Sympathomimetics

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Sympathomimetics

- **Drugs that mimic the actions of epinephrine (adrenaline) or norepinephrine (noradrenaline).**
- **These neurotransmitters are 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.**

Sympathomimetics

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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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 neurons	Probably multiple
	Platelets	Aggregation
	Adrenergic and cholinergic nerve terminals	Inhibits transmitter release
	Some vascular smooth muscle	Contraction
	Fat cells	Inhibits lipolysis

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

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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	$\beta_1 = \beta_2 >>>> \alpha$
Albuterol, terbutaline, metaproterenol, ritodrine	$\beta_2 >> \beta_1 >>>> \alpha$
Dopamine agonists	
Dopamine	$D_1 = D_2 >> \beta >> \alpha$
Fenoldopam	$D_1 >> D_2$

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Pharmacodynamics:

1. Cardiovascular system:

A. Blood vessels:

- **Catecholamines are important in the regulation of peripheral vascular resistance and venous capacitance.**

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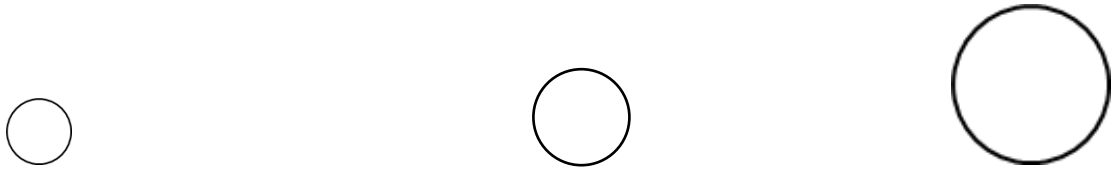
- **α-Receptors contract vascular smooth muscle, constrict arterioles and thus, increase arterial resistance.**
- **β_2-Receptors relax vascular smooth muscle, dilates arterioles and thus, reduces arterial resistance.**



Constricted **Normal** **Dilated**

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- **Skin and splanchnic vessels have predominantly α-receptors → constriction.**
- **Skeletal muscle blood vessels have predominantly β-receptors → dilation.**
- **Dopamine D_1 receptors promote vasodilation of renal resistance vessels (arterioles).**
- **Vasoconstriction reduces blood flow, while vasodilation increases blood flow.**

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B. Heart:

- **Effects on the heart are predominantly mediated through β_1 receptors.**
- **Increase pacemaker activity → increase heart rate = "positive chronotropic effect".**
- **Conduction velocity in the atrioventricular (AV) node is increased "positive dromotropic effect".**

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- **AV node refractory period is decreased.**
- **Myocardial contractility is increased = "positive inotropic effect".**
- **Sympathomimetics that stimulate β_1-receptors in the heart, increase cardiac output and thus, systolic blood pressure.**
- **Cardiac output is also increased by an increase in venous return to the heart.**

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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 → rise in diastolic blood pressure.**
- **β_2-agonists decrease peripheral vascular resistance and thus diastolic blood pressure.**

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2. 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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3. Genitourinary tract:

- **β_2-receptors mediate relaxation of the pregnant human uterus.**
- **The urinary bladder base, urethral sphincter and prostate contain α-receptors that mediate contraction and urinary retention.**
- **The thermoregulatory eccrine sweat glands are sympathetic cholinergic (muscarinic).**

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4. Exocrine glands:

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

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5. Metabolic effects:

- **β_3-receptor stimulation increases lipolysis with release of fatty acids and glycerol.**
- **α_2-receptor stimulation inhibits lipolysis.**
- **β-receptor stimulation enhances glycogenolysis in the liver leading to increased glucose release into the circulation.**
- **β_2-receptor stimulation promote uptake of potassium into cells.**

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6. Effects on endocrine function:

- **β-receptor stimulation increases insulin release by pancreas.**
- **α_2-receptor stimulation inhibits insulin release.**
- **β_1-receptor stimulation increases renin secretion.**
- **αα_2-receptor stimulation inhibits renin secretion.**

Specific Sympathomimetics

1. **Catecholamines:**

   Epinephrine, norepinephrine, dopamine, fenoldopam & dobutamine.

2. **Noncatecholamines:**

   Phenylephrine, amphetamine, methamphetamine, methylphenidate & others.

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 no significant effect on β_2 receptors.**

Dopamine

- **Activates D_1 receptors and produce vasodilation, which is specially clinically important in renal vascular bed → increase renal blood flow.**
- **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.**
- **Very useful intravenously in treating severe hypertension.**

Dobutamine

- **Is a selective β_1 agonist.**
- **It increases cardiac output (positive inotropic action).**

β_2-Selective Agents

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

Phenylephrine

- **It is a relatively pure α_1 agonist.**
- **Causes contraction of smooth muscle of blood vessels and others.**

Tyramine

- **Found in high concentration in wine, fermented food such as cheese.**
- **It is readily metabolized by MAO in the liver, and is inactive when taken orally.**
- **It produces indirect sympathomimetic action by releasing catecholamines from sympathetic nerve terminals → hypertension.**
- **Patients taking MAO inhibitors should avoid tyramine-rich food to avoid hypertensive crisis.**