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.

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

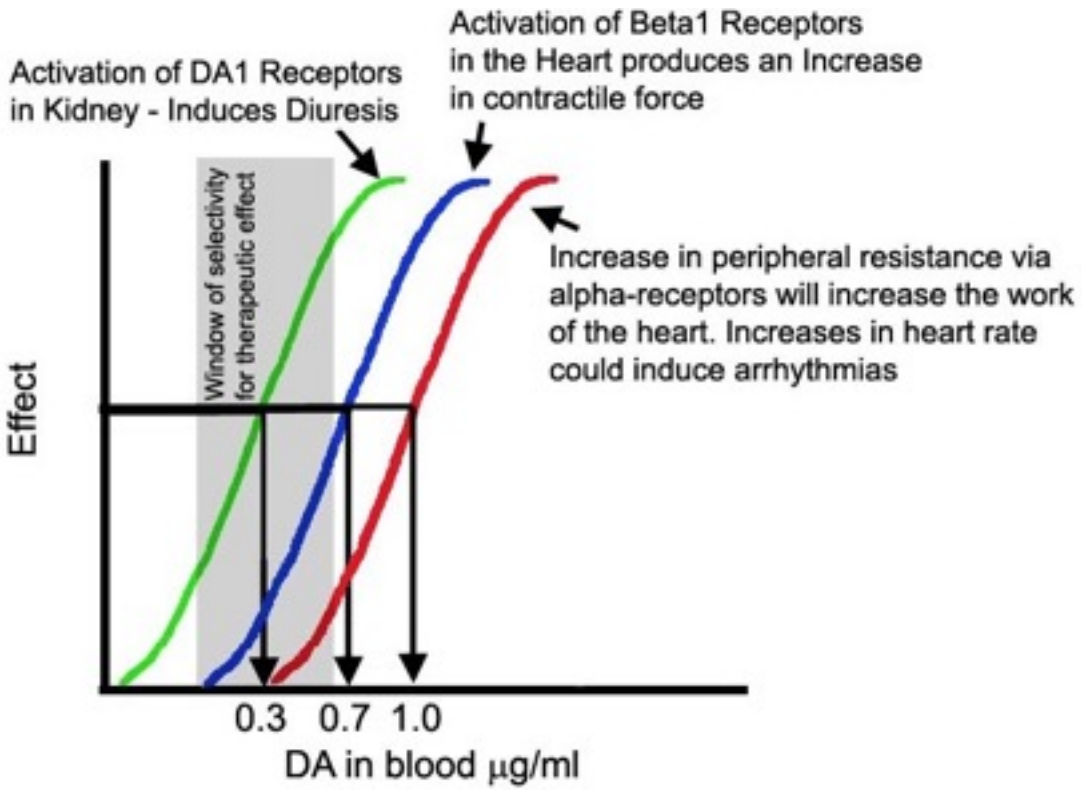
immediate precursor in the synthesis of NE

Stimulates :

Low dose **D1 & D2** rec.

Medium dose **β** rec.

High dose **α** receptors

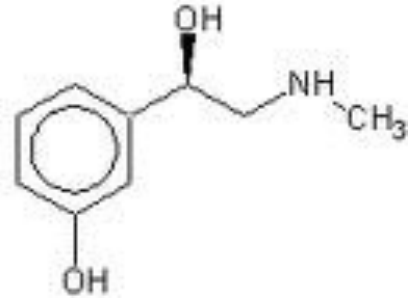


Endogenous DA regulates **sodium excretion** and renal function.

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

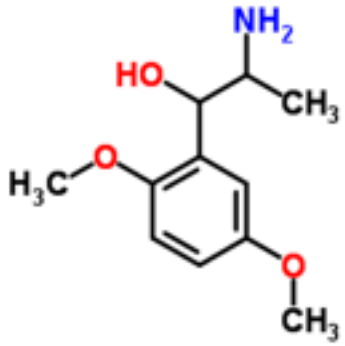


Phenylephrine

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**.



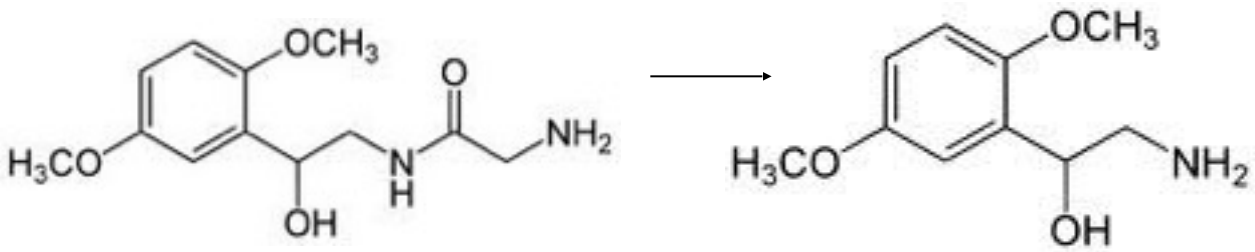
Methoxamine

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



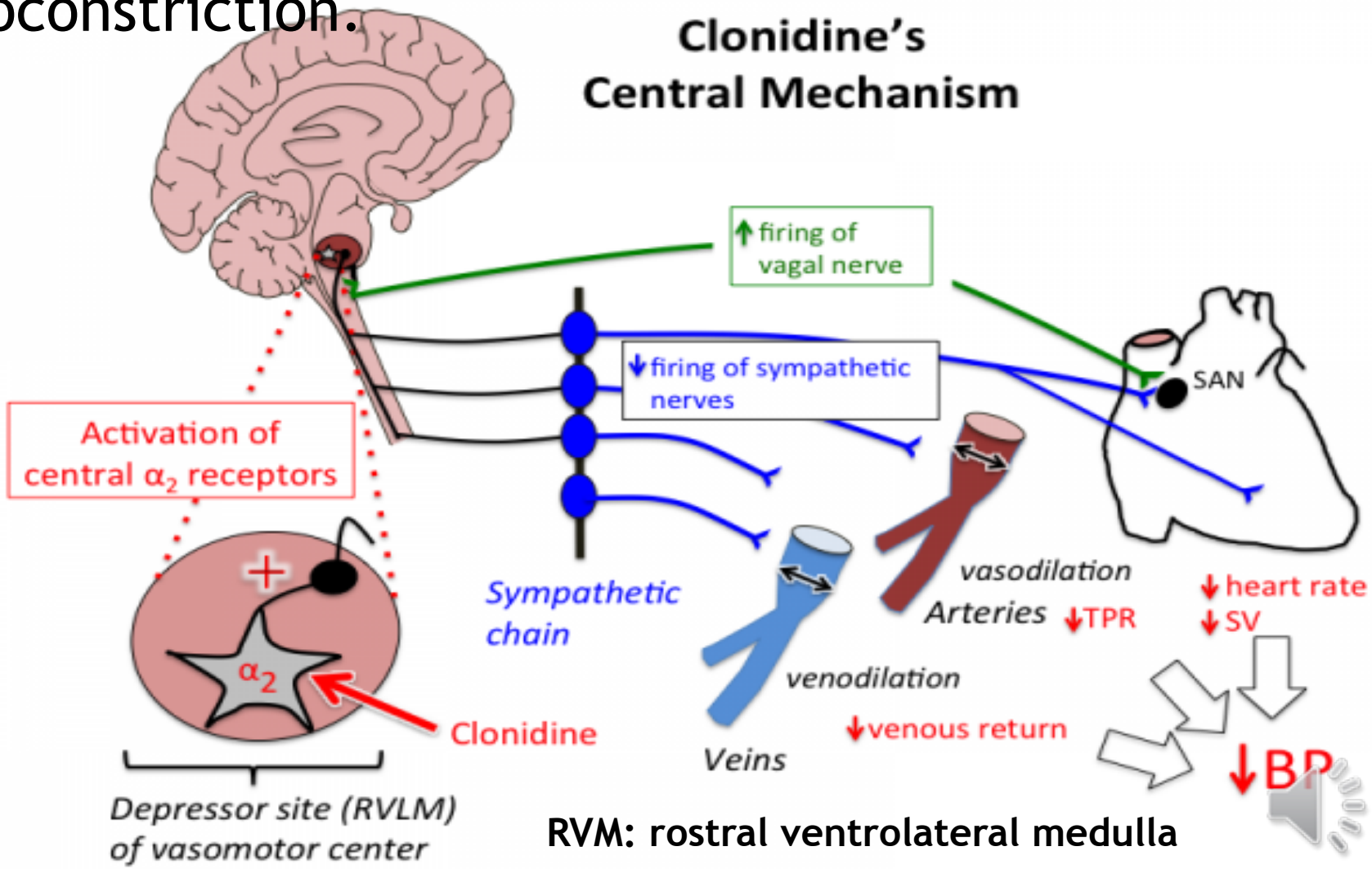
A **prodrug**, enzymatically hydrolyzed to a selective **α 1-receptor** agonist.

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 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 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

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.

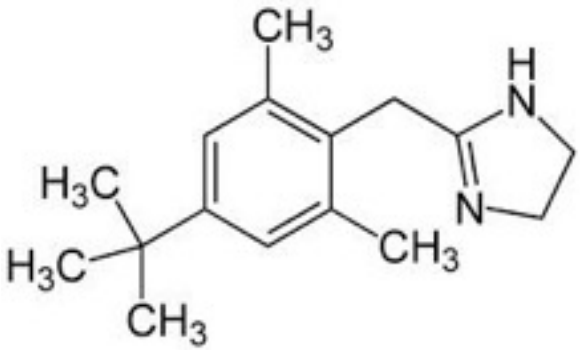
It also reduces the requirements for opioids in pain control.

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

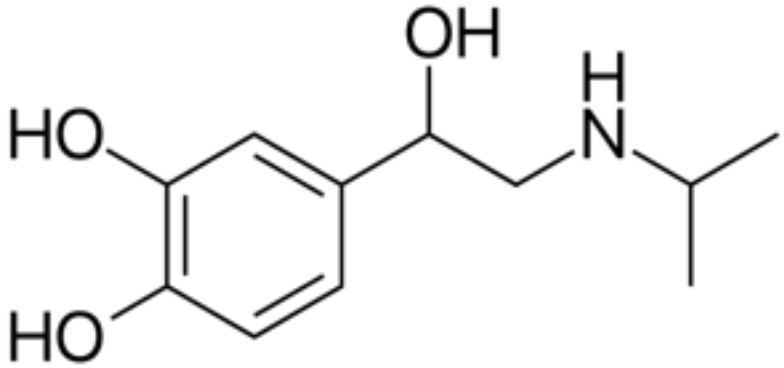


Direct-acting **α1 agonist** with significant affinity for **α 2A** receptors.

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 and inotropic actions (β1).**

it is a potent vasodilator (**β 2**).

These actions lead to:

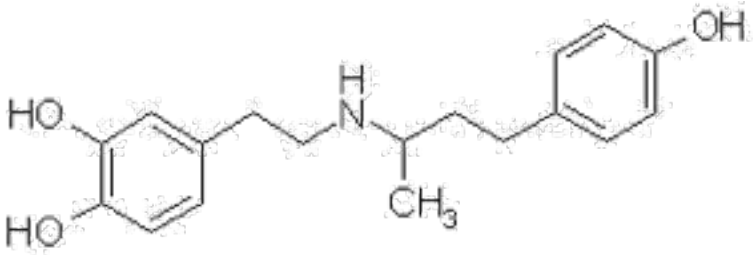
a marked increase in cardiac output

a fall in diastolic and mean arterial pressure

slight decrease or increase in systolic pressure.

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.

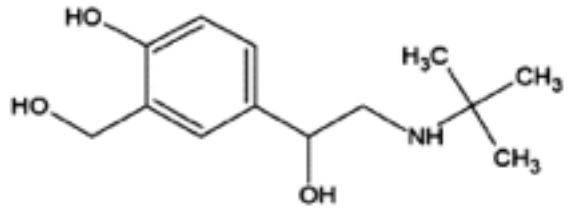
Has a **positive inotropic** action caused by the isomer with predominantly **β1** receptor activity.

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

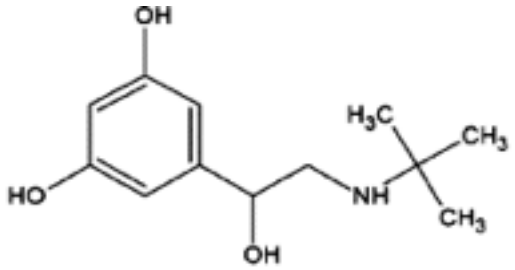
Beta2-selective agents

Salbutamol, terbutaline

Bronchodilators, used in the treatment of asthma.

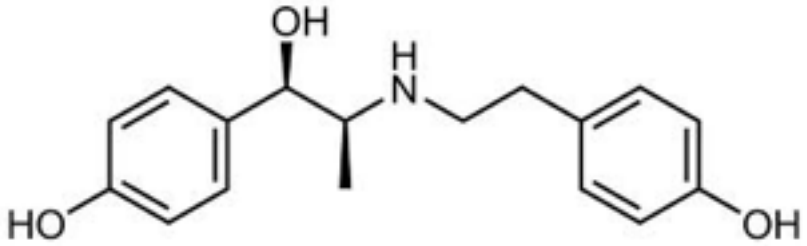


Salbutamol



Terbutaline

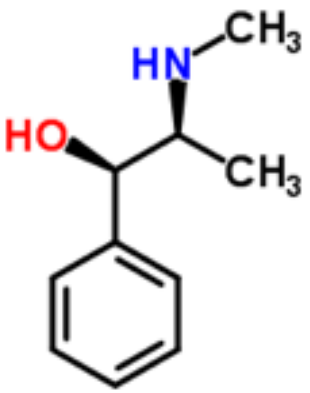
Ritodrine



Used to achieve uterine relaxation in premature labor.

Mixed-Acting Sympathomimetics

Ephedrine

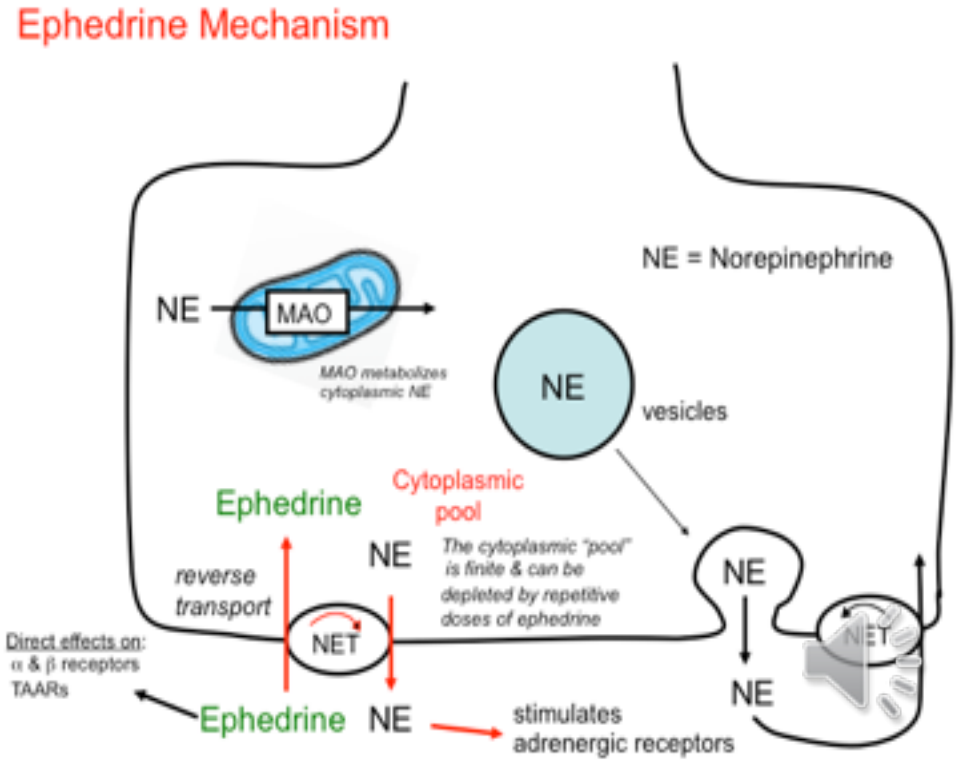


The plant Ephedra sinica, has been used in traditional Chinese medicine for 5,000 years for the treatment of asthma, hay fever & the common cold

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

Pseudoephedrine

One of four ephedrine enantiomers.

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