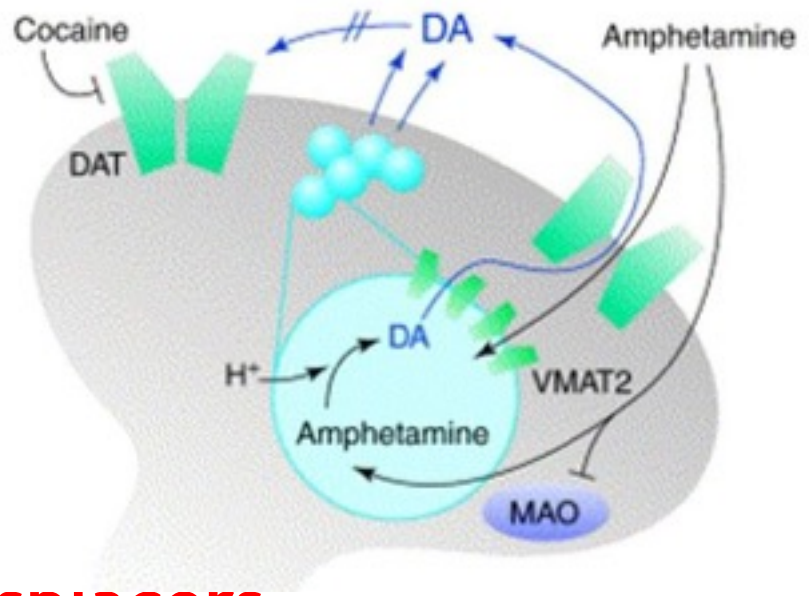
Sympathomimetics 3

Indirect-Acting Sympathomimetics

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

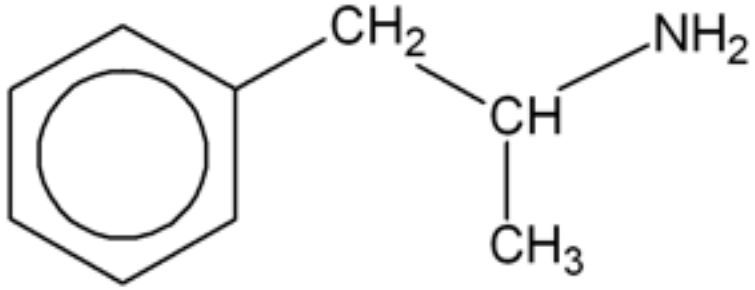
- May enter the sympathetic nerve ending and **displace stored catecholamine** transmitter.



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

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

Amphetamine-Like Amphetamine

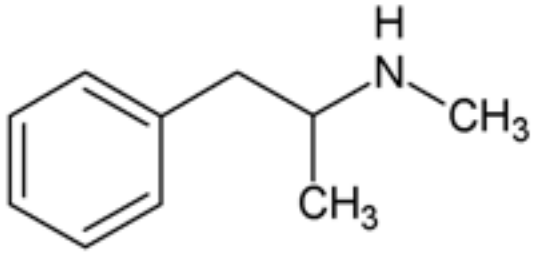


A racemic mixture that is important because of its use and misuse as a **CNS stimulant** .

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 w

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**

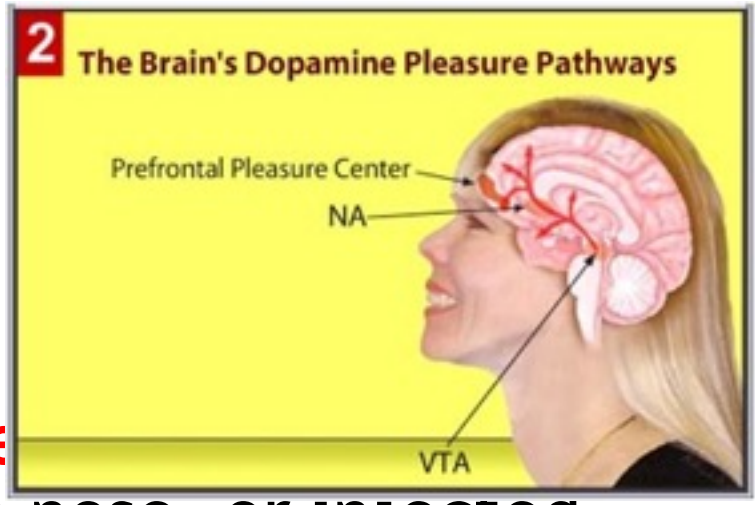
Sibutramine

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 cente**

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

NE, phenylephrine, and **methoxamine**

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

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

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.

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Cardiac Applications

E 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.

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

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 1** 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

ß 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 ß 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.**

angioedema

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 ß -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.