Medical Committee
The University of Jordan

PHARMACOLOGY

Slide # :11-Sympathomimetics

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SLIDES

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Sympathomimetics

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Sympathomimetics

- **Drugs that mimic the actions of epinephrine (adrenaline) or norepinephrine (noradrenaline) [Also called catecholamines].**
- **Norepinephrine is released by sympathetic nerves upon nerve stimulation, while epinephrine is released by the adrenal medulla in response to a variety of stimuli such as stress.**

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Mode of Action:

1. **Direct stimulation of adrenoceptors.**
2. **Displacement of stored catecholamines from the adrenergic nerve endings (amphetamine, tyramine).**
3. **Inhibition of catecholamine reuptake (cocaine, tricyclic antidepressants).**

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Table 9–2. Relative selectivity of adrenoceptor agonists.

	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[1]	$\beta_1 > \beta_2 >>>> \alpha$
Isoproterenol	$\beta_1 = \beta_2 >>>> \alpha$
Terbutaline, metaproterenol, albuterol, ritodrine	$\beta_2 >> \beta_1 >>>> \alpha$
Dopamine agonists	
Dopamine	$D_1 = D_2 >> \beta >> \alpha$
Fenoldopam	$D_1 >> D_2$

[1]See text.

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Table 9–3. Distribution of adrenoceptor subtypes.

Type	Tissue	Actions
α_1	Most vascular smooth muscle (innervated)	Contraction
	Pupillary dilator muscle	Contraction (dilates pupil)
	Pilomotor smooth muscle	Erects hair
	Prostate	Contraction
	Heart	Increases force of contraction
α_2	Postsynaptic CNS adrenoceptors	Probably multiple
	Platelets	Aggregation
	Adrenergic and cholinergic nerve terminals	Inhibition of transmitter release
	Some vascular smooth muscle	Contraction
	Fat cells	Inhibition of lipolysis

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β_1	Heart	Increases force and rate of contraction
β_2	Respiratory, uterine, and vascular smooth muscle	Promotes smooth muscle relaxation
	Skeletal muscle	Promotes potassium uptake
	Human liver	Activates glycogenolysis
β_3	Fat cells	Activates lipolysis
D_1	Smooth muscle	Dilates renal blood vessels
D_2	Nerve endings	Modulates transmitter release

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Pharmacodynamics:

1.Cardiovascular system:

A. Blood vessels:

Vascular smooth muscle tone is regulated by adrenoceptors. Therefore, catecholamines are important in the regulation of peripheral vascular resistance and venous capacitance.

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α-receptors increase arterial resistance, whereas, β_2-receptors relax vascular smooth muscle.

- **Skin and splanchnic vessels have predominantly α receptors → constriction.**

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- **Skeletal muscle vessels may constrict or dilate depending on the proportion of α or β receptors, respectively.**
- **Dopamine D1 receptors promote vasodilation of renal, splanchnic, coronary, cerebral and other resistance vessels.**

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B. Heart:

- **Effects on the heart are predominantly mediated through β_1 receptors although β_2 receptors and to a lesser extent α receptors may be involved.**
- **Increase pacemaker (both normal and abnormal) activity = "positive chronotropic effect".**

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- **Conduction velocity in the atrioventricular (AV) node is increased and its refractory period is decreased (positive dromotropic effect).**
- **Myocardial contractility is increased = “positive inotropic effect”.**

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C. Blood pressure:

The effect of sympathomimetics on blood pressure is dependent on their effect on heart (β_1), peripheral vascular resistance (α, β_2) and venous return. An increase in venous return increases cardiac output.

- **Systolic blood pressure is related to cardiac output and is increased by drugs that increase myocardial contractility.**

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- **Diastolic blood pressure is related to systemic vascular resistance and is increased by vasoconstrictors and reduced by vasodilators.**
- **α-agonists increase peripheral arterial resistance and decrease venous capacitance → rise in blood pressure.**

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- **β-agonists effect is to increase systolic blood pressure by stimulation of the heart (β_1), and decrease peripheral vascular resistance and thus diastolic blood pressure (β_2).**

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2. Eye:

A. Activation of α-receptors in radial pupillary muscle of the iris dilates the pupil (mydriasis).

B. α-agonists also reduce aqueous humor formation and reduce intraocular pressure.

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3. Respiratory tract:

A. Bronchial smooth muscles relax in response to β_2 receptor stimulation → bronchodilation.

B. Blood vessels of upper respiratory tract mucosa constrict in response to α receptor stimulation → decongestion.

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4. Gastrointestinal tract:

A. β receptor stimulants relax smooth muscle of GIT.

B. α_2-selective agonists decrease muscle activity indirectly by presynaptically reducing the release of acetylcholine and other stimulants of the enteric nervous system (more significant).

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C. α_2 receptors stimulation decreases salt and water flux into the lumen of the intestine.

5. Genitourinary tract:

A. β_2 receptors mediate relaxation of the pregnant human uterus.

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

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C. The β_2 receptors of the bladder wall mediate relaxation.

D. Ejaculation depends on normal α receptors activation in vas deferens, seminal vesicles and prostate.

E. The detumescence of erectile tissue that follows ejaculation is brought about by norepinephrine.

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6. Exocrine glands:

A. In the salivary glands, adrenoceptors regulate secretion of amylase and water.

B. The apocrine sweat glands located in the palms of the hands respond to adrenoceptor stimulants with increased sweat production. This is nonthermoregulatory sweating associated with psychologic stress.

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C. The thermoregulatory eccrine sweat glands are sympathetic cholinergic (muscarinic).

7. Metabolic effects:

A. β_3 receptor stimulation increases lipolysis with release of fatty acids and glycerol.

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B. α_2 receptor stimulation inhibits lipolysis.

C. β receptor stimulation enhances glycogenolysis in the liver leading to increased glucose release into the circulation.

D. β_2 receptor stimulation promote uptake of potassium into cells.

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8. Effects on endocrine function:

A. β receptor stimulation increases insulin release by pancreas.

B. α_2 receptor stimulation inhibits insulin release.

C. β_1 receptor stimulation increases renin secretion.

D. α_2 receptor stimulation inhibits renin secretion.

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9. Effects on the central nervous system:

- **Depend on the ability of the drug to cross the blood-brain-barrier. Catecholamines do not dross the BBB.**
- **Amphetamines produce variable effects ranging from mild alerting with improved attention, to boring tasks through elevation of mood, insomnia, euphoria and anorexia to full-blown psychotic behavior.**

Specific Sympathomimetics

1. **Catecholamines:**

   Epinephrine, norepinephrine, isoproterenol, dopamine, fenoldopam & dobutamine.

2. **Noncatecholamines:**

   Phenylephrine, methoxamine, midodrine, ephedrine, oxymetazoline, amphetamine, methamphetamine, phenmetrazine, & methylphenidate.

Epinephrine

- **Stimulates all adrenoceptors (α_1, α_2, β_1, β_2).**
- **Very potent vasoconstrictor and cardiac stimulant.**
- **Positive inotropic and chronotropic actions on the heart (β_1).**
- **Vasoconstrictor in many vascular beds (α_1), and vasodilator in skeletal muscle blood vessels (β_2) → increase blood flow during exercise.**

Norepinephrine

- **Similar to epinephrine except it has little effect on β_2 receptors.**

Isoproterenol

- **Very potent β receptor agonist with little effect on α receptors.**
- **Has positive inotropic and chronotropic actions and is a potent vasodilator → increases cardiac output and systolic pressure and reduces diastolic pressure.**

Dopamine

- **Is the immediate precursor of norepinephrine.**
- **Activates D_1 receptors and produce vasodilation, which is specially clinically important in renal vascular bed → increase renal blood flow.**
- **Activation of presynaptic D_2 receptors suppresses norepinephrine release.**

Dopamine

- **Activates β_1 receptors in the heart.**
- **At high concentration, it activates vascular α receptors leading to vasoconstriction including the renal vascular bed.**

Fenoldopam

- **Is a selective D_1 receptor agonist causing peripheral vasodilation in some vascular bed.**
- **Very useful intravenously in treating severe hypertension.**

Phenylephrine

- **Is a relatively pure α agonist.**
- **It is not inactivated by COMT, thus it 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 and midodrine are similar to phenyephrine.**

Ephedrine

- **The first orally active sympathomimetic drug.**
- **Found in various plants, *Ephedra sinica* known in China for > 2000 years as ma huang.**
- **Have higher bioavailability and longer duration of action than catecholamines.**

Ephedrine

- **It stimulates all adrenoceptors and crosses the BBB and causes CNS stimulation.**
- **Releases catecholamines.**
- **Tolerance develops.**

Dobutamine

- **Is a selective β_1 agonist.**
- **It increases cardiac output (positive inotropic action).**
- **It is available as a mixture of isomers:**

1. **The (+) isomer is a potent β_1 agonist and an α_1 antagonist.**
2. **The (-) isomer is an α_1 agonist.**

- **Long-term use leads to tolerance of action.**

β_2-Selective Agents

- **Important in treatment of bronchial asthma (salbutamol, terbutaline, salmetrol, metaproterenol).**
- **Uterine relaxation in premature labor (Ritodrine).**

Tyramine

- **Is a by-product of tyrosine metabolism.**
- **Found in high concentration in fermented food such as cheese.**
- **It is readily metabolized by MAO in the liver, and is inactive when taken orally.**

Tyramine

- **If used parenterally it produces indirect sympathomimetic action by releasing catecholamines from sympathetic nerve terminals → hypertension.**
- **Patients taking MAO inhibitors should avoid tyramine-rich food (cheese, wine, chicken liver) to avoid hypertensive crisis.**

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Therapeutic Uses:

1. **Anaphylaxis: epinephrine is the physiologic antidote of histamine.**
2. **Decongestion of nose in common cold (α agonists).**
3. **Hypotensive states (α agonists).**
4. **Cardiogenic shock and heart failure (dopamine, dobutamine).**
5. **Bronchial asthma (β_2-agonists)**

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6. **Mixed with local anesthetics to reduce their absorption from site of application, thus reducing their toxicity and prolonging their action.**
7. **Mydriatic and conjunctival decongestion (phenylephrine).**
8. **Glaucoma (α_2 agonists - apraclonidine and brimonidine).**

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9. Hypertension (α_2 agonists - clonidine, methyldopa).
10. Suppression of premature labor (β_2-agonists – ritodrine, terbutaline).

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Adverse Effects:

- **Are usually extension of pharmacologic effects on CVS &CNS:**

1. **Marked elevation of blood pressure, increased cardiac work, ischemia and arrhythmias.**
2. **Restlessness, tremor, insomnia, anorexia, anxiety, and paranoid states**