Adrenoceptor Agonists & Sympathomimetic Drugs
## Relative Receptor Affinities

### Alpha agonists

| Phenylephrine, methoxamine | $\alpha_1 > \alpha_2 >>>>> \beta$ |
| Clonidine, methylnorepinephrine | $\alpha_2 > \alpha_1 >>>>> \beta$ |

### Mixed alpha and beta agonists

| Norepinephrine | $\alpha_1 = \alpha_2; \; \beta_1 >> \beta_2$ |
| Epinephrine | $\alpha_1 = \alpha_2; \; \beta_1 = \beta_2$ |

### Beta agonists

| Dobutamine | $\beta_1 > \beta_2 >>>\alpha$ |
| Isoproterenol | $\beta_1 = \beta_2 >>>\alpha$ |

| Albuterol (Salbutamol), terbutaline, ritodrine | $\beta_2 >> \beta_1 >>>\alpha$ |
Medicinal Chemistry of Sympathomimetic Drugs

Phenylephrine

Methoxamine

Ephedrine

Amphetamine

Catechol

Phenylethylamine

Norepinephrine

Epinephrine

Isoproterenol

Dopamine

None catecholamines

catecholamines

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Organ System Effects of Sympathomimetics.

Cardiovascular System.

- The net effect of a Sympathomimetic drug depends on:
  - its relative selectivity for $\alpha$ or $\beta$ adrenoceptors
  - and the compensatory baroreflex mechanisms aimed at restoring homeostasis.
• Effects of Alpha1-Receptor Activation
• A pure $\alpha$ agonist such as phenylephrine causes arterial and venoconstriction, increases peripheral arterial resistance and decreases venous capacitance.
• The enhanced 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, however, is observed only when $\alpha_2$ 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 $\alpha_2$ receptors, which lead to inhibition of sympathetic tone and a decrease in BP.
• Hence, $\alpha_2$ agonists are used in the treatment of hypertension.
• Effects of Beta-Receptor Activation

• Stimulation of $\beta$ receptors in the heart increases cardiac output by stimulating contractility and by increasing the heart rate.

• Beta agonists also decrease peripheral resistance by activating $\beta_2$ receptors, leading to vasodilation in certain vascular beds.

• Isoproterenol activates both $\beta_1$ and $\beta_2$ 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 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
• IV administration 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 may also induce natriuresis.
• The renal effects of dopamine have been used clinically to improve perfusion to the kidney in situations of oliguria (abnormally low urinary output).
• Dopamine activates $\beta_1$ receptors in the heart.
• At low doses, peripheral resistance may decrease.
• At higher rates of infusion, dopamine activates vascular $\alpha$ receptors, leading to vasoconstriction, including in the renal vascular bed (alpha receptor).
• Consequently, high rates of infusion of dopamine may mimic the actions of epinephrine.
Noncardiac Effects of Sympathomimetics

- Activation of $\beta_2$ receptors in bronchial smooth muscle leads to bronchodilation, and $\beta_2$ agonists are important in the treatment of asthma.
- In the eye, $\alpha$ 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 \( \alpha_1 \) receptor involved in mediating constriction of the bladder base and prostate is uncertain, but \( \alpha_1A \) 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 $\beta$ receptors and inhibited by $\alpha_2$ receptors.

• Renin secretion is stimulated by $\beta_1$ and inhibited by $\alpha_2$ 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 with indirect actions, such as **amphetamines**, which readily enter the CNS 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 or other effects of these drugs in the CNS.
Metabolism.
Activation of $\beta_3$ receptors in fat cells increases lipolysis with enhanced release of free fatty acids and glycerol into the blood.
Activation of $\beta$ receptors enhance glycogenolysis in the liver, increasing glucose release into the blood.
Activation of $\beta_2$ 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, $\beta$ receptors increase and $\alpha_2$ 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 $\alpha$ and $\beta$ receptors.
  • Very potent vasoconstrictor and cardiac stimulant.
  • Causes a rise in systolic BP by its positive inotropic and chronotropic actions on the heart ($\beta_1$) and the vasoconstriction induced in many vascular beds ($\alpha$).
  • Epinephrine also activates $\beta_2$ receptors in skeletal muscle blood vessels, leading to their dilation. Consequently, total peripheral resistance may fall.
  • Activation of $\beta_2$ receptors in skeletal muscle contributes to increased blood flow during exercise.
• **Norepinephrine** (noradrenaline)

  • Agonist at $\alpha_1$, $\alpha_2$ and $\beta_1$ receptors with similar potency as epinephrine, but has relatively little effect on $\beta_2$ 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; however, 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.
• **Direct-Acting Sympathomimetics**

• **Phenylephrine**
  - A relatively pure α₁ agonist.
  - Not a catechol derivative, it is not inactivated by COMT and has a longer duration of action than the catecholamines.
  - It is an effective **mydriatic** and **decongestant** and can be used to raise the blood pressure.

• **Methoxamine**
  - A direct-acting α₁ 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 α1-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.
• Clonidine, methyldopa, guanfacine are useful in the treatment of hypertension
• Dexmedetomidine is a centrally acting α2-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 $\alpha$ 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 $\alpha\,2A$ receptors.
• **Isoproterenol (isoprenaline)**
• Very potent $\beta$-receptor agonist and has little effect on $\alpha$ receptors.
• Has **positive chronotropic and inotropic actions**.
• Activates $\beta$ 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 $\alpha$ and $\beta$ receptors.
  - Dobutamine is a racemic mixture of (−) and (+) isomers.
  - The (+) isomer is a potent $\beta_1$ agonist and an $\alpha_1$ receptor antagonist.
  - The (−) isomer is a potent $\alpha_1$ agonist
  - The resultant effects of dobutamine is $\beta_1$ stimulation.
  - Dobutamine has a positive inotropic action caused by the isomer with predominantly $\beta_1$ receptor activity. It has relatively greater inotropic than chronotropic effect compared with isoproterenol.
• Beta2-selective agents
• Salbutamol, terbutaline
  Important in the treatment of asthma.

• 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.
• **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-isomer**. Amphetamine's actions are mediated through the release of **NE** and, to some extent, **dopamine**.
• **Methamphetamine**

(\(N\)-methylamphetamines)

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 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 α₁ 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.

β₂-selective agents:
Albuterol (Salbutamol), metaproterenol, terbutaline all are available for this indication.

Sympathomimetics other than the β₂-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- $\beta_1$ increases cardiac output.
  2- $\beta_2$ relaxes constricted bronchioles.
  3- $\alpha_1$ constricts capillaries.
• **Glucocorticoids** and **antihistamines** 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.