Sympathomimetics

2

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.

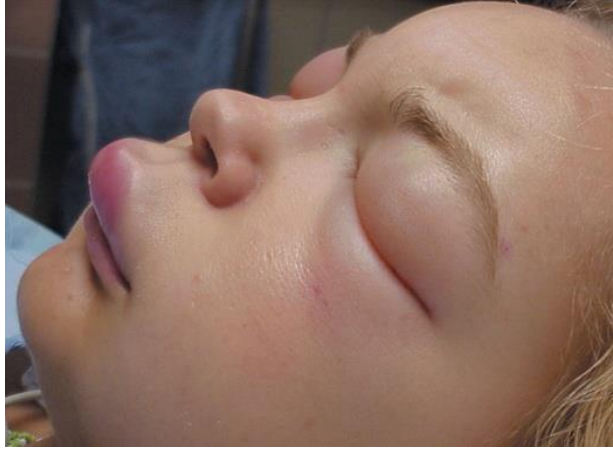
β 2 activate glycogenolysis in the liver

β 3 stimulation → lypolysis → ↑ free fatty acids.

Epinephrine is the primary drug administered during cardiopulmonary resuscitation (CPR) to reverse cardiac arrest.

Epinephrine increases arterial blood pressure and coronary perfusion during CPR via alpha-1-adrenoceptor agonist effects.

Epinephrine1:200,000 with **local anesthetics** (L.A.) greatly prolongs the duration of local anesthesia & the total dose & reduce toxicity of L.A.



Anaphylaxis

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.

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.

NE and direct-acting α agonists are used in a hypotensive emergency to preserve cerebral and coronary blood flow.

The treatment is of short duration while the IV fluid or blood is being administered.

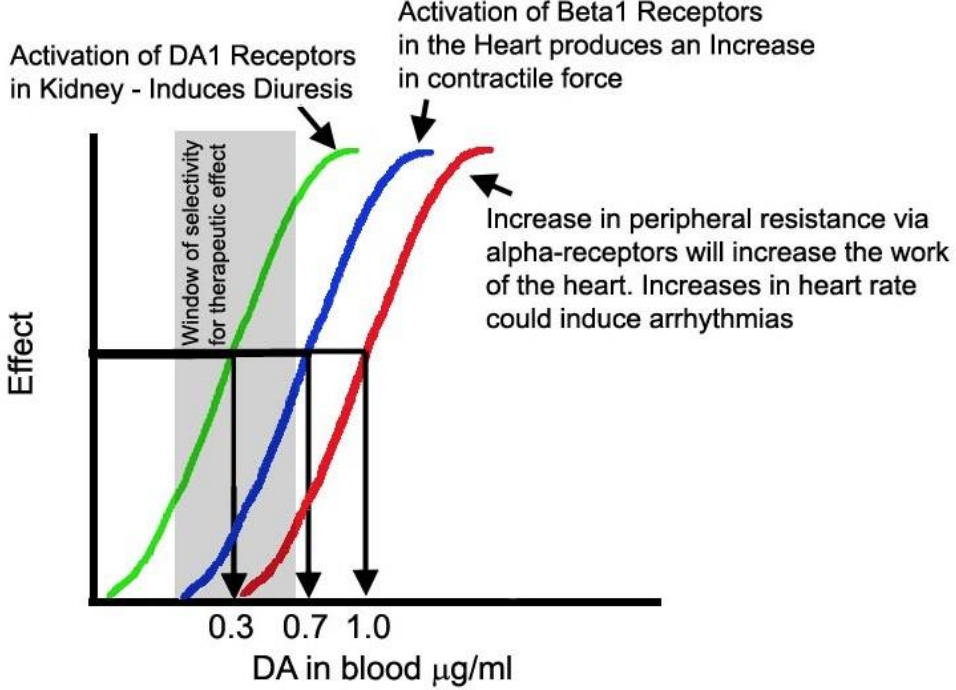
Dopamine

Low dose **D1 & D2** rec.

Medium dose **β** rec.

High dose **α** receptors

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

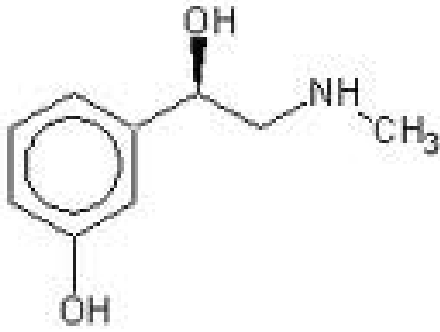


Its deficiency in the basal ganglia leads to **Parkinson's disease**, which is treated with its precursor **levodopa.**

Dopamine antagonists are **antipsychotic drugs**.

Dopamine provides a short-term relief of heart failure symptoms in patients with advanced ventricular dysfunction.

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**.

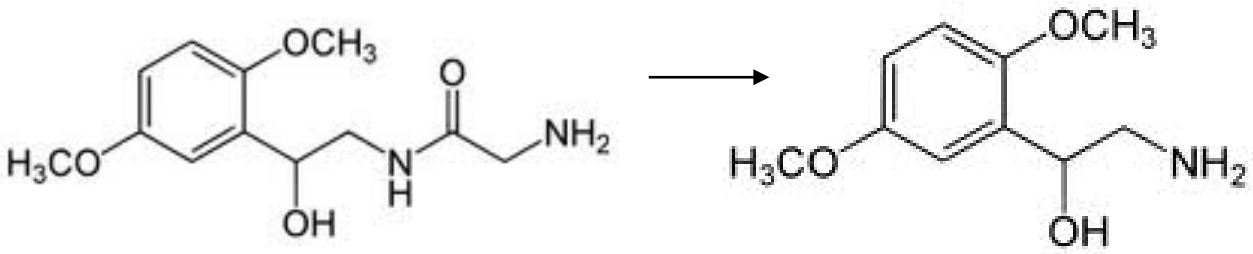
Methoxamine

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 to raise BP.

Midodrine



A **prodrug**, enzymatically hydrolyzed to a selective

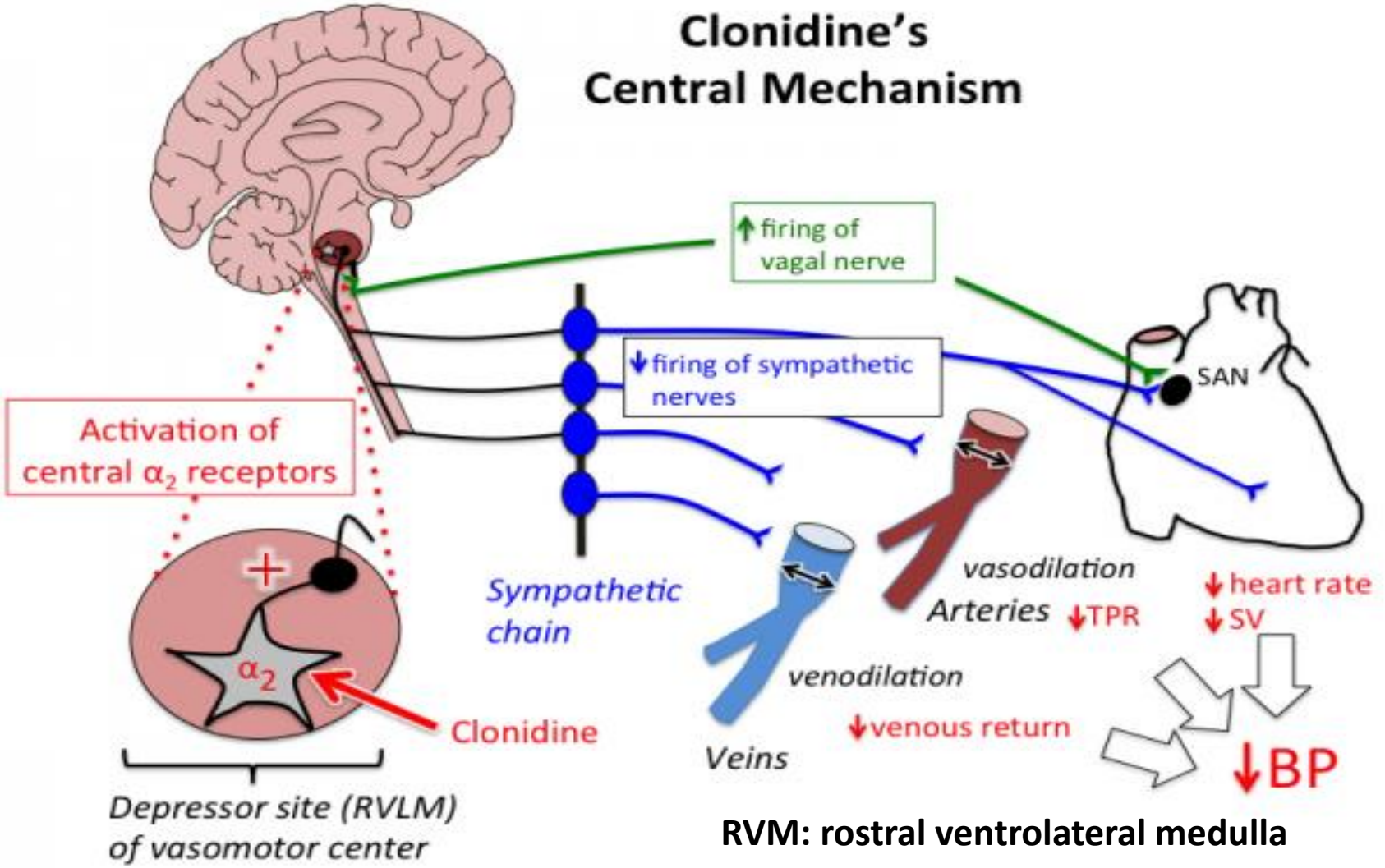
α 1-receptor agonist.

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.



RVM: rostral ventrolateral medulla

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 receptors & cause hypertension by vasoconstriction.

Clonidine 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 are unknown.

Uses:

ADHD (attention deficit hyperactivity disorder) in children, opioid withdrawal, restless legs syndrome, hypertension, alcohol withdrawal

Low dose of Clonidine is used in migraine prophylaxis, menopausal flushing and chorea (abnormal involuntary movement disorder)

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.

Also used in **treatment of attention-deficit/hyperactivity disorder (ADHD)** in children six to 17 years of age.

May help manage behavioral symptoms, such as aggression and self-injurious behavior, associated with **Prader-Willi syndrome (PWS)** caused by **a** genetic change on chromosome number 15.

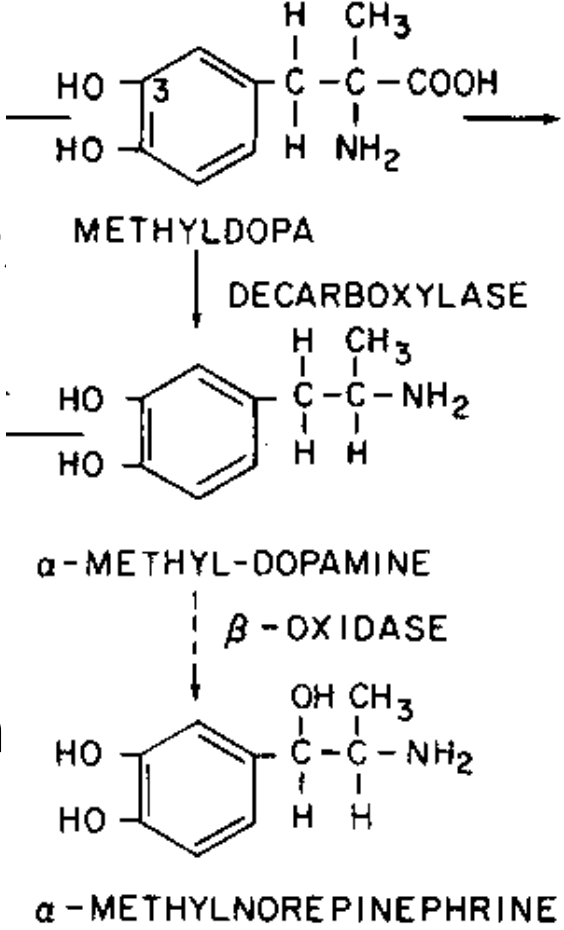
Dexmedetomidine

A centrally acting α 2-selective agonist used 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.

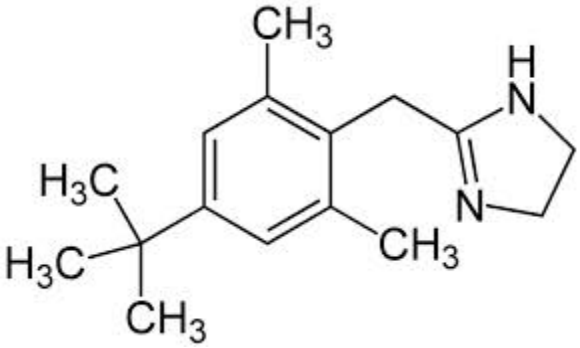
Methyldopa

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

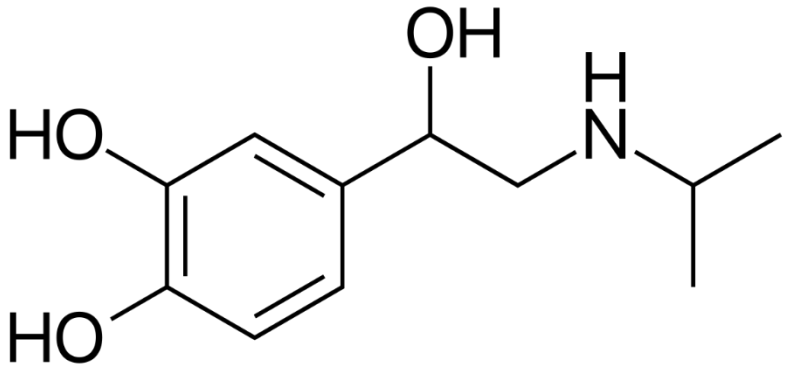


Direct-acting **α1 agonist** with significant affinity for **α 2A** receptors.

Used as **topical decongestant** because of promoting constriction of the nasal mucosa.

When taken in large doses, oxymetazoline may cause **hypotension**, because of a **central clonidine -like effect.**

Isoproterenol (isoprenaline)



Very potent **β** -receptor agonist and has little effect on **α** receptors.

Has **positive chronotropic & inotropic actions (β1).**

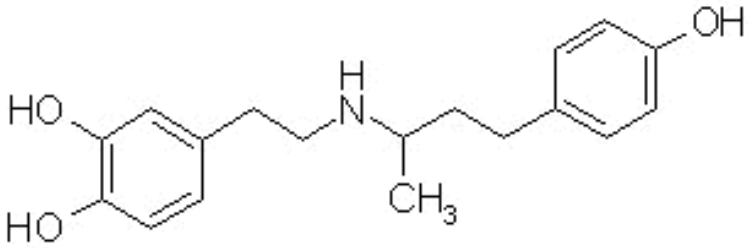
it is a potent vasodilator (**β 2**).

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.

Isoproterenol is used in the temporary emergency management of complete **heart block**

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.

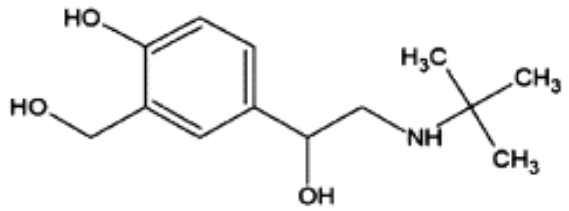
Has relatively **greater inotropic than chronotropic** effect compared with isoproterenol.

Used to provide a short-term relief of heart failure symptoms

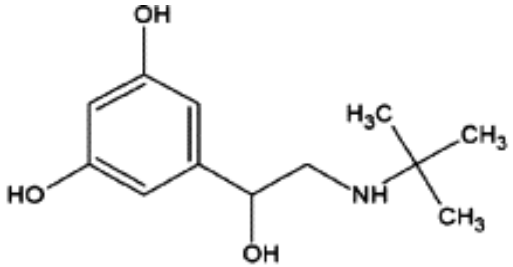
Beta2-selective agents

Salbutamol, terbutaline

Bronchodilators, used in the treatment of asthma.

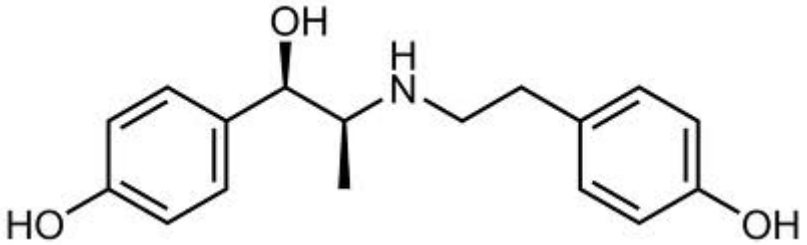


Salbutamol



Terbutaline

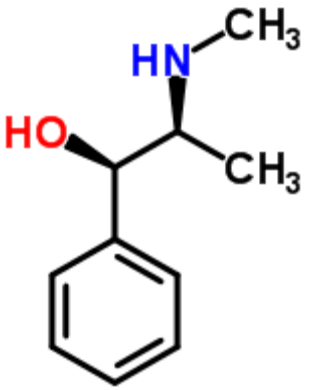
Ritodrine



Used to achieve uterine relaxation in premature labor.

Mixed-Acting Sympathomimetics

Ephedrine

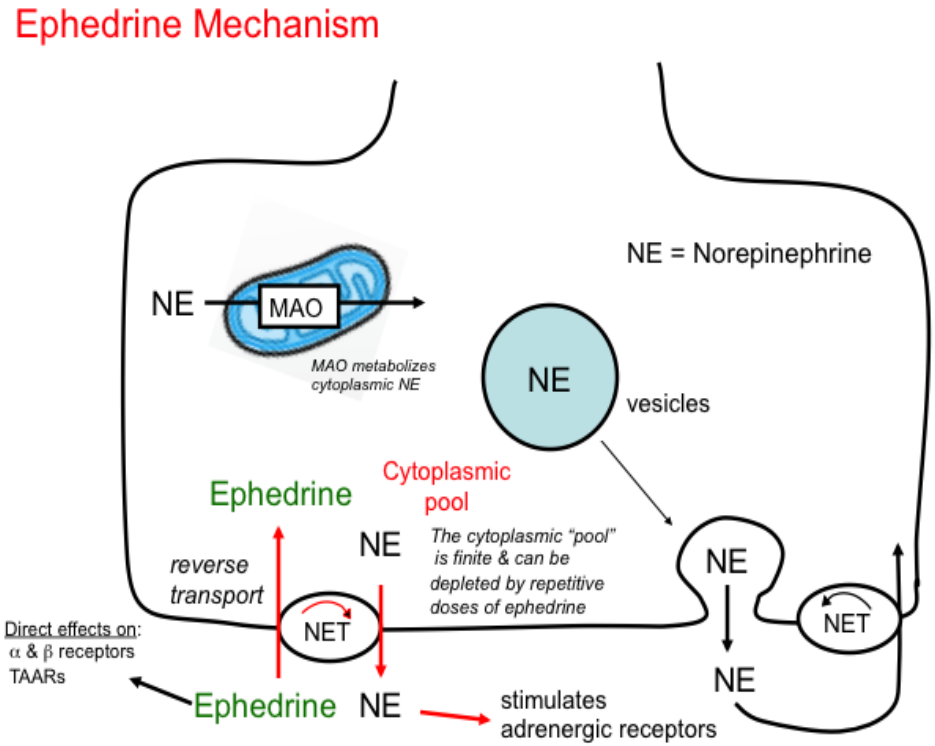


The plant Ephedra sinica, has been used in traditional Chinese medicine for 5,000 years for the treatment of asthma, hay fever & the common cold

has high bioavailability & a relatively long duration.

It releases NE & **activates β2** receptors directly.

it is a mild CNS stimulant.



Indications:

Bronchodilator, decongestant and also used as a pressor agent during spinal anesthesia

Oral **ephedrine** or **pseudoephedrine** are 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).

Pseudoephedrine

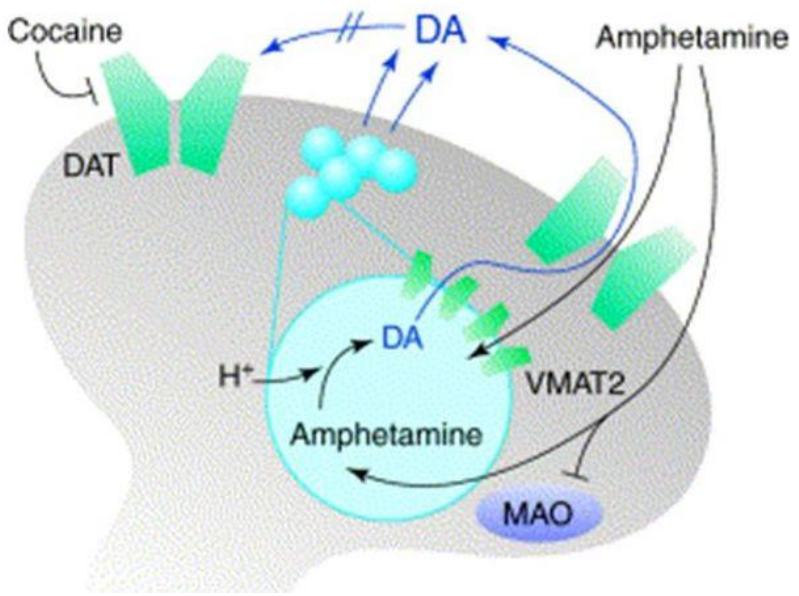
One of four ephedrine enantiomers.

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

Indirect-Acting Sympathomimetics

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

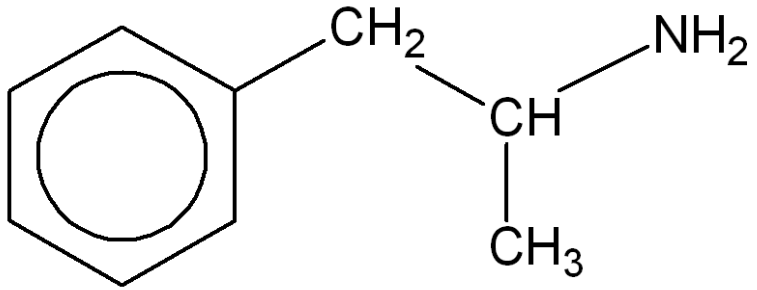
- May enter the sympathetic nerve ending and **displace stored catecholamine** transmitter.



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

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

Amphetamine-Like Amphetamine

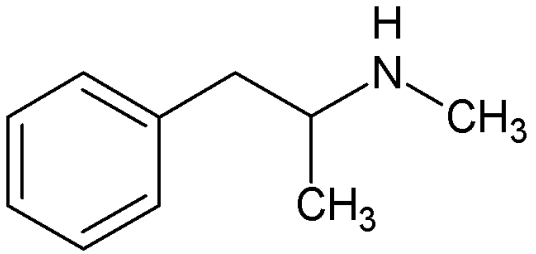


A racemic mixture that is important because of its use and misuse as a **CNS stimulant** .

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-isomer**. 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.

Modafinil may also be useful in ADHD.

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 **attention deficit hyperactivity disorder**.

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.

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

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**