Pharmacology

Sympathomimetic Agents – ANS
Pharmacology

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The sympathetic autonomous system works by the release of neurotransmitters that act on the adrenoreceptors, with their various types and subtypes. The effects produced can be mimicked by drugs that stimulate these receptors, known as sympathomimetics. Some sympathomimetics have a higher affinity for a certain receptor type or subtype while others are rather non-selective.

Definition of Sympathomimetics

Sympathomimetics are drugs that mimic the action of stimulators of the sympathetic autonomic nervous system, specifically the adrenoreceptors: α, β or dopamine receptors. They are also known as adrenergic agonists.

Classification of Sympathomimetics

Sympathomimetics can be divided based on the type of receptors, for which they have a higher affinity, i.e., their spectrum of action.

For example, epinephrine is both α and β agonist, whereas phenylephrine is predominantly an α1 agonist. Dopamine, obviously, is a strong dopamine receptor agonist, but it can also activate α and β receptors at certain doses. Thus, a sympathomimetic drug can be a selective agonist; however, no sympathomimetic is
Sympathomimetics can also be classified based on their mechanism of action into **direct-**, **indirect-** and **mixed-acting drugs**.

**Direct-acting** drugs are those that directly act on and activate the receptors to produce the desired pharmacological effects, e.g., **dobutamine**, which acts selectively on β1 receptors.

**Indirect-acting** drugs are those that act indirectly to increase the concentration of the endogenous neurotransmitter by causing its release (e.g., **amphetamine derivatives**) or inhibiting its reuptake (e.g., **tricyclic antidepressants**).

**Mixed-acting** drugs employ both mechanisms, e.g., **ephedrine**, which, in addition to acting on the α and β receptors, causes **noradrenaline release**.

Always remember that **epinephrine, norepinephrine and dopamine** are **endogenous catecholamines**. Please note that **adrenaline** is another name of **epinephrine** and similarly noradrenaline is the other name of **norepinephrine**.

### Difference between epinephrine and norepinephrine

Epinephrine is a hormone released from the **adrenal medulla**, whereas norepinephrine is a neurotransmitter released at **postganglionic neurons**. There is a difference in the structure of epinephrine and norepinephrine also; norepinephrine lacks the methyl substitution at the amine group.

Epinephrine has profound effect on the heart rate and cardiac output as compared to norepinephrine. Also norepinephrine doesn't drastically affect the metabolic effects, such as increased blood sugar and lactic acid levels, as seen with the epinephrine.
Pharmacokinetics of Sympathomimetics

Catecholamines (epinephrine, norepinephrine and dopamine—endogenous adrenoceptor agonists—and other related drugs):

- Short duration of action, because of one or both of the following:
  - Rapidly metabolized by *catechol-O-methyltransferase* (COMT) and *monoamine oxidase* (MAO)
  - Readily taken up into nerve endings (exception: isoproterenol)
- Inactive orally (midodrine is an orally active $\alpha_1$ agonist)
- Low central nervous system (CNS) penetration but can penetrate CNS at higher doses (“adrenaline rush”).

**Epinephrine** and **norepinephrine** are not active orally; they are given by IV route in an emergency.

**Phenylisopropylamine derivatives (amphetamines and ephedrine):**

- Resistant to MAO and also to COMT
- Orally active
- Better CNS penetration
- Longer lasting effects than those of catecholamines.

Mechanism of Action of Sympathomimetics

As previously mentioned, sympathomimetics act by stimulating $\alpha$, $\beta$ and/or dopamine receptors and/or causing release or inhibiting reuptake of neurotransmitters.

Brief review of the neurotransmission of adrenergic neurons

Norepinephrine is synthesized from tyrosine and stored in vesicles at the end of the neuron. Calcium influx from an action potential causes the vesicles to fuse with the synapse membrane and release noradrenaline in the synaptic space. It then binds to the adrenoreceptor on the effector cells and produces effects by various mechanisms. The excess norepinephrine not bound to the postsynaptic receptor binds to $\alpha_2$ presynaptic receptors to decrease its own release. It then either diffuses out, is metabolized by COMT or is taken back up by the presynaptic neuron.
Direct acting sympathomimetics

**α-receptor stimulation:** **α1 agonists** act by G-protein activation of the enzyme phospholipase C, resulting eventually in the release of calcium, thereby **increasing the intracellular calcium concentration.** Alpha2 (α2) agonists act by inhibiting adenylyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP). This leads to **decreased intracellular cAMP levels.**

Alpha receptors are further subdivided into **α1A, α1B, α1C and α1D** as well as **α2A, α2B and α2C.** This differentiation is important as the search for more selective newer drugs continues, and selectivity at the sub-type level helps narrow down the effects of a drug.

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-selective</td>
<td>Norepinephrine</td>
</tr>
<tr>
<td>α1 selective</td>
<td>Phenylephrine</td>
</tr>
<tr>
<td>α2 selective</td>
<td>Clonidine</td>
</tr>
</tbody>
</table>

**β-receptor stimulation:** β agonists – selective to a subtype (β1, β2 and β3) or non-selective – stimulate adenylyl cyclase, causing **increased intracellular cAMP levels.**

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<th>Receptor</th>
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</tr>
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<tr>
<td>Non-selective</td>
<td>Epinephrine, Isoproterenol</td>
</tr>
<tr>
<td>β1 selective</td>
<td>Dobutamine</td>
</tr>
<tr>
<td>β2 selective</td>
<td>Albuterol, Salbutamol, Terbutaline</td>
</tr>
</tbody>
</table>

**Dopamine-receptor stimulation:** Dopamine receptor agonists can act on D1 or D2 receptors. D1 receptors activate adenylyl cyclase and **increase intracellular cAMP mainly in neurons and vascular smooth muscle.** D2 receptors reduce **intracellular cAMP** and are found in the brain and as pre-synaptic receptors.

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<td>Non-selective</td>
<td>Dopamine</td>
</tr>
<tr>
<td>D1 selective</td>
<td>Fenoldopam</td>
</tr>
</tbody>
</table>
**Indirect acting sympathomimetics**

**Indirect-acting** drugs are those that act indirectly to increase the concentration of the endogenous neurotransmitter by causing its release (e.g., amphetamine derivatives and ephedrine) or inhibiting its reuptake (e.g., cocaine and tricyclic antidepressants).

**Mixed-acting sympathomimetics**

**Mixed-acting** drugs employ both mechanisms, e.g., ephedrine, which, in addition to acting on the $\alpha$ and $\beta$ receptors, causes noradrenaline release.

**Ephedrine** is used to treat nasal congestion.

### Effects on Various Organ Systems and Clinical Uses of Sympathomimetics

Sympathomimetics ($\alpha$ and $\beta$ agonists) have varying effects on various organ systems.

The effects of sympathomimetics on various organ systems are summarized in the following table:

<table>
<thead>
<tr>
<th><strong>Organ system</strong></th>
<th><strong>Effects</strong></th>
<th><strong>Receptor</strong></th>
<th><strong>Clinical uses/Other comments</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchi</td>
<td>Bronchiolar smooth muscle relaxation</td>
<td>$\beta_2$</td>
<td>Relieving acute bronchoconstriction in asthma (e.g., short-acting $\beta_2$ agonists such as albuterol and terbutaline) COPD (long-acting $\beta_2$ agonists such as salmeterol and formoterol)</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>Smooth muscle relaxation</td>
<td>$\alpha$ or $\beta$</td>
<td>Phenylephrine is an effective mydiatic. Brimonidine ($\alpha_2$ agonist) is used in open-angle glaucoma and ocular hypertension.</td>
</tr>
<tr>
<td>Eye</td>
<td>Contraction of the smooth muscle of the iris dilator muscle (mydriasis) <strong>Mnemonics:</strong> the $\alpha$ receptors look like an eye. Always correlate the $\alpha$ with eyes ($\alpha$) to remember its action on eyes. Increase aqueous humor outflow (a lower IOP) Reducing synthesis of aqueous humor (a lower IOP)</td>
<td>$\alpha_1$ $\alpha_2$</td>
<td>Tamsulosin is an alpha blocker or antagonist used to improve urination in benign prostate hyperplasia (BPH) because it causes relaxation of bladder muscles (opposite actions to the alpha agonists). Always remember: To remember the effects of alpha antagonists on various organ systems, first learn the effects of alpha agonist and just reverse the actions of alpha agonists.</td>
</tr>
<tr>
<td>Genitourinary (bladder and prostate)</td>
<td>Constriction of bladder sphincter. Control of urine flow (no urination in stressful situations). Causes ejaculation by inducing contraction of the prostate.</td>
<td>$\alpha_1$ (Antagonistic action)</td>
<td></td>
</tr>
<tr>
<td>CNS</td>
<td>Amphetamines: Mild increase in alertness or decrease in fatigue, followed by mild anorexia, euphoria and insomnia. Amphetamine is used as a CNS stimulant and used to treat narcolepsy and ADHD.</td>
<td>DA receptor Probably due to dopamine release</td>
<td>Modafinil, an amphetamine derivative, is an atypical weak dopamine reuptake inhibitor and is used for narcolepsy.</td>
</tr>
<tr>
<td>Uterus</td>
<td>Relaxation of uterus $\alpha_1$</td>
<td>Terbutaline (selective $\beta_2$ agonist) and ritodrine are used to suppress premature labor.</td>
<td></td>
</tr>
</tbody>
</table>
Cardiovascular effects of sympathomimetics

α and β agonists have significant effects on vascular systems. These effects are essential to understand and learn the cardiovascular pharmacology of α and β agonists/sympathomimetics.

It is interesting to mention the mechanism of action of clonidine. Other α agonists increase the blood pressure; however, clonidine is used in the treatment of hypertension (it decreases the BP). Clonidine acts on α adrenoceptors in the medulla of the brain. It is a centrally acting α2 agonist. It decreases the BP by decreasing peripheral vascular resistance, thus lowering blood pressure and reduces the release of catecholamine levels in the blood. It also decreases heart rate and cardiac output, though decreased blood return eventually results in reflex tachycardia.

Cardiovascular effects of sympathomimetics are summarized in the following table:

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Effects</th>
<th>Examples/Clinical Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>α1</td>
<td>Vascular smooth muscle contraction (increased peripheral resistance, increased blood pressure, reflex bradycardia)</td>
<td>Phenylephrine: spinal shock and can also be used locally, e.g., nasal sprays, to relieve congestion (stimulates the mucous secretion) Midodrine: chronic orthostatic hypotension</td>
</tr>
<tr>
<td>α2</td>
<td>Stimulation of presynaptic α2 agonists in the central nervous system; inhibits the sympathetic autonomic system</td>
<td>Clonidine: refractory hypertension and hypertension complicated by renal disease (as it does not affect renal blood flow/glomerular filtration) Methyldopa: Hypertension in pregnancy, eclampsia (use otherwise limited because of side effects)</td>
</tr>
<tr>
<td>β1</td>
<td>Heart Increased heart rate, conduction velocity and increased contractility. Increased AV node conduction.</td>
<td>Dobutamine, adrenaline and isoprenaline are used in: Cardiogenic shock Hypotensive crisis Acute heart failure Cardiac arrest Remember: Beta blockers are used in the treatment of hypertension.</td>
</tr>
<tr>
<td>β2</td>
<td>Promote the dilation of arterioles and veins, consequently a decrease in TPR, BP and afterload.</td>
<td></td>
</tr>
<tr>
<td>D1</td>
<td>Vasodilatation in the kidney and spleen</td>
<td>Dopamine</td>
</tr>
</tbody>
</table>

Other clinical uses of sympathomimetics

Epinephrine: anaphylaxis

Epinephrine is a mixed-acting agonist. It is the drug of choice for anaphylaxis and cardiac arrest. This is because it antagonizes the effects of many mediators of anaphylaxis. It counteracts hypotension through β1 receptor stimulation and causes bronchial muscle relaxation, thereby relieving bronchospasms through β2 receptor stimulation.

Toxicity of Sympathomimetics

Toxicities of sympathomimetic drugs are basically the extension of their physiologic effects of α or β receptor stimulation – excessive vasoconstriction, cardiac arrhythmias, myocardial infarction, stroke, pulmonary edema, pulmonary hemorrhage, etc.

Obviously, drugs that have more selective subtype affinity will have toxicities more related to stimulation of that subtype. For example, β1 agonists will cause tachycardia and arrhythmias, and toxicity of α1 agonists will manifest as hypertension.
Side Effects of Sympathomimetics

Common side effects of α agonists

- Headache
- Reflex bradycardia
- Excitability
- Restlessness

Common side effects of β agonists

- Cardiac arrhythmia
- Headache
- Tremors
- CNS effects of catecholamines are limited because of their low CNS penetration; however, higher doses can cause some CNS effect. CNS toxicity of phenylisopropylamine derivatives depends on the dosage. It can be mild to severe, ranging from nervousness and insomnia to anxiety and aggressiveness and even paranoid behavior and convulsions.
- As mentioned in the introduction, the selectivity is only relative, and, at high doses, other receptor types can be activated.
- An important interaction is observed between tyramine and MAOa inhibitors. Both of these drugs should be contraindicated as MAOa inhibitors as they increase the bioavailability, resulting in severe increase in blood pressure (hypertensive crisis).

Review Questions

The correct answers can be found below the references.

1. A patient presents with chronic obstructive pulmonary disease (COPD), which is an obstructive airway disease that causes problems in breathing because of poor airflow. Which of the following types of drug would you preferably administer to this patient?
   A. Long-acting α2 receptor agonist
   B. Long-acting β1 receptor antagonist
   C. Short-acting β2 receptor agonist
   D. Long-acting β2 receptor agonist
   E. Short-acting α2 receptor agonist

2. Which of the following drugs is the most useful for terminating an acute attack of asthma?
   A. Salmeterol
   B. Formoterol
   C. Olodaterol
   D. Clonidine
   E. Terbutaline

3. Which of the following drugs would be the most appropriate to treat nasal congestion?
   A. Pseudoephedrine
   B. Xylometazoline
   C. Adrafinil
References


Correct answers: 1D, 2E, 3B

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