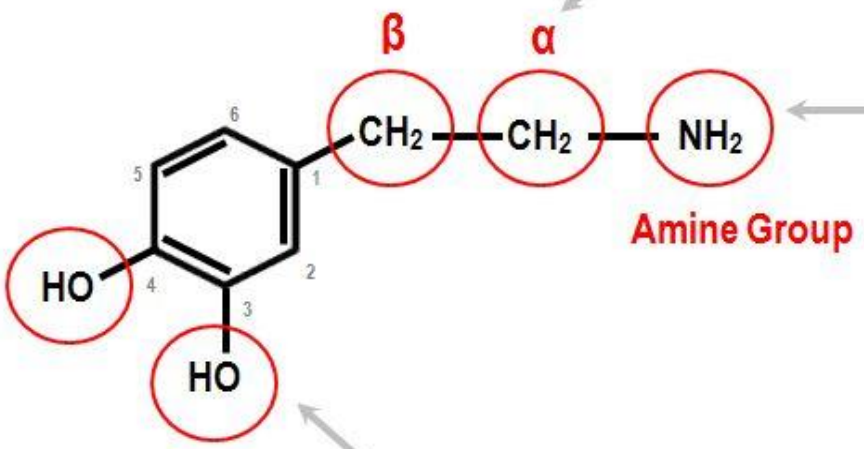
Dopamine

catecholamines

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 e.g. **phenylephrine** causes:

arterial and venoconstriction

↑ **peripheral arterial resistance**

↓ **venous capacitance**.

↑ 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.

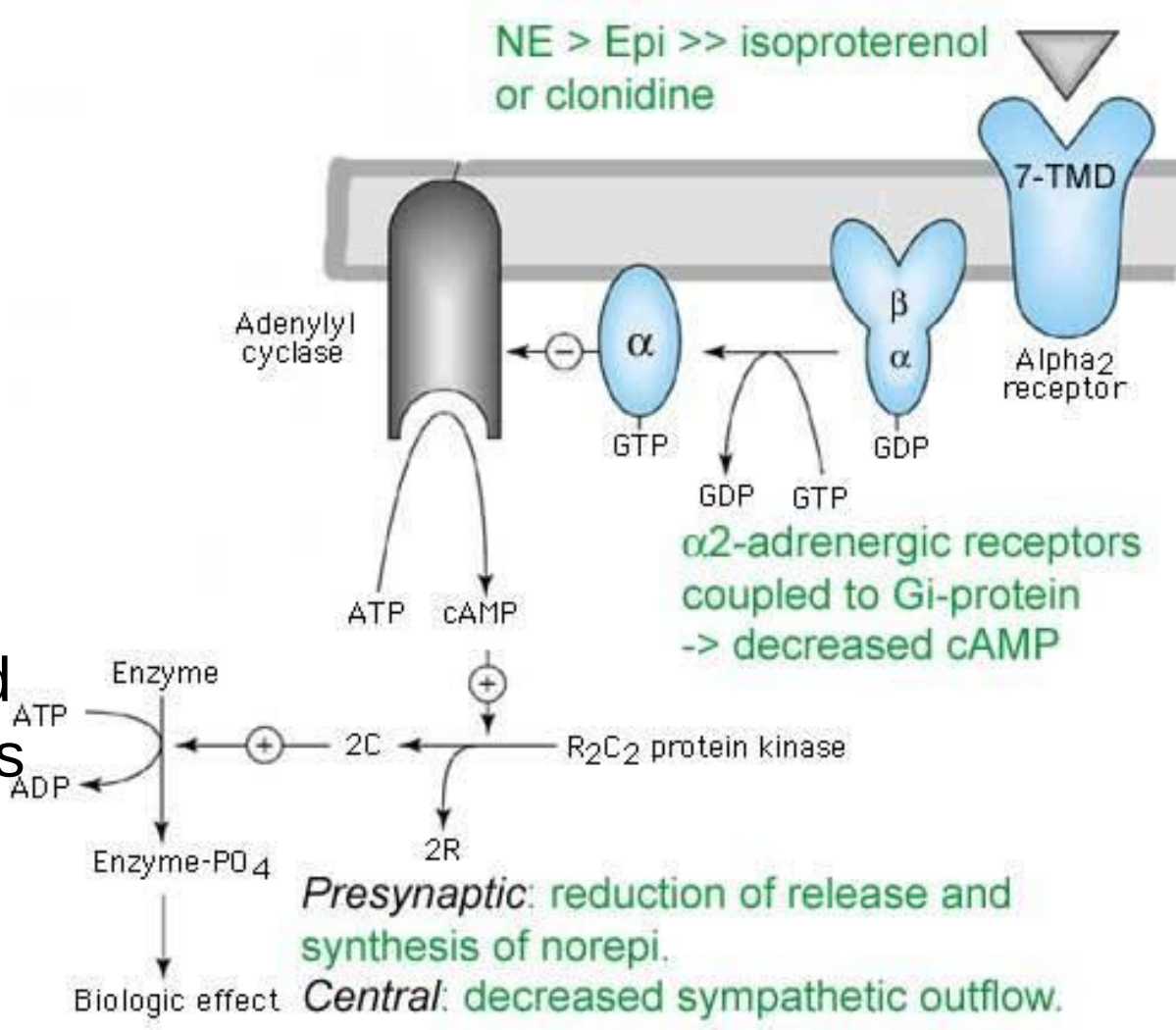
Vessels in **skeletal muscle** may constrict or dilate depending on whether alpha or **beta 2** receptors are activated.

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 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.

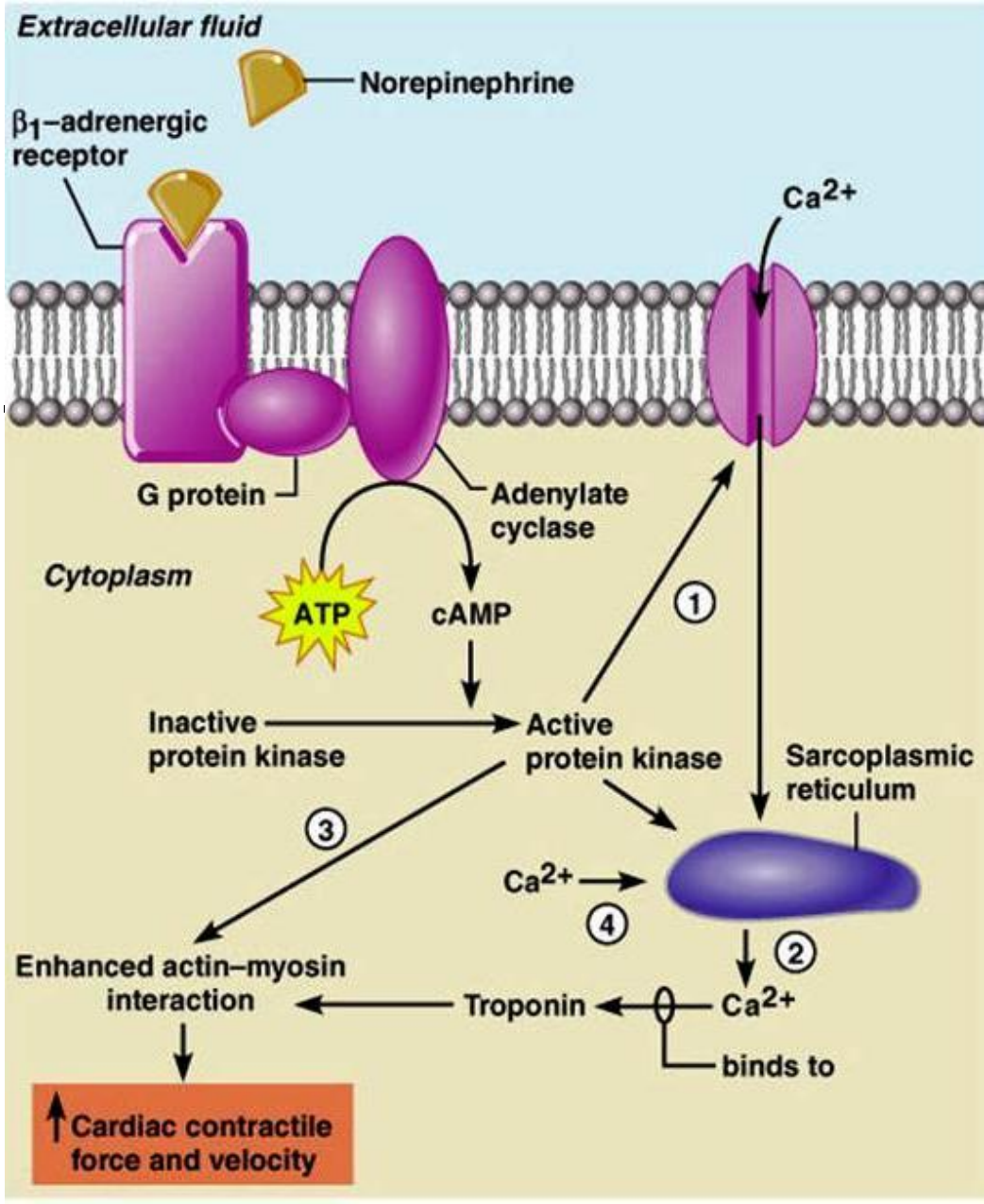
Hence, α 2 agonists are used in the treatment of hypertension .

Effects of Beta-Receptor Activation

Stimulation of β receptors in the **heart** increases **cardiac output** by:

- stimulating contractility
- increasing the heart rate

β agonists also **decrease peripheral resistance** by activating **β 2** receptors, causing vasodilation in vascular beds of 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 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 (HR) may be dominated by a **reflex** response to BP changes.

Physiologic stimulation of the heart by catecholamines increases coronary blood flow.

Effects of Dopamine-Receptor Activation

Low IV infusion 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 induce **natriuresis (**↑Na+ excretion**).**

The renal effects of dopamine have been used clinically to improve perfusion to the kidney in situations of oliguria (abnormally low urinary output).

Moderate infusion rate of DA stimulate **β1 receptors** in the heart leading to increasing contractility & the HR increases slightely.

DA is used to treat congestive heart failure.

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 (α 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 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 (**amphetamines**), which readily enter the CNS produce CNS effects.

These actions vary from mild alerting, with improved attention to boring tasks to full-blown psychotic behavior.

May also cause elevation of mood, insomnia, euphoria, & anorexia

Effects on Metabolism.

Increase lipolysis (**β 3**)with enhanced release of free fatty acids and glycerol into the blood.

Glycogenolysis in the liver, increasing glucose release into the blood **(β)**.

Promotes uptake of **K** into cells, leading to a fall in extracellular **potassium (β 2)**

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 ↑ blood flow during exercise.

β 2 activate glycogenolysis in the liver

β 3 stimulation → lypolysis → ↑ free fatty acids.

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.

increases peripheral resistance and both diastolic and systolic blood pressure.

Compensatory **baroreflex** activation overcome the direct positive chronotropic effects of NE producing bradycardia.

The positive inotropic effects on the heart are maintained.

Dopamine

immediate precursor

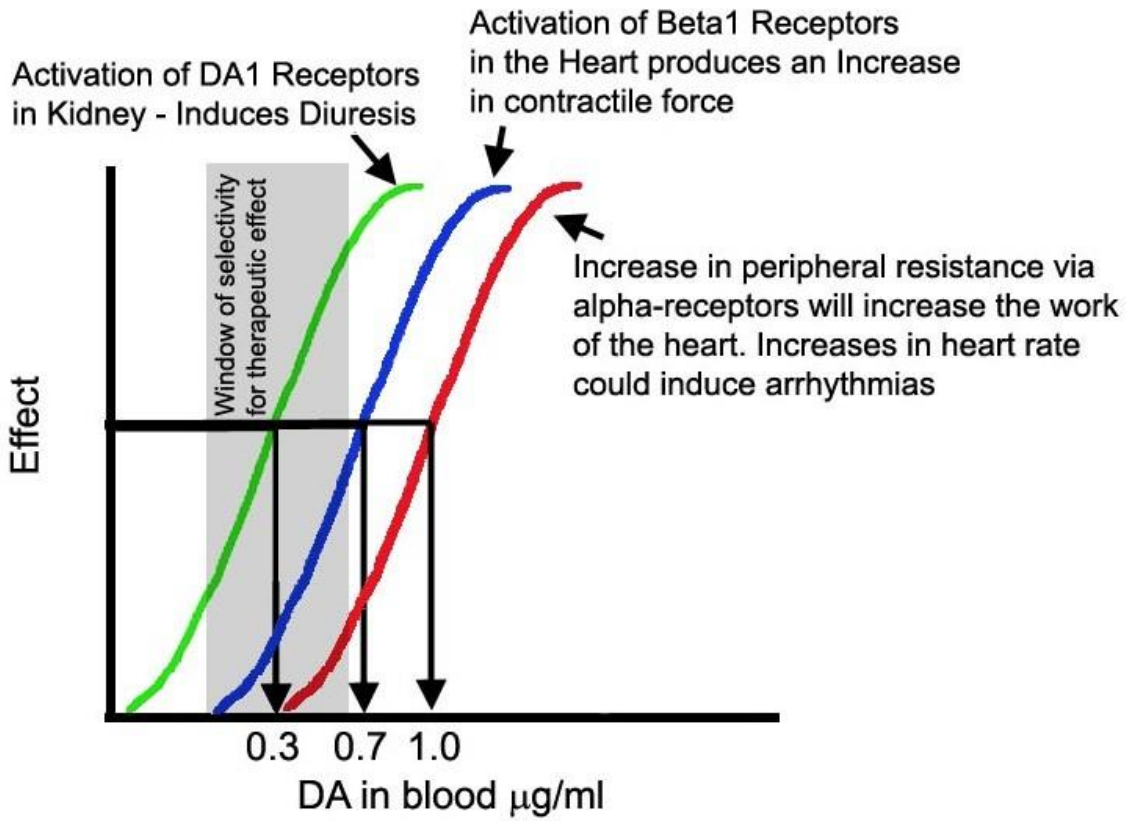
in the synthesis of NE

Stimulates :

Low dose D1 & D2 rec.

Medium dose β rec.

High dose α receptors

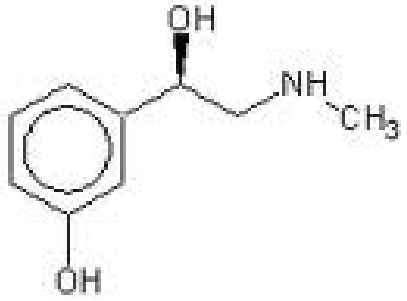


Endogenous DA regulates **sodium excretion** and renal function.

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 catecholamine (CA), it is not inactivated by COMT & has a longer duration of action than the CA.

Effective **mydriatic** and **decongestant** and can be **used to raise the blood pressure**.

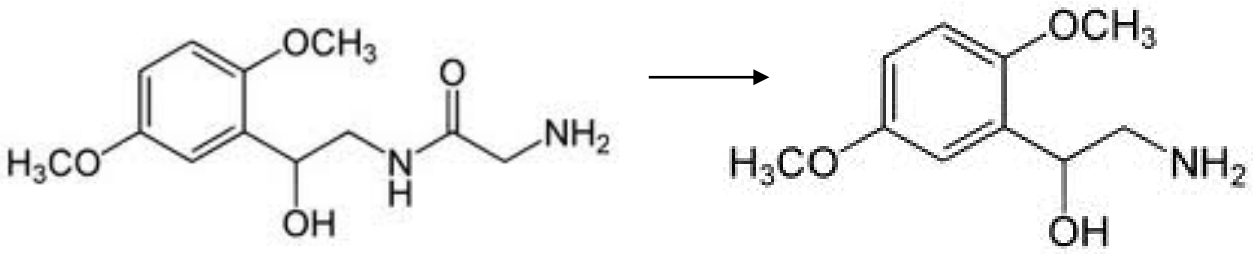
Methoxamine

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



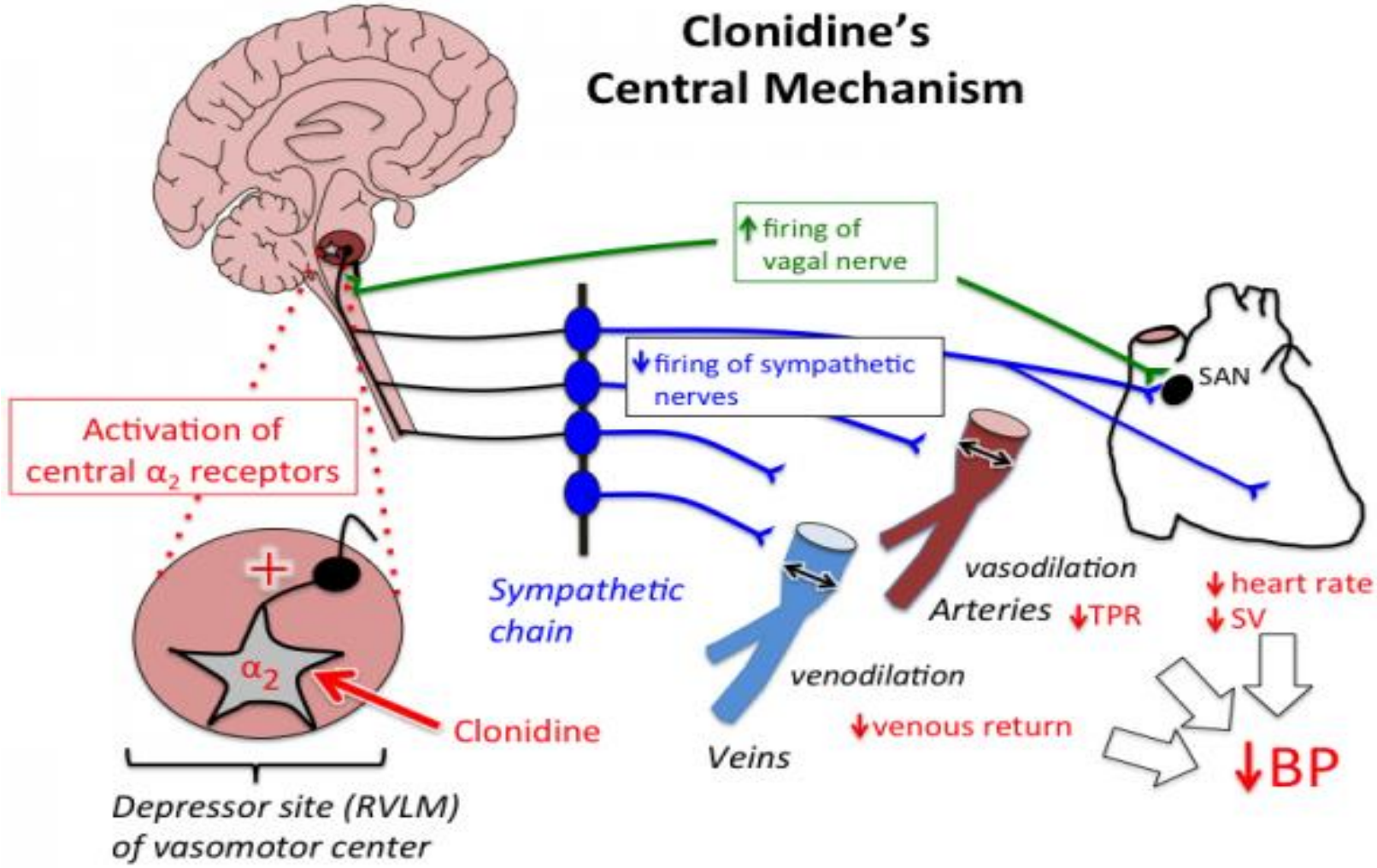
A **prodrug**, enzymatically hydrolyzed to **desglymidodrine**, a selective **α 1-receptor** agonist.

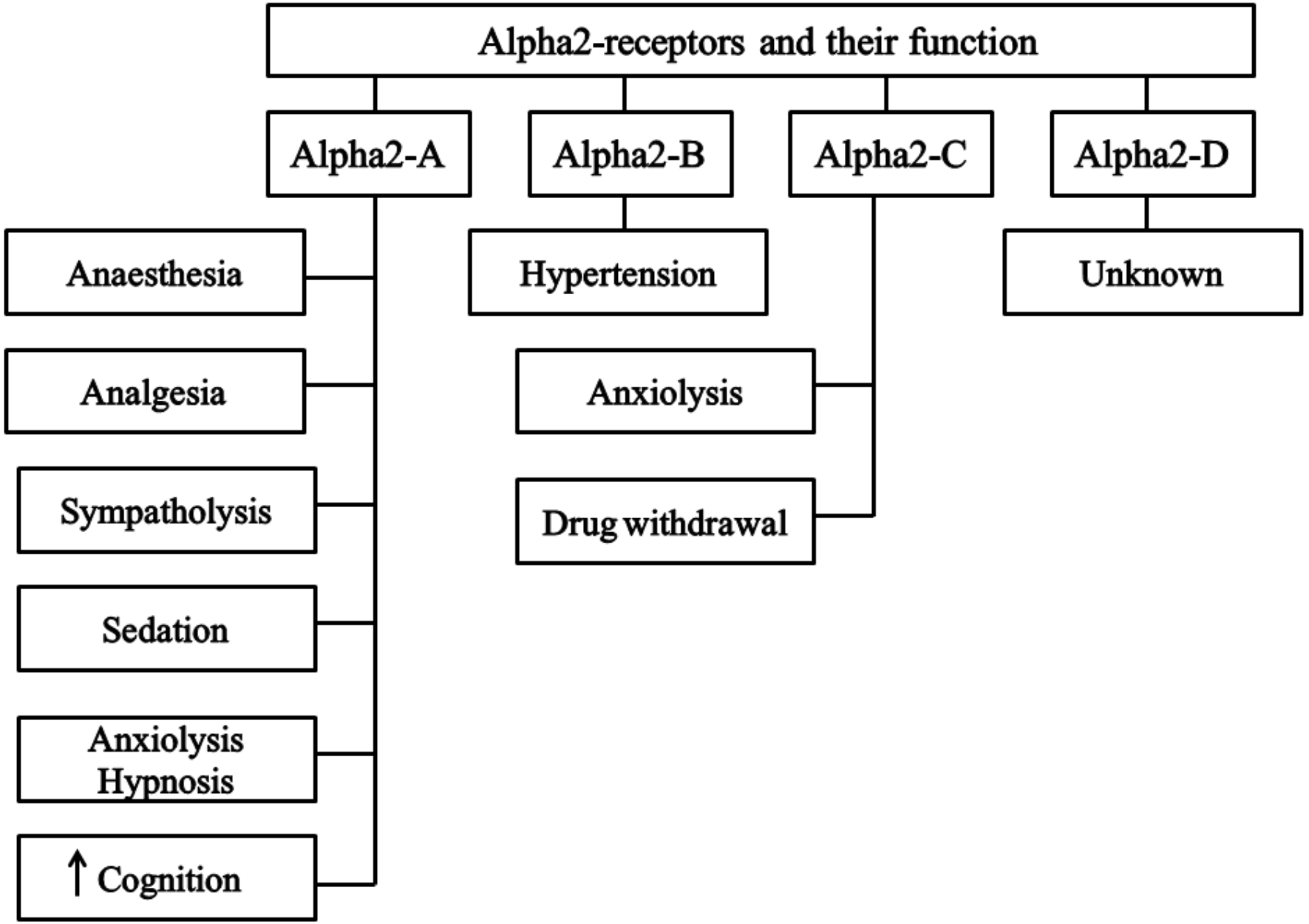
The primary indication for midodrine is the **treatment of orthostatic hypotension**, due to impaired autonomic nervous system function.

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.




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 NE 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, clonidine ↓HR (↓ NE release) and 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

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.

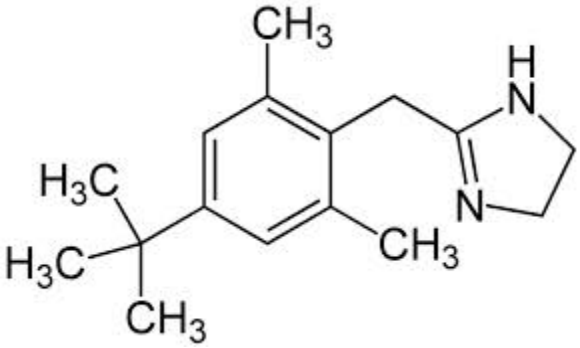
It also reduces the requirements for opioids in pain control.

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).

Oxymetazoline

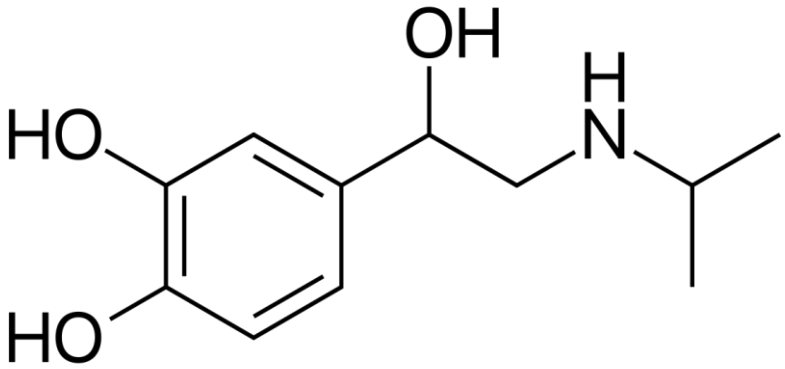


Direct-acting **α agonists** with significant affinity for **α 2A** receptors.

Used as **topical decongestant** 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**

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 (**β 2**).

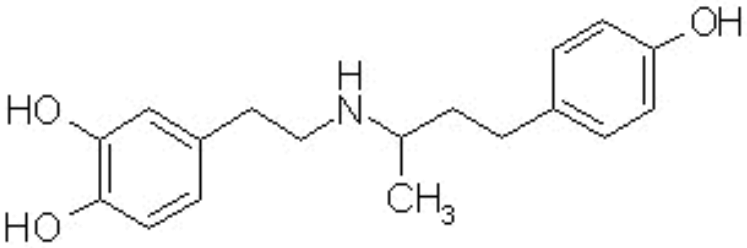
These actions lead to:

a marked increase in cardiac output

a fall in diastolic and mean arterial pressure

slight decrease or increase in systolic pressure.

Beta1-selective agents



Dobutamine

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.

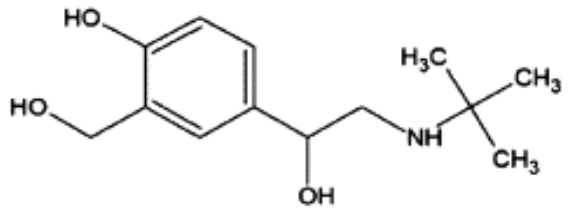
Has a **positive inotropic** action caused by the isomer with predominantly **β1** receptor activity.

It has relatively **greater inotropic than chronotropic** effect compared with isoproterenol.

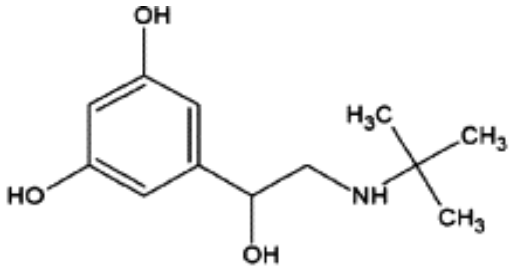
Beta2-selective agents

Salbutamol, terbutaline

Bronchodilators, used in the treatment of asthma.

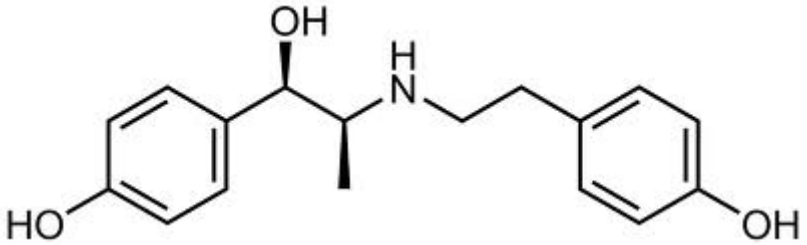


Salbutamol



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, hay fever & the common cold

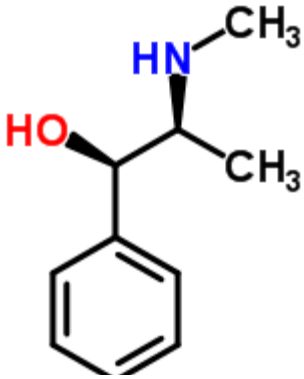
has high bioavailability &

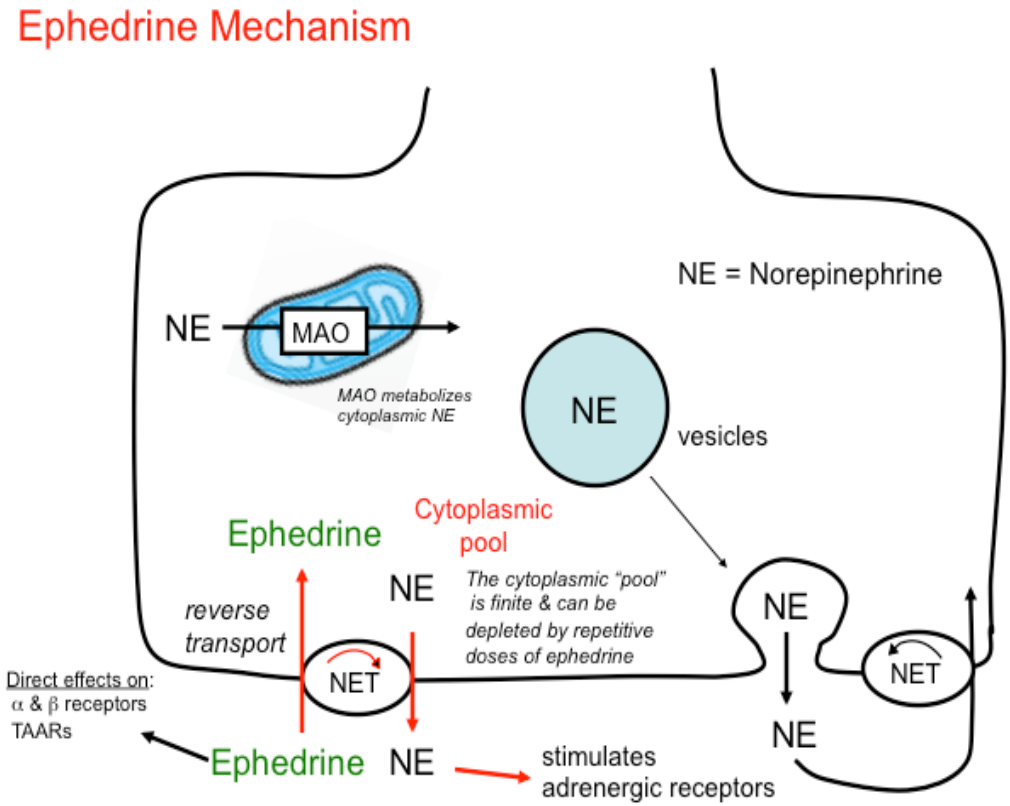
a relatively long duration.

It releases NE & **activates**

β2 receptors directly.

it is a mild stimulant.





Indications: Bronchodilator, Decongestant, **Used as a pressor agent during spinal anesthesia**

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.**

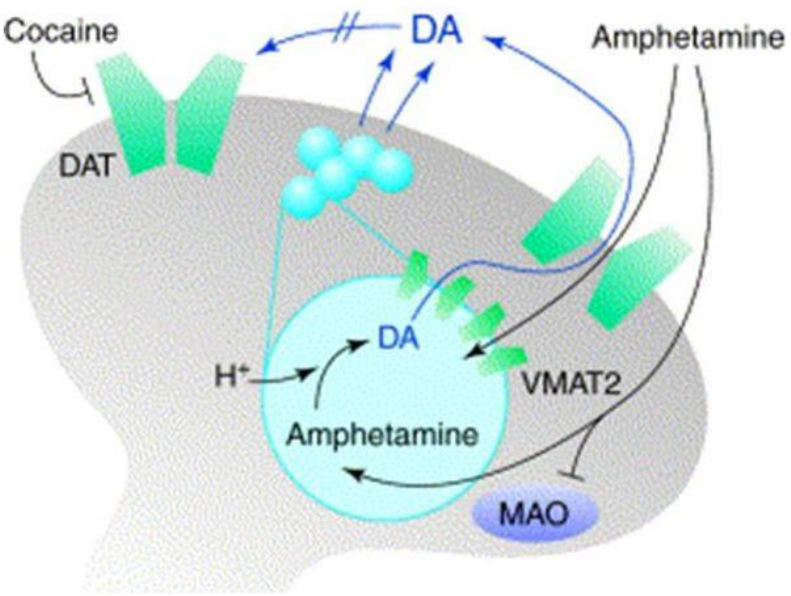
Removed from the market because its use was associated with hemorrhagic strokes in young women.

The mechanism of this potential adverse effect is unknown.

Indirect-Acting Sympathomimetics

Indirect-acting sympathomimetics can have one of two different mechanisms:

- May enter the sympathetic nerve ending and **displace stored catecholamine** transmitter.

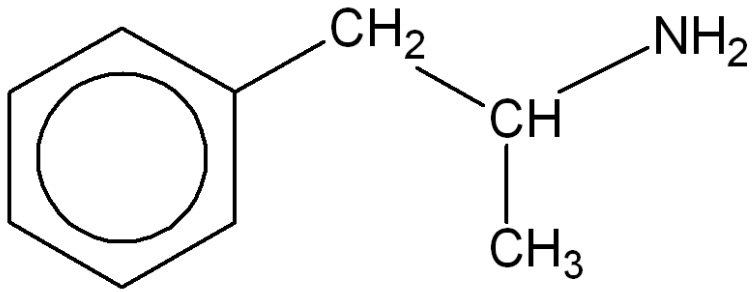


Such drugs have been called **amphetamine-like or "displacers.**

- May **inhibit the reuptake** of released transmitter by interfering with the action of the NE transporter, NET.

Amphetamine-Like

Amphetamine

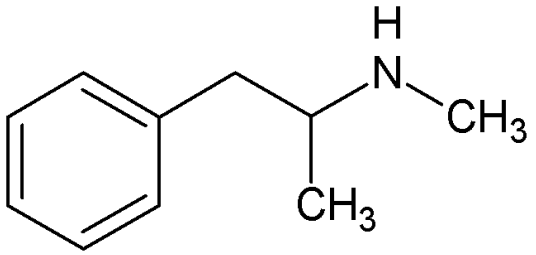


A racemic mixture that is important because of its use and misuse as a **CNS stimulant** .

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 **dopamine.**

Methamphetamine



(*N*- methylamphetamine)

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

Methylphenidate

Its 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 & DA transporters, & 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 mild increases in BP & HR.

Tyramine

Found in ↑ conc. in some fermented foods such as **cheese**.

Metabolized by MAO in GIT & the liver so it is inactive orally.

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 (Cheese reaction).**

Catecholamine Reuptake Inhibitors

Many antidepressants, particularly **tricyclic antidepressants** inhibit **NE** & **serotonin** reuptake 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**

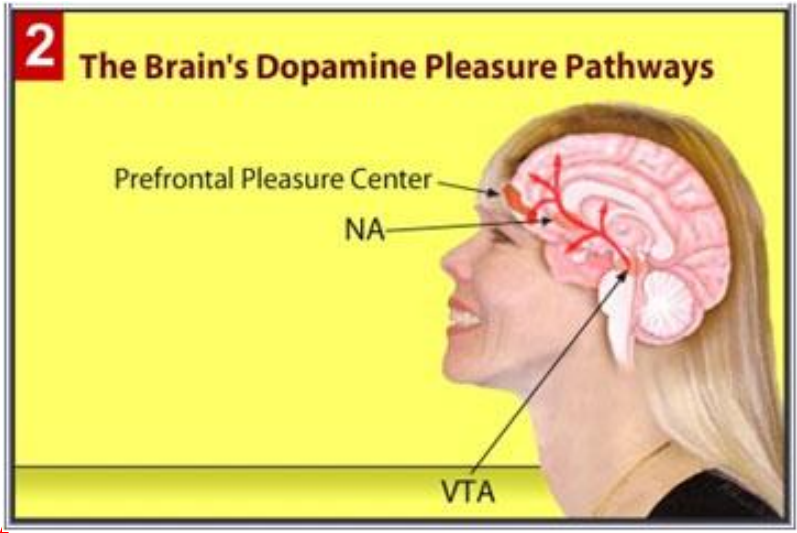
Sibutramine

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

Cocaine

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

Readily enters CNS causing 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**.

it can be smoked, snorted into the nose, or injected.

It is a **heavily abused drug**

- Coca Cola name refers to kola nuts, a source of caffeine, and coca leaves a source of cocaine.
- In 1903 cocaine was removed from coca cola drink.

Dopamine Agonists

Levodopa

Converted to dopamine in the body.

Valuable 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** provide short-term relief of heart failure symptoms in patients with advanced ventricular dysfunction.

In low to moderate doses, these drugs 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.

Other sympathomimetics, such as oral **ephedrine** or **phenylephrine**, can be tried.

Cardiac Applications

Isoproterenol and **epinephrine**

used in the temporary emergency management of complete **heart block and cardiac arrest**.

Inducing Local Vasoconstriction

Epinephrine applied topically for epistaxis or for gingivectomy (removal of diseased gum tissue).

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

Combining α agonists with **local anesthetics** (L.A.) greatly prolongs the duration of local anesthesia & the total dose & reduce toxicity of L.A.

Epinephrine1:200,000, 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 but are usually minimal.

Mucous membrane **decongestants** are **α** agonists.

Rebound congestion may follow their use.

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

β 2-selective agents are used in the therapy of **bronchial asthma**.

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 **antihistamines** may be useful as secondary therapy in anaphylaxis.

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 & itching of the conjunctival membranes.

Glaucoma

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, with fewer side effects than amphetamine is used 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** & related agents or to **clonidine.**

Modafinil may also be useful in ADHD.