ADRENOCEPTOR AGONISTS & SYMPATHOMIMETIC DRUGS
OVERVIEW

- The sympathetic nervous system is an important regulator of virtually all organ systems.

- The ultimate **effects of sympathetic stimulation** are mediated by:
  - release of **norepinephrine** from **nerve terminals**, which then activates **adrenoceptors** *(pre- or post-synaptically)*.

- Also, in **response to a variety of stimuli** such as **stress**, the **adrenal medulla** releases **epinephrine**, which is transported in the blood to target tissues.......**HORMONE**

- **CATECHOLAMINES.....RECEPTORS**
sympathomimetic amines that contain 3,4-dihydroxybenzene group (such as: epinephrine, norepinephrine, isoproterenol, and dopamine) are called catecholamines.

Drugs that mimic the actions of epinephrine or norepinephrine have traditionally been termed sympathomimetic drugs.
There are two main groups of adrenergic receptors, α and β, with several subtypes.

These were initially identified on the basis of their responses to the adrenergic agonists: epinephrine, norepinephrine, and isoproterenol.

All the adrenoceptors are G-protein coupled receptors (GPCRs)....G?????
Epinephrine
Norepinephrine
Isoprotenol

α Adrenoceptors

Epinephrine
Norepinephrine
Isoprotenol

β Adrenoceptors

Isoprotenol
Epinephrine
Norepinephrine

High affinity
Low affinity
The development of selective antagonists revealed the presence of subtypes of these receptors, which were finally characterized by molecular cloning. These proteins/receptors belong to a multigene family.

**Adrenergic Receptors**

- $\alpha$
  - $\alpha_1$
    - $\alpha_{1A}$
    - $\alpha_{1B}$
    - $\alpha_{1D}$
  - $\alpha_2$
    - $\alpha_{2A}$
    - $\alpha_{2B}$
    - $\alpha_{2C}$

- $\beta$
  - $\beta_1$
  - $\beta_2$
  - $\beta_3$

Necessary for understanding the selectivity of some drugs. *Tamsulosin* (selective $\alpha_{1A}$ antagonist), benign prostate hyperplasia, (urinary tract and prostate gland)
<table>
<thead>
<tr>
<th>Receptor</th>
<th>Agonist</th>
<th>Antagonist</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha_1$ type ($\alpha_{1A}, \alpha_{1B}, \alpha_{1D}$)</td>
<td>Phenylephrine</td>
<td>Prazosin</td>
<td>↑ IP3, DAG common to all</td>
</tr>
<tr>
<td>$\alpha_2$ type ($\alpha_{2A}, \alpha_{2B}, \alpha_{2C}$)</td>
<td>Clonidine</td>
<td>Yohimbine</td>
<td>↓ cAMP common to all</td>
</tr>
<tr>
<td>$\beta$ type ($\beta_1, \beta_2, \beta_3$)</td>
<td>Isoproterenol</td>
<td>Propranolol</td>
<td>↑ cAMP common to all</td>
</tr>
<tr>
<td>Dopamine type</td>
<td>Dopamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D1-like ($D_1, D_5$)</td>
<td></td>
<td></td>
<td>↑ cAMP</td>
</tr>
<tr>
<td>D2-like ($D_2, D_3, D_4$)</td>
<td></td>
<td></td>
<td>↓ cAMP</td>
</tr>
</tbody>
</table>
ADRENERGIC RECEPTORS (ADRENOCEPTORS)

**ALPHA RECEPTORS**

- The $\alpha_1$ receptors have a higher affinity for phenylephrine than do the $\alpha_2$ receptors.

- Conversely, clonidine is more selective to $\alpha_2$ receptors (has less effect on $\alpha_1$ receptors)

- Both epinephrine and norepinephrine have similar affinity for $\alpha$ and $\beta$ receptors
SELECTIVITY

Selectivity?? A drug may preferentially bind to one subgroup of receptors at concentration too low to interact extensively with other subgroup! (e.g., important in β receptors)

Selectivity not absolute...
- higher concentration, the drug interacts with other subgroups!! >>>>>>>>(drug are not specific!)

The effect depends also on the
- expression of the subtype on a given tissue

The function of specific subtype receptor is known through development of “knockout mice”
Adrenergic Receptors (Adrenoceptors)

**Alpha Receptors**

I. $\alpha_1$ Adrenoceptors:
- These receptors are **present on the postsynaptic membrane** of the effector organs and mediate many of the classic involving **contraction of smooth muscle**
- $\alpha_1$ receptors are **coupled** via $G_q$ proteins to **phospholipase C**.
- Activation of $\alpha_1$ receptors result in the generation of inositol-1,4,5-trisphosphate (IP$_3$) and diacylglycerol (DAG) from phosphatidylinositol. **IP$_3$ initiates the release of Ca$^{2+}$ from the endoplasmic reticulum** into the cytosol and the activation of various calcium-dependent protein kinases.
- Activation of these receptors may **also increase influx** of calcium across the **cell's plasma membrane**.
- **DAG activates protein kinase C**, which modulates activity of many signaling pathways.
II. $\alpha_2$ Adrenoceptors:

- These receptors, located primarily on presynaptic nerve endings and on other cells, such as the β cell of the pancreas, and on certain vascular smooth muscle cells, control adrenergic neuromediator and insulin output, respectively.

- $\alpha_2$ receptors are coupled via $G_i$ protein to adenylyl cyclase.
  - $\alpha_2$ receptors inhibit adenylyl cyclase activity and cause intracellular cyclic adenosine monophosphate (cAMP) levels to decrease.
Feedback control of noradrenaline release
**BETA RECEPTORS**

- $\beta_1$ Receptors have approximately **equal affinities** for epinephrine and norepinephrine,

- whereas $\beta_2$ receptors have a **higher affinity** for epinephrine than for norepinephrine.
  - Thus, tissues with a **predominance of $\beta_2$** receptors (such as the **vasculature of skeletal muscle**) are particularly **responsive** to the hormonal effects of circulating **epinephrine** released by the adrenal medulla

- $\beta_3$ Receptors may **mediate responses** to **catecholamine** at sites with "atypical" pharmacological characteristics (e.g., **adipose tissue**)

All the β-adrenoceptors (β₁, β₂, β₃) are coupled via G proteins to the Gₛ family to adenyl cyclase.

...stimulation of adenyl cyclase and increased cAMP!
BETA RECEPTORS

cAMP is the major second messenger of β-receptor activation!

For example:
❖ **In the heart,**
  ❖ increases the influx of calcium across the cell membrane and its sequestration inside the cell

❖ cAMP also promotes the relaxation of smooth muscle
  ❖ (uncertain mechanism....may involve the phosphorylation of myosin light-chain kinase to an inactive form) (see Figure 12–1)

❖ **In the liver,** β-receptor-activated cAMP synthesis leads to activation of glycogen phosphorylase
Remember interplay between signaling mechanism???
Ex. Non-selective adrenergic agent ($\alpha$ and $\beta$ receptors)
The endogenous catecholamine “dopamine” is imp. In
- brain and
- in the splanchnic and renal vasculature
- (5 receptor subtypes)

The $D_1$-like receptor is typically associated with the
- stimulation of adenylyl cyclase (for example, $D_1$-receptor-induced smooth muscle relaxation is presumably due to cAMP accumulation in the smooth muscle of those vascular beds in which dopamine is a vasodilator)

$D_2$-like receptors have been found to:
- inhibit adenylyl cyclase activity,
- open potassium channels,
- and decrease calcium influx
Responses mediated by adrenoceptors are \textbf{not fixed and static}.

\textbf{Prolonged exposure} to the \textit{catecholamines}

- reduces the tissue response to further stimulation by that agent.

This process has potential clinical significance because it may \textbf{limit the therapeutic response} to sympathomimetic agents.
Two major categories of desensitization of responses mediated by G protein-coupled receptors:

- **Homologous desensitization:**
  - refers to **loss of responsiveness exclusively** of the receptors that have been **exposed to repeated or sustained** activation by an **agonist**:

- **Inability to couple to G protein,**
  - because the receptor has been **phosphorylated** on the cytoplasmic side by G protein-coupled receptor kinase (GRK) family
FIGURE 2–12 Rapid desensitization, resensitization, and down-regulation of β-adrenoceptors. 

A: Response to a β-adrenoceptor agonist (ordinate) versus time (abscissa). (Numbers refer to the phases of receptor function in B.) Exposure of cells to agonist (indicated by the light-colored bar) produces a cyclic AMP response. A reduced cAMP response is observed in the continued presence of agonist; this "desensitization" typically occurs within a few minutes. If agonist is removed after a short time (typically several to tens of minutes, indicated by broken line on abscissa), cells recover full responsiveness to a subsequent addition of agonist (second light-colored bar). This "resensitization" fails to occur, or occurs incompletely, if cells are exposed to agonist repeatedly or over a more prolonged time period. 

B: Agonist binding to receptors initiates signaling by promoting receptor interaction with G proteins (G_i) located in the cytoplasm (step 1 in the diagram). Agonist-activated receptors are phosphorylated by a G protein-coupled receptor kinase (GRK), preventing receptor interaction with G_i and promoting binding of a different protein, β-arrestin (β-Arr), to the receptor (step 2). The receptor-arrestin complex binds to coated pits, promoting receptor internalization (step 3). Dissociation of agonist from internalized receptors reduces β-Arr binding affinity, allowing dephosphorylation of receptors by a phosphatase (P'ase, step 4) and return of receptors to the plasma membrane (step 5); together, these events result in the efficient resensitization of cellular responsiveness. Repeated or prolonged exposure of cells to agonist favors the delivery of internalized receptors to lysosomes (step 6), promoting receptor down-regulation rather than resensitization.
Heterologous desensitization:
- refers to the process by which desensitization of one receptor by its agonists
  - also results in desensitization of another receptor that has not been directly activated by the agonist in question

This can be mediated by second-messenger feedback mechanism:
- For example, $\beta_1$-adrenoceptors stimulate cAMP accumulation, which leads to activation of protein kinase A;
  - which can phosphorylate serine residues of intracellular tail of $\beta_2$ receptors, resulting in inhibition of this receptor function
Sympathomimetic drugs

- Sympathomimetic drugs are classified as:
  
  I. **Direct acting sympathomimetics**: act directly on one or more of the adrenergic receptors

  II. **Indirect acting sympathomimetics**: increase the availability of norepinephrine or epinephrine to stimulate adrenergic receptors

  1) **Displacement of stored catecholamines** from the adrenergic nerve ending (e.g. tyramine & amphetamine) *(amphetamine-like or ‘displacers’)*

  2) **Inhibition of reuptake** of catecholamines already released (e.g. cocaine & tricyclic antidepressants)

  3) **Blocking the metabolizing enzymes**, monoamine oxidase (MAO) *(e.g., pargyline)* or catechol-O-methyltransferase (COMT) *(e.g., entacapone)*
Tyramine "cheese effect"
**III. Mixed acting sympathomimetics:**
- *indirectly induce* the *release* of norepinephrine from the presynaptic terminal
- *and directly activate* receptors
- *(e.g. Ephedrine)*
SYMPATHOMIMETIC DRUGS (CONT’D)

N.B:
The pharmacologic effects of direct agonists depend on:
- the route of administration,
- their relative affinity for adrenoreceptor subtypes,
- and the relative expression of these receptor subtypes in target tissues

The pharmacologic effects of indirect sympathomimetics are greater under conditions of:
- increased sympathetic activity
- and norepinephrine storage and release
Phenylethylamine may be considered the:
  - parent compound from which sympathomimetic drugs are derived
  - This compound consists of a benzene ring with an ethylamine side chain

Substitutions may be made on (1) the benzene ring, (2) the terminal amino group, and/or (3) the carbons of the amino chain

These modifications produce a great variety of compounds with:
  - varying affinities to α and β receptors,
  - as well as to influence the intrinsic ability to activate the receptors,
  - their pharmacokinetic properties,
  - and different abilities to penetrate the CNS
Maximal $\alpha$- and $\beta$- activity is found with catecholamines

Catecholamines are subject to inactivation by COMT (found in the gut and liver)

So...catecholamines are not active orally

Furthermore, absence of ring $-\text{OH}$ groups increase distribution of the molecule to the central nervous system

(ephedrine and amphetamine are:
  • orally active,
  • have a prolonged duration of action,
  • and produce central nervous system effects)
Substitutions at the α-carbon block oxidation by monoamine oxidase (MAO) and prolong the action of such drugs (phenylisopropylamines) (alpha methyl compounds)

α-substitution give indirect activity (displacement)
The response of any cell or organ to sympathomimetics depends on:

- the **density** and **proportion** of **α and β adrenergic** receptors;
- their **relative selectivity** for the **different adrenoceptor** subtype,
- and its **pharmacological action** on **those receptors**
- Don’t forget compensatory **baroreflex mechanisms** (CV system)

Adrenergically innervated organs and tissues tend to have a predominance of one type of receptor......tissues such as the **vasculature of skeletal** muscle have predominantly **β₂ receptors**

......the **heart** contains **mainly β₁ receptors**
<table>
<thead>
<tr>
<th>Type</th>
<th>Tissue</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha_1$</td>
<td>Most vascular smooth muscle (innervated)</td>
<td>Contraction</td>
</tr>
<tr>
<td></td>
<td>Pupillary dilator muscle</td>
<td>Contraction (dilates pupil)</td>
</tr>
<tr>
<td></td>
<td>Pilomotor smooth muscle</td>
<td>Erects hair</td>
</tr>
<tr>
<td></td>
<td>Prostate</td>
<td>Contraction</td>
</tr>
<tr>
<td></td>
<td>Heart</td>
<td>Increases force of contraction</td>
</tr>
<tr>
<td>$\alpha_2$</td>
<td>Postsynaptic CNS adrenoceptors</td>
<td>Probably multiple</td>
</tr>
<tr>
<td></td>
<td>Platelets</td>
<td>Aggregation</td>
</tr>
<tr>
<td></td>
<td>Adrenergic and cholinergic nerve terminals</td>
<td>Inhibition of transmitter release</td>
</tr>
<tr>
<td></td>
<td>Some vascular smooth muscle</td>
<td>Contraction</td>
</tr>
<tr>
<td></td>
<td>Fat cells</td>
<td>Inhibition of lipolysis</td>
</tr>
<tr>
<td>$\beta_1$</td>
<td>Heart, juxtaglomerular cells</td>
<td>Increases force and rate of contraction; increases renin release</td>
</tr>
<tr>
<td>$\beta_2$</td>
<td>Respiratory, uterine, and vascular smooth muscle</td>
<td>Promotes smooth muscle relaxation</td>
</tr>
<tr>
<td></td>
<td>Skeletal muscle</td>
<td>Promotes potassium uptake</td>
</tr>
<tr>
<td></td>
<td>Human liver</td>
<td>Activates glycogenolysis</td>
</tr>
<tr>
<td>$\beta_3$</td>
<td>Fat cells</td>
<td>Activates lipolysis</td>
</tr>
<tr>
<td>$D_1$</td>
<td>Smooth muscle</td>
<td>Dilates renal blood vessels</td>
</tr>
<tr>
<td>$D_2$</td>
<td>Nerve endings</td>
<td>Modulates transmitter release</td>
</tr>
</tbody>
</table>
### TABLE 9–2 Relative receptor affinities.

<table>
<thead>
<tr>
<th>Alpha agonists</th>
<th>Relative Receptor Affinities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylephrine, methoxamine</td>
<td>$\alpha_1 &gt; \alpha_2 &gt;&gt;&gt; \beta$</td>
</tr>
<tr>
<td>Clonidine, methylnorepinephrine</td>
<td>$\alpha_2 &gt; \alpha_1 &gt;&gt;&gt; \beta$</td>
</tr>
</tbody>
</table>

**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$^1$                          | $\beta_1 > \beta_2 >>> \alpha$ |
| Isoproterenol                           | $\beta_1 = \beta_2 >>> \alpha$ |
| Albuterol, terbutaline, metaproterenol, | $\beta_2 >> \beta_1 >>> \alpha$ |
| ritodrine                               |                               |

**Dopamine agonists**

| Dopamine                                | $D_1 = D_2 >> \beta >> \alpha$ |
| Fenoldopam                              | $D_1 >> D_2$                    |

$^1$See text.
CARDIOVASCULAR SYSTEM

- Alpha$_1$-Receptor Activation
  - Alpha$_1$ receptors expressed in most vascular beds, and
  - their activation causes vasoconstriction
  - and rise in peripheral resistance......dose-dependent rise in blood pressure

- In the presence of normal cardiovascular reflexes, the
  - rise in blood pressure elicits a baroreceptor-mediated increase in vagal tone with slowing of the heart rate (bradycardia) (fig. 9-7)

- Trimethaphan: ganglion blocker....bradycardia is no longer observed
- Phenylephrine given as I.V bolus to a dog

- Reflex are blunted (but not eliminated) in anesthetized animal
Note that the increase in BP is associated with a baroreflex-mediated compensatory decrease in HR.

Patients with impaired autonomic function (diabetic autonomic neuropathy) may have exaggerated increases in heart rate or blood pressure when taking sympathomimetics.
CARdiovascular system

- **Alpha₂-Receptor Activation**
  - \( \alpha_2 \) adrenoceptors are present in the vasculature,
    - and their activation leads to vasoconstriction
    - This effect, is observed only when \( \alpha_2 \) agonists are given locally, by rapid I.V 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 blood pressure (sympatholytic effect)

- **Clonidine**: used to treatment (Tx.) Hypertension

- Patients with *pure autonomic failure*??
CARDIOVASCULAR SYSTEM

- **Beta-Receptor Activation**
  - *Isoproterenol* activates both *beta1* and *beta2* adrenoceptors??

- **Direct effects** on the heart are determined largely by $\beta_1$ receptors.
  - Positive *chronotropic effect, inotropic effect* and *dromotropic effect*...increase coronary blood flow
  - .....resulting in a markedly *increased cardiac output* and cardiac *oxygen consumption*

- $\beta_2$ receptors activation, leads to *vasodilation* in certain vasculature of smooth muscles
  - Increase blood flow in skeletal muscle during exercise
Net effect is to maintain or slightly increase SYSTOLIC pressure and decrease DYASTOLIC pressure. Mean BP decreased...

Beta1, Alpha1 and Beta2 adrenoceptors
Dopamine receptors??

D1: vasodilation of renal, splanchnic, coronary, cerebral and other resistance vessels

D2: presynaptic receptor (unclear role)

Dopamine activates beta1 receptors on the heart and.....

..... (at higher doses) alpha receptors on the vessels....

.....at high doses vasoconstriction (similar to epinephrine)
# Table 9-4 Cardiovascular responses to sympathomimetic amines.

<table>
<thead>
<tr>
<th></th>
<th>Phenylephrine</th>
<th>Epinephrine</th>
<th>Isoproterenol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vascular resistance (tone)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cutaneous, mucous membranes (α)</td>
<td>↑↑</td>
<td>↑↑</td>
<td>0</td>
</tr>
<tr>
<td>Skeletal muscle (β₂, α)</td>
<td>↑</td>
<td>↓ or ↑</td>
<td>↓</td>
</tr>
<tr>
<td>Renal (α, D₁)</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Splanchnic (α, β)</td>
<td>↑↑</td>
<td>↓ or ↑¹</td>
<td>↓</td>
</tr>
<tr>
<td>Total peripheral resistance</td>
<td>↑↑↑</td>
<td>↓ or ↑¹</td>
<td>↓</td>
</tr>
<tr>
<td>Venous tone (α, β)</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Cardiac</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contractility (β₁)</td>
<td>0 or ↑</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Heart rate (predominantly β₁)</td>
<td>↓↓ (vagal reflex)</td>
<td>↑ or ↓</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Stroke volume</td>
<td>0, ↓, ↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>↓</td>
<td>↑</td>
<td>↑↑</td>
</tr>
<tr>
<td><strong>Blood pressure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>↑↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Diastolic</td>
<td>↑↑</td>
<td>↓ or ↑¹</td>
<td>↓</td>
</tr>
<tr>
<td>Systolic</td>
<td>↑↑</td>
<td>↑↑</td>
<td>0 or ↓</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>0</td>
<td>↑↑</td>
<td>↑↑</td>
</tr>
</tbody>
</table>

¹Small doses decrease, large doses increase.

↑ = increase; ↓ = decrease; 0 = no change.
THE EYE......./ ...RESPIRATORY SYSTEM

- The Eye
  - Activation of $\alpha_1$ receptors mediates contraction of the radial pupillary dilator muscle of the iris and results in mydriasis
  - Reduces intraocular pressure due to (alpha)
    - vasoconstriction and increase the outflow of aqueous humor from the eye
  - $\beta$ receptors antagonists reduce the production of aqueous humor (ciliary epithelium)

- Respiratory system
  - Activation of $\beta_2$ receptors in bronchial smooth muscle leads to:
    - bronchodilation and
    - also inhibits the release of allergy mediator such as histamines from mast cells
    - (albuterol, salmeterol used for treatment (Tx.) of asthma)
GENITOURINARY TRACT

- The bladder base, urethral sphincter, and prostate contain α receptors that mediate contraction... urinary continence

- The specific $\alpha_{1A}$ receptor subtype seems to be involved in mediating constriction of the bladder base and prostate (urinary retention is a potential ADE of the $\alpha_1$ agonist midodrine)

- Alpha-receptor activation in the ductus deferens, seminal vesicles, and prostate plays a role in normal ejaculation.

- Uterus: Similar effect on uterine smooth muscle (ritodrine) for the Tx of prematur labor
EXOCRINE GLANDS

- **Salivary glands**: contain adrenoceptors that regulate the secretion of amylase and water.

- However, certain sympathomimetic drugs (clonidine) produce symptoms of dry mouth...mechanism uncertain; (probably CNS effects are responsible, though peripheral effects may contribute)

- **Apocrine sweat glands**: contain adrenoceptors and their stimulation increase sweat production (nonthermoregulatory glands associated with psychological stress) (sympathetic adrenergic)
Catecholamines encourage the conversion of energy stores (glycogen and fat) to freely available fuels (glucose and free fatty acids), and cause an increase in the plasma concentration of these substances.

1. Activation of $\beta_3$ receptors in adipocytes stimulate lipolysis......enhance release of FFA and glycerol into the blood

2. $\alpha_2$ receptors activation inhibit lipolysis by decreasing intracellular cAMP

3. Stimulate glycogenolysis in the liver and muscles, which leads to increased glucose release into the circulation......mediated mainly by $\beta$ receptors
METABOLISM

- Activation of $\beta_2$ receptors promotes $K^+$ uptake into cells, particularly skeletal muscles......

- Stress result in
  - ......Fall in plasma $K^+$ potassium concentration (hypokalemia) during stress

- and protect against a rise in plasma potassium during exercise
**HORMONES SECRETION**

- **β** receptors enhance **insulin** secretion and **renin** secretion.
- ....while......
- **α₂** receptors **inhibit** **insulin** secretion and **renin** secretion
- **Adrenoceptors** also modulate the secretion of
  - parathyroid hormone,
  - calcitonin,
  - thyroxine,
  - and gastrin......**limited physiologic significance**
The catecholamines are almost completely unable to enter the CNS.

At highest rates of infusion effects are noted as nervousness.

Tremor and tachycardia are peripheral effect and are similar to the somatic manifestations of anxiety.

Noncatecholamines with indirect actions (amphetamines), readily enter the CNS.

...their actions vary from mild alerting, with improved attention to boring tasks; through elevation of mood, insomnia, euphoria, and anorexia; to full-blown psychotic behavior.
Major effects mediated by α and β adrenoceptors

**ADRENOCEPTORS**

- **α₁**
  - Vasoconstriction
  - Increased peripheral resistance
  - Increased blood pressure
  - Mydriasis
  - Increased closure of internal sphincter of the bladder

- **α₂**
  - Inhibition of norepinephrine release
  - Inhibition of acetylcholine release
  - Inhibition of insulin release

- **β₁**
  - Tachycardia
  - Increased lipolysis
  - Increased myocardial contractility
  - Increased release of renin

- **β₂**
  - Vasodilation
  - Slightly decreased peripheral resistance
  - Bronchodilation
  - Increased muscle and liver glycogenolysis
  - Increased release of glucagon
  - Relaxed uterine smooth muscle
Therapeutic Uses of Sympathomimetic Drugs

Selection of a particular sympathomimetic drug depends on:

1. Whether activation of $\alpha$, $\beta_1$, or $\beta_2$ receptors is desired
2. The desirable duration of action
3. The preferred route of administration
DIRECT ACTING ADRENERGIC AGONISTS

**ENDOGENOUS CATECHOLAMINE**

a. Epinephrine (adrenaline)
   - **Potent stimulant** of both α and β adrenoceptors

   - **CV effect:** **potent vasoconstrictor** and **cardiac stimulant**
     - +ve inotropic and chronotropic actions on the heart (B1)
     - and **vasoconstriction** induced in many vascular beds (a1)
     - Epinephrine also activates β2 receptors in some vessels (eg, skeletal muscle blood vessels), leading to their dilation

   - Therefore, the net effect is:
     - an **increase in systolic blood pressure**,  
     - coupled with a **slight decrease** in **diastolic pressure**
Epinephrine (adrenaline)

- **Respiratory:**
  - causes **powerful bronchodilation** by acting **directly** on bronchial smooth muscle and
  - inhibiting the release of allergic mediators such as histamine from mast cells ($\beta_2$ action)

- **Hyperglycemia:** epinephrine has a **significant hyperglycemic effect** because of
  - increased glycogenolysis in the liver ($\beta_2$ effect),
  - and a decreased release of insulin ($\alpha_2$ effect)

- **Lipolysis:** epinephrine initiates **lipolysis** through its **agonist** activity on the $\beta$ receptors of adipose tissue
**THERAPEUTIC USES OF SYMPATHOMIMETIC DRUGS ANAPHYLAXIS**

- Epinephrine (IM) is the **1ry Tx for anaphylaxis** (drug of choice “DOC”)
- Epinephrine activates $\alpha$, $\beta_1$, and $\beta_2$ receptors
- Can **relief anaphylactic shock:**
  - bronchospasm,
  - mucous membrane congestion,
  - angioedema,
  - and severe hypotension

- **Glucocorticoids and antihistamines** useful as **2ry therapy**
- “**EpiPen**” recommended for patients at risk for:
  - insect sting hypersensitivity,
  - severe **food allergies**, 
  - or other types of anaphylaxis
b. Norepinephrine (noradrenaline, levarterenol)

- At therapeutic doses to human, stimulate the $\alpha$-adrenergic receptors (both $\alpha_1$ & $\alpha_2$) and the $\beta_1$ receptors with similar potency as epinephrine, but has relatively little effect on $\beta_2$ receptors.

- Norepinephrine:
  - Increases peripheral resistance
  - And both diastolic and systolic blood pressure
  - Compensatory baroreflex activation tends to overcoming the direct positive chronotropic effects of norepinephrine; however, the positive inotropic effects on the heart are maintained.
c. Dopamine

- Important neurotransmitter in the CNS and is involved in the reward stimulus relevant to addiction

- Its deficiency in the basal ganglia leads to Parkinson's disease (treated with levodopa)

- Its increment seems to be the cause of psychosis (Tx dopamine antagonist)

- Dopamine promotes vasodilation via activation of $D_1$ receptors.
- The activation of presynaptic $D_2$ receptors suppresses norepinephrine release
d. Phenylephrine

- Direct-acting and synthetic $\alpha_1$ receptors agonist
- Not a catechol derivative and, therefore, not a substrate for COMT (longer duration of action)

- It is a vasoconstrictor that raises both systolic and diastolic blood pressures

- Has no effect on the heart itself but rather induces reflex bradycardia when given parenterally
THERAPEUTIC USES OF SYMPATHOMIMETIC DRUGS

- **Phenylephrine** is an effective:
  - **mydriatic agent** frequently used to facilitate **examination of the retina**
  - Topically on the **nasal mucous membrane** as a **decongestant** for minor **allergic** hyperemia and **itching of the conjunctival membranes**

- **N.B:** Nasal blood vessels are rich in **α receptors**... vasoconstriction

**Tetrahydrozoline** used also to **induce mydriasis**

.....**both drugs do not cause cycloplegia**
Xylometazoline and oxymetazoline

- Both are **direct-acting α-adrenoceptor** agonists
- These drugs have been used as **topical decongestants** because of their ability to **promote constriction of the nasal mucosa** (available as **over-the-counter nasal spray products**)

- When taken **in large doses**, oxymetazoline may cause **hypotension** ($\alpha_{2A}$ receptors)
DIRECT ACTING ADRENERGIC AGONISTS
DIRECT ACTING SYMPATHOMIMETICS

Midodrine
- It is a prodrug that is enzymatically hydrolyzed to DesGlyMidodrine... selective $\alpha_1$-receptor agonist

- **USE**: primarily indicated for the treatment of orthostatic hypotension,
  - typically due to impaired autonomic nervous system function

- **Effective** when the patient is standing, but may cause HTN when the subject is supine... can be minimized by
  - avoiding dosing prior to bedtime
  - and elevating the head of the bed
c. Methoxamine

- \( \alpha_1 \) receptors agonist

- It may cause a prolonged increase in blood pressure due to vasoconstriction;

- It also causes a vagally mediated bradycardia

**USE:** clinical applications are rare....overcome hypotensive states during surgery involving halothane anesthetics (parenterally)
d. **Alpha$_2$-selective agonists**

“Clonidine, Methyldopa, Guanfacine, Guanabenz”

- **Primarily used** for the treatment of **systemic hypertension**
  - due to their ability to **decrease blood pressure** through actions in the **central nervous system**

- **Apraclonidine** and **brimonidene** ($\alpha_2$-selective agonists)
  - **lower intraocular pressure** and are **approved** for use in **glaucoma** (used more than non-selective alpha agonist).

- **Tizanidine** ($\alpha_2$ agonist) that is used as a muscle relaxant
DIRECT ACTING ADRENERGIC AGONISTS
DIRECT ACTING SYMPATHOMIMETICS

f. Isoproterenol (isoprenaline)
   - Direct acting synthetic catecholamine that predominantly stimulates β adrenoceptors. Little effect on α-receptors
   - Produces intense stimulation of the heart to increase its rate and force of contraction...increases cardiac output (β₁ effect)
   - Dilates the arterioles of skeletal muscle (β₂ effect), resulting in decreased peripheral resistance
   - Net effect: marked fall in diastolic and a lesser decrease or a slight increase in systolic pressure
   - Rarely used therapeutically......used to stimulate the heart in emergency situations.....
Advantage......increase cardiac output with less reflex tachycardia (no vasodilation effect)

FIGURE 9-8 Examples of $\beta_1$- and $\beta_2$-selective agonists.
g. Beta-selective agonists

- **β₁-selective agents:** *dobutamine* & *prenalterol* (partial agonist)

- **Clinical preparations** of *dobutamine* are a *racemic mixture* of 
  
  (-) and (+) isomers,
  
  - (+) isomer......potent *β₁* agonist and *α₁* antagonist
  - (-) isomer.....potent *α₁* agonist (cause significant vasoconstriction when given alone)

- The **resultant CV effects** of dobutamine reflect this *complex* pharmacology:
  
  - Increases cardiac output (positive inotropic action)
  - with little change in HR,
  - and *peripheral resistance does not decrease significantly*
  - **Does not significantly elevate O2 demands** of the *myocardium* — advantage over other sympathomimetic drugs
g. Beta-selective agonists

- **β₂-selective agents:**
  - These agents are used primarily as *bronchodilator* and their use have achieved an important place in the *treatment of asthma (reliever)*

- **Short-acting (inhalers):**
  - “albuterol (salbutamol), metaproterenol, terbutaline”.
  - ..effective for *Tx* of *acute symptoms*.

- **Long-acting (inhalers):**
  - “salmeterol, formeterol”..... combined with *corticosteroid* used as *prophylaxis*

- Nonselective drugs (epinephrine), β-selective agents (isoproterenol), are available
THERAPEUTIC USES OF SYMPATHOMIMETIC DRUGS

GENITOURINARY APPLICATIONS

- Beta-selective agonists

- *Ritodrine (B2-selective)* used clinically to achieve uterine relaxation in premature labor (arrest premature labor)

- “Terbutaline” have been used to suppress premature labor

The goal is to defer labor long enough to ensure adequate maturation of the fetus.

This may afford time to administer corticosteroid drugs, which decrease the incidence of neonatal respiratory distress syndrome (IRDS)
MIXED-ACTING SYMPATHOMIMETICS

- **EPHEDRINE**
  - 1st **orally active** sympathomimetic (**non-chatecol**)
  - Relatively **long duration** of action
  - Can **enter the CNS** with **mild stimulant** effect

- **PSEUDOEPHEDRINE**
  - One of the four ephedrine enantiomers
  - Was available as **OTC component** of many **decongestant mixtures**
  - Used as a **precursor** in the **illicit manufacture** of **methamphetamine** (restrictions on its sale)

- **GENITOURINARY APPLICATION**: “Ephedrine or pseudoephedrine” is occasionally useful in the treatment of **stress incontinence**

![Chemical structures of Ephedrine and Amphetamine](image)
INDIRECT ACTING ADRENERGIC AGONISTS
A. AMPHETAMINE-LIKE OR DISPLACERS

1. Amphetamine:
    It is a racemic mixture of phenylisopropylamine (D-isomer is more potent than L-isomer)

    Amphetamine's actions are mediated through the release of norepinephrine and, to some extent, dopamine

    Amphetamine and other phenylisoprotylaminines are widely abused as CNS stimulants (orally active)

    Legitimate indications include:
     - narcolepsy,
     - attention deficit disorder
     - and weight reduction
INDIRECT ACTING ADRENERGIC AGONISTS
A. AMPHETAMINE-LIKE OR DISPLACERS

2. Methamphetamine:
   - Very similar to amphetamine with an even higher ratio of central to peripheral actions.
   - In the brain, methamphetamine:
     - releases dopamine and other biogenic amines,
     - and inhibits MAO

3. Phenmetrazine:
   - It is a variant phenylisopropylamine with amphetamine-like effects.
     - It has been promoted as an anorexiant
     - and is also a popular drug of abuse
**Therapeutic Uses of Sympathomimetic Drugs**

**CNS Applications**

- **Obesity:**
  - an encouraging *initial appetite-suppressing effect* of these agents may be observed in *obese humans*,
  - but there is *no evidence* that *long-term improvement in weight control* can be achieved with *amphetamines alone*.....
  - intensive dietary and psychological counseling and support is needed
INDIRECT ACTING ADRENERGIC AGONISTS

A. AMPHETAMINE-LIKE OR DISPLACERS

4. Methylphenidate:
   - Amphetamine variant whose major pharmacologic effects and abuse potential are similar to those of amphetamine
   - It is a mild CNS stimulant
     - with more prominent effects on mental than on motor activities
   - CNS application: attention-deficit hyperactivity disorder (ADHD).
   - Some patients respond well to low doses of methylphenidate or to clonidine.

- Extended-release formulations may
  - simplify dosing regimens
  - and increase adherence to therapy, especially in school-age children
5. **Modafinil**: a new amphetamine substitute

- It is a psycostimulant that **differs from amphetamine**
  - in structure,
  - neurochemical profile,
  - and behavioral effects

- **Mech of action not fully known**
  - Inhibits both NET and DAT,
  - and **increases interstitial concentrations:**
    - not only of **norepinephrine and dopamine**, but also **serotonin and glutamate**
    - while **decreasing GABA levels**
All amphetamine-like and displacer have:
- a mood-elevating (euphoriant) effect,
- alerting, & sleep-deferring action
- that is manifested by improved attention to repetitive tasks

**Modafinil** is approved for use in **NARCOLEPSY** (chronic sleep disorder)

**MODAFINIL** is claimed to have fewer disadvantages than amphetamine in this condition
- ......LESS excessive mood changes,
- LESS insomnia
- and LESS abuse potential
TYRAMINE

- It is by-product of tyrosine metabolism in the body and is also found in high concentrations in some fermented foods such as cheese (table 9-5)
- Tyramine's spectrum of action is similar to that of norepinephrine
- Inactive orally...readily metabolized by MAO in the liver
- If the patient is taking MAOI "inhibitors" (MAO-A), BE CAREFUL!.....can precipitate serious vasopressor effects
1. Atomoxetine & reboxetine

- They are **selective inhibitors** of the NET

- **Surprisingly** it has **little cardiovascular effect**
  - because it has a **clonidine-like effect** in the **central nervous system** to **decrease sympathetic outflow**

- while at the same **time potentiating** the **effects of norepinephrine in the periphery**
INDIRECT ACTING ADRENERGIC AGONISTS

B. CATECHOLAMINE REUPTAKE INHIBITORS

2. Sibutramine: is a serotonin and norepinephrine reuptake inhibitor
   - and is the only appetite suppressant approved by the FDA for long-term treatment of obesity

3. Duloxetine: is also a widely used antidepressant with
   - serotonin and norepinephrine reuptake inhibitory effects
COCAINEx

- Local anesthetic with peripheral indirect sympathomimetic action

- Enters the CNS and produces a shorter lasting but more intense amphetamine-like effect through
  - inhibiting dopamine reuptake into neurons in the "pleasure centers" of the brain

- + can be smoked, snorted into the nose, or injected for rapid onset of effect.....have made it a heavily abused drug

- INTERESTING....that dopamine-transporter knockout mice still self-administer cocaine, suggesting that cocaine may have additional pharmacologic targets
THERAPEUTIC USES OF SYMPATHOMIMETIC DRUGS
CARDIOVASCULAR APPLICATIONS

- **Condition in which:**
  - an increase in **cardiac output** and **blood flow** to the tissue is desired
  - (severe hypotension, cardiac shock, heart failure)

- **β agonist** may be useful in this situation because they:
  - increase cardiac contractility
  - and reduce diastolic pressure by β2 effect

- Dobutamine and dopamine are used (**dopamine is DOC**)

- **Isoproterenol and epinephrine** have been used:
  - in the temporary **emergency management** of complete **heart block** and **cardiac arrest**
  - (electronic pacemaker are safer and more effective)
Shock: Acute cardiovascular syndrome that results in:
- a critical reduction in perfusion of vital tissues,
- altered mental state,
- hypotension
- and oliguria

Usually due to:
- hypovolemia,
- cardiac insufficiency,
- and altered vascular resistance

Treatment:
- volume replacement
- and treatment of the underlying disease are the mainstays of the treatment
- Adrenergic receptor agonists may be used......:
- β receptor agonists increase heart rate and force of contraction, α receptor agonists increase peripheral vascular resistance, and dopamine (DOC) promotes dilation of renal and splanchnic vascular beds, in addition to activating α and β receptors
THERAPEUTIC USES OF SYMPATHOMIMETIC DRUGS
CARDIOVASCULAR APPLICATIONS

- Condition in which a **DECREASE in blood flow** or **increase in blood pressure** is desired

- **Decrease blood flow:**
  - **α₁ agonist** are **useful** in situation in which vasoconstriction is appropriate
    - Such as **decongestant effect** (phenylephrine)
  - **α agonist** are **often mixed** with **local anesthetic** to:
    - **reduce** the **loss of anesthetic** from the **area of injection** into the **circulation** (epinephrine is **DOC**)**
Increase blood pressure
spinal shock (NE) in which maintenance of blood pressure may help in maintain perfusion to brain, heart, & liver (we need increase in blood pressure)

Shock due to MI is
- usually made worse by vasoconstriction

Chronic orthostatic hypotension: On standing, gravitational forces induce venous pooling, resulting in decreased venous return
- Increasing peripheral resistance is one of the strategies to treat chronic orthostatic hypotension
- Midodrine, an orally active $\alpha_1$ agonist, is frequently used for this indication
Horner's syndrome

- is a condition (usually unilateral) that results from
  - interruption of the sympathetic nerves to the face
  - (caused by either preganglionic or postganglionic lesion, such as a tumor)

- Symptoms include:
  - vasodilation,
  - ptosis,
  - miosis,
  - and loss of sweating on the side affected.
HORNER'S SYNDROME

● **Sympathomimetics** administered as ophthalmic drops
  ● are also useful in **localizing** the **lesion** in Horner's syndrome

● If the **lesion** is **postganglionic**,
  ● **indirectly** acting **sympathomimetics** (eg, cocaine, amphetamine) will **not dilate** the abnormally **constricted** pupil
    ● because **catecholamines** have **been lost from** the nerve endings in the **iris**
  ● But **phenylephrine** will **dilate** the pupil (**acts directly** on the $\alpha$ receptors on the **smooth muscle** of the **iris**)

● If the **lesion** is **preganglionic**,
  ● it will show a **normal response to both drugs**,
  ● since the **postganglionic fibers** and their **catecholamine stores** remain **intact** in this situation
Horner's syndrome