Autonomic Pharmacology:
Actions of sympathetic system

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Adrenoreceptors and Dopamine Receptors

- Adrenoreceptors and dopamine receptors are members of G protein–linked families on the basis of their transmembrane signaling mechanisms.

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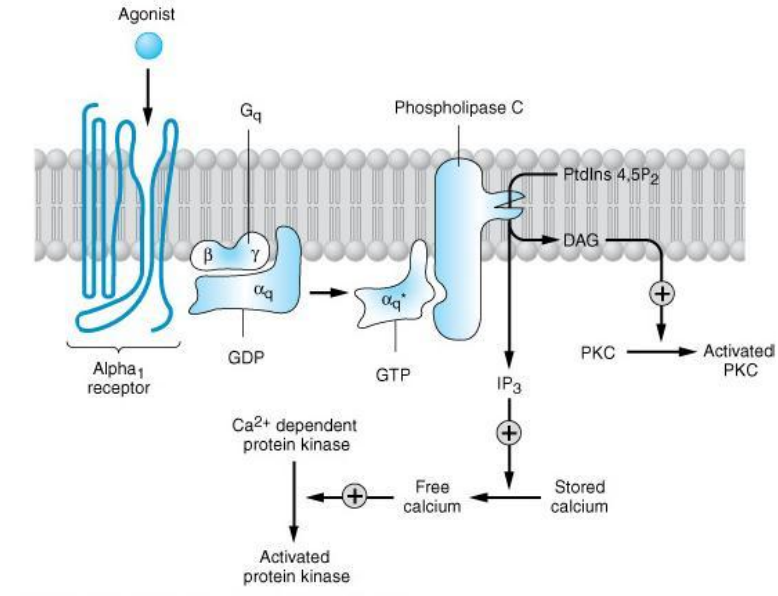

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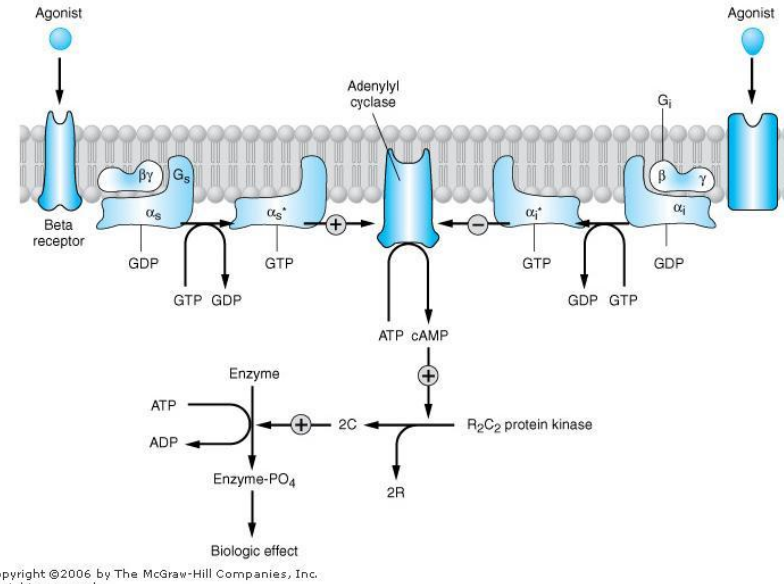

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Adrenoreceptors

Adrenoceptors		
$Alpha_1$	Postsynaptic effector cells, especially smooth muscle	Formation of IP_3 and DAG, increased intracellular calcium
$Alpha_2$	Presynaptic adrenergic nerve terminals, platelets, lipocytes, smooth muscle	Inhibition of adenylyl cyclase, decreased cAMP
$Beta_1$	Postsynaptic effector cells, especially heart, lipocytes, brain; presynaptic adrenergic and cholinergic nerve terminals, juxtaglomerular apparatus of renal tubules, ciliary body epithelium	Stimulation of adenylyl cyclase, increased cAMP
$Beta_2$	Postsynaptic effector cells, especially smooth muscle and cardiac muscle	Stimulation of adenylyl cyclase and increased cAMP. Activates cardiac G_i under some conditions.
$Beta_3$	Postsynaptic effector cells, especially lipocytes; heart	Stimulation of adenylyl cyclase and increased cAMP[1]

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Dopamine receptors

Dopamine receptors		
D_1 (DA_1), D_5	Brain; effector tissues, especially smooth muscle of the renal vascular bed	Stimulation of adenylyl cyclase and increased cAMP
D_2 (DA_2)	Brain; effector tissues, especially smooth muscle; presynaptic nerve terminals	Inhibition of adenylyl cyclase; increased potassium conductance
D_3	Brain	Inhibition of adenylyl cyclase
D_4	Brain, cardiovascular system	Inhibition of adenylyl cyclase

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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
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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Adrenoceptor Types and Subtypes

Receptor	*Agonist*	*Antagonist*	*Effects*
α_1 type	*Phenylephrine*	*Prazosin*	*↑ IP_3, DAG common to all*
α_{1A}			
α_{1B}			
α_{1D}			
α_2 type	*Clonidine*	*Yohimbine*	*↓ cAMP common to all*
α_{2A}	*Oxymetazoline*		
α_{2B}		*Prazosin*	
α_{2C}		*Prazosin*	
β type	*Isoproterenol*	*Propranolol*	*↑ cAMP common to all*
β_1	*Dobutamine*	*Betaxolol*	
β_2	*Albuterol*	*Butoxamine*	
β_3			
Dopamine type	*Dopamine*		
D_1	*Fenoldopam*		*↑ cAMP*
D_2	*Bromocriptine*		*↓ cAMP*
D_3			*↓ cAMP*
D_4		*Clozapine*	*↓ cAMP*
D_5			*↑ cAMP*

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Blood Vessels (1/2)

- Vascular smooth muscle tone is regulated by adrenoceptors; consequently, catecholamines are important in controlling peripheral vascular resistance and venous capacitance.
- Alpha receptors increase arterial resistance, whereas β_2 receptors promote smooth muscle relaxation.
- There are major differences in receptor types in the various vascular beds.
- The skin vessels have predominantly receptors and constrict in response to epinephrine and norepinephrine, as do the splanchnic vessels.

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Blood Vessels (2/2)

- Vessels in skeletal muscle may constrict or dilate depending on whether or receptors are activated.
- Consequently, the overall effects of a sympathomimetic drug on blood vessels depend on the relative activities of that drug at and receptors and the anatomic sites of the vessels affected.
- In addition, D_1 receptors promote vasodilation of renal, splanchnic, coronary, cerebral, and perhaps other resistance vessels. Activation of the D_1 receptors in the renal vasculature may play a major role in the natriuresis induced by pharmacologic administration of dopamine.

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Heart (1/2)

- Direct effects on the heart are determined largely by β_1 receptors, although β_2 and to a lesser extent receptors are also involved, especially in heart failure.
- Beta-receptor activation results in **increased calcium influx** in cardiac cells.
- Pacemaker activity, both normal (sinoatrial node) and abnormal (eg, Purkinje fibers), is increased **(positive chronotropic effect).** Conduction velocity in the atrioventricular node is increased, and the refractory period is decreased.

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Heart (2/2)

- Intrinsic contractility is increased **(positive inotropic effect),** and relaxation is accelerated.
- In the presence of normal reflex activity, the direct effects on heart rate may be dominated by a reflex response to blood pressure changes.
- Physiologic stimulation of the heart by catecholamines tends to increase coronary blood flow.

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Blood pressure (1/2)

- The effects of sympathomimetic drugs on blood pressure can be explained on the basis of their effects on the heart, the peripheral vascular resistance, and the venous return.
- A relatively pure agonist such as phenylephrine increases peripheral arterial resistance and decreases venous capacitance. The enhanced arterial resistance usually leads to a dose-dependent rise in blood pressure.

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Blood pressure (2/2)

- The blood pressure response to a pure β-adrenoceptor agonist is quite different. Stimulation of receptors in the heart increases cardiac output.
- A relatively pure agonist such as isoproterenol also decreases peripheral resistance by activating β_2 receptors, leading to vasodilation in certain vascular beds.
- The net effect is to maintain or slightly increase systolic pressure while permitting a fall in diastolic pressure owing to enhanced diastolic runoff.

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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	$\beta_1 > \beta_2 >>>> \alpha$
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	$D_1 >> D_2$

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Cardiovascular Responses to Sympathomimetic Amines

	Phenylephrine	Epinephrine	Isoproterenol
Vascular resistance (tone)			
Cutaneous, mucous membranes (α)	↑↑	↑↑	0
Skeletal muscle (β_2, α)	↑	↑or ↓	↓↓
Renal α, D_1)	↑	↑	↓
Splanchnic (α, β)	↑↑	↑or ↓[1]	↓
Total peripheral resistance	↑↑↑	↑or ↓[1]	↓↓
Venous tone (α,β)	↑	↑	↓
Cardiac			
Contractility (β_1)	0 or ↑	↑↑↑	↑↑↑
Heart rate (predominantly β_1)	↓↓ (vagal reflex)	↑or ↓	↑↑↑
Stroke volume	0, ↓, ↑	↑	↑
Cardiac output	↓	↑	↑↑
Blood pressure			
Mean	↑↑	↑	↓
Diastolic	↑↑	↑or ↓[1]	↓↓
Systolic	↑↑	↑↑	0 or ↓
Pulse pressure	0	↑↑	↑↑

[1]Small doses decrease, large doses increase.

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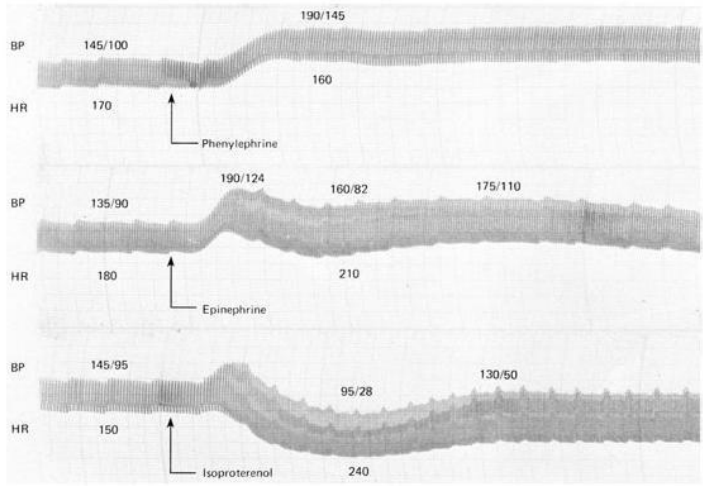

Effects of an α-selective (phenylephrine), β-selective (isoproterenol), and nonselective (epinephrine) sympathomimetic, given as an intravenous bolus injection to a dog. (BP, blood pressure; HR, heart rate.) Reflexes are blunted but not eliminated in this anesthetized animal.

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Eye

- The radial pupillary dilator muscle of the iris contains α receptors; activation by drugs such as phenylephrine causes mydriasis
- Alpha stimulants also have important effects on intraocular pressure by increasing the outflow of aqueous humor from the eye and reduce intraocular pressure.
- In contrast, agonists have little effect, but *antagonists* decrease the production of aqueous humor. These effects are important in the treatment of glaucoma, a leading cause of blindness.
- Beta stimulants relax the ciliary muscle to a minor degree, causing an insignificant decrease in accommodation.
- In addition, adrenergic drugs may directly protect neuronal cells in the retina.

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Respiratory Tract

- Bronchial smooth muscle contains β_2 receptors that cause relaxation. Activation of these receptors results in bronchodilation.
- The blood vessels of the upper respiratory tract mucosa contain α receptors; the decongestant action of adrenoceptor stimulants is clinically useful.

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Gastrointestinal Tract

- Relaxation of gastrointestinal smooth muscle can be brought about by both α- and β-stimulant agents.
- Beta receptors appear to be located directly on the smooth muscle cells and mediate relaxation via hyperpolarization and decreased spike activity in these cells. Alpha stimulants, especially α_2-selective agonists, decrease muscle activity *indirectly* by presynaptically reducing the release of acetylcholine and possibly other stimulants within the enteric nervous system.
- The α-receptor-mediated response is probably of greater pharmacologic significance than the β-stimulant response.
- Alpha$_2$ receptors may also decrease salt and water flux into the lumen of the intestine.

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Genitourinary Tract (1/2)

- The human uterus contains and β_2 receptors. The fact that the receptors mediate relaxation may be clinically useful in pregnancy.
- The bladder base, urethral sphincter, and prostate contain α receptors that mediate contraction and therefore promote urinary continence. The specific subtype of α_1 receptor involved in mediating constriction of the bladder base and prostate is uncertain, but α_{1A} receptors probably play an important role. The β_2 receptors of the bladder wall mediate relaxation.

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Genitourinary Tract (2/2)

- Ejaculation depends on normal α-receptor (and possibly purinergic receptor) activation in the ductus deferens, seminal vesicles, and prostate.
- The detumescence of erectile tissue that normally follows ejaculation is also brought about by norepinephrine (and possibly neuropeptide Y) released from sympathetic nerves.

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Exocrine Glands

- The salivary glands contain adrenoceptors that regulate the secretion of amylase and water.
- The apocrine sweat glands, located on the palms of the hands and a few other areas, respond to adrenoceptor stimulants with increased sweat production. These are the apocrine nonthermoregulatory glands usually associated with psychologic stress.

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Metabolic Effects (1/2)

- Sympathomimetic drugs have important effects on intermediary metabolism. Activation of adrenoceptors in fat cells leads to increased lipolysis with enhanced release of free fatty acids and glycerol into the blood. $Beta_3$ adrenoceptors play a role in mediating this response.
- Sympathomimetic drugs enhance glycogenolysis in the liver, which leads to increased glucose release into the circulation.
- Catecholamines in high concentration may also cause metabolic acidosis.

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Metabolic Effects (1/2)

- Activation of β_2 adrenoceptors by endogenous epinephrine or by sympathomimetic drugs promotes the uptake of potassium 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.
- Beta receptors and α_2 receptors that are expressed in pancreatic islets tend to increase and decrease, respectively, insulin secretion, although the major regulator of insulin release is the plasma concentration of glucose.

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Effects on Endocrine Function

- Catecholamines are important endogenous regulators of hormone secretion from a number of glands. As mentioned above, insulin secretion is stimulated by α receptors and inhibited by β_2 receptors.
- Similarly, renin secretion is stimulated by β_1 and inhibited by α_2 receptors; indeed, β-receptor antagonist drugs may lower plasma renin and blood pressure in patients with hypertension at least in part by this mechanism.
- Adrenoceptors also modulate the secretion of parathyroid hormone, calcitonin, thyroxine, and gastrin; however, the physiologic significance of these control mechanisms is probably limited.

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Effects on Leukocytosis

- In high concentrations, epinephrine and related agents cause leukocytosis, in part by promoting demargination of white blood cells sequestered away from the general circulation.

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Effects on the Central Nervous System (1/2)

- The action of sympathomimetics on the central nervous system varies dramatically, depending on their ability to cross the blood-brain barrier. The catecholamines are almost completely excluded by this barrier, and subjective central nervous system effects are noted only at the highest rates of infusion.
- These effects have been described as ranging from "nervousness" to "a feeling of impending disaster," sensations that are undesirable. Furthermore, peripheral effects of β-adrenoceptor agonists such as tachycardia and tremor are similar to the somatic manifestations of anxiety.

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Effects on the Central Nervous System (1/2)

- In contrast, noncatecholamines with indirect actions, such as amphetamines, which readily enter the central nervous system from the circulation, produce qualitatively very different central nervous system 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 are not readily assigned to either α- or β-mediated actions and may represent enhancement of dopamine-mediated processes or other effects of these drugs in the central nervous system.

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Thank you...

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