Autonomic Pharmacology:
Sympatholytics

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Relative Selectivity of Antagonists for Adrenoceptors

	Receptor Affinity
α Antagonists	
Prazosin, terazosin, doxazosin	$\alpha_1 >>>> \alpha_2$
Phenoxybenzamine	$\alpha_1 > \alpha_2$
Phentolamine	$\alpha_1 = \alpha_2$
Rauwolscine, yohimbine, tolazoline	$\alpha_2 >> \alpha_1$
Mixed antagonists	
Labetalol, carvedilol	$\beta_1 = \beta_2 \geq \alpha_1 > \alpha_2$
β Antagonists	
Metoprololol, acebutolol, alprenolol, atenolol, betaxolol, celiprolol, esmolol	$\beta_1 >>> \beta_2$
Propranolol, carteolol, penbutolol, pindolol, timolol	$\beta_1 = \beta_2$
Butoxamine	$\beta_2 >>> \beta_1$

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Basic Pharmacology of the Alpha-Receptor Antagonist Drugs

- Alpha-receptor antagonists may be reversible or irreversible in their interaction with these receptors.
- Reversible antagonists dissociate from receptors and the block can be surmounted with sufficiently high concentrations of agonists; irreversible drugs do not dissociate and cannot be surmounted.
- Phentolamine and prazosin are examples of reversible antagonists.
- Phenoxybenzamine, an agent related to the nitrogen mustards, forms a reactive ethyleneimonium intermediate that covalently binds to α receptors, resulting in irreversible blockade.

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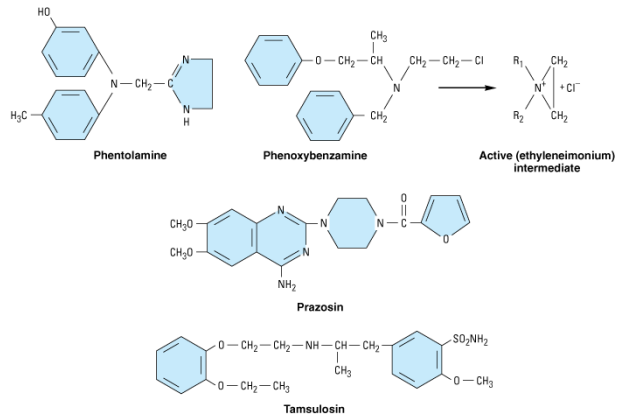
Alpha blockers



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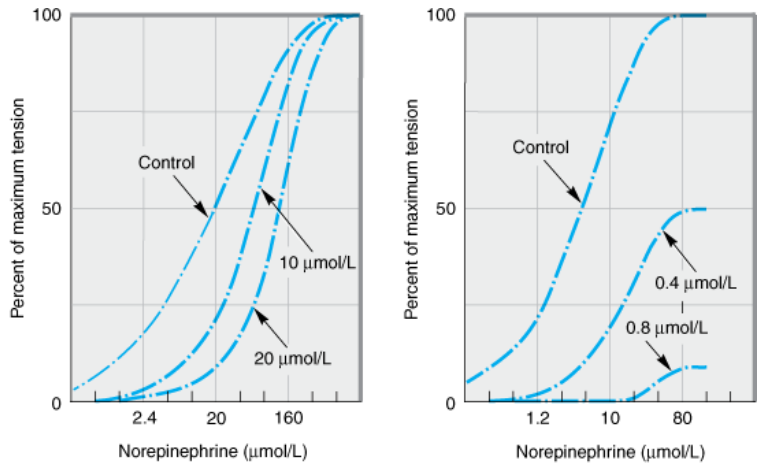
Dose-response curves to norepinephrine in the presence of two different α-adrenoceptor-blocking drugs



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Alpha1-selective blockers (1/2)

- **Prazosin** is highly selective for α_1 receptors and typically 1000-fold less potent at α_2 receptors. This may partially explain the relative absence of tachycardia seen with prazosin compared with that reported with phentolamine and phenoxybenzamine. Prazosin leads to relaxation of both arterial and venous vascular smooth muscle, as well as smooth muscle in the prostate, due to blockade of α_1 receptors.
- **Terazosin** is another reversible α_1-selective antagonist that is effective in hypertension; it is also approved for use in men with urinary symptoms due to benign prostatic hyperplasia (BPH).

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Alpha1-selective blockers (2/2)

- **Doxazosin** is efficacious in the treatment of hypertension and BPH. It differs from prazosin and terazosin in having a longer half-life.
- **Tamsulosin** is a competitive a_1 antagonist with a structure quite different from that of most other α_1-receptor blockers. Tamsulosin has higher affinity for α_{1A} and α_{1D} receptors than for the α_{1B} subtype. Evidence suggests that tamsulosin has relatively greater potency in inhibiting contraction in *prostate* smooth muscle versus *vascular* smooth muscle compared with other α_1-selective antagonists.

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Indications of alpha blockers

- Pheochromocytoma
- Hypertensive Emergencies
- Chronic Hypertension
- Peripheral Vascular Disease
- Local Vasoconstrictor Excess
- Urinary Obstruction
- Erectile Dysfunction

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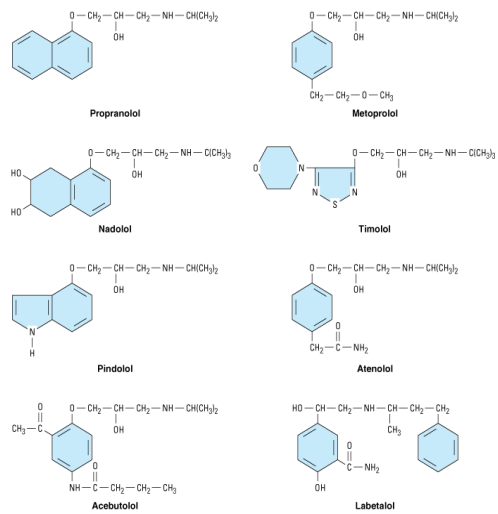
Beta blockers



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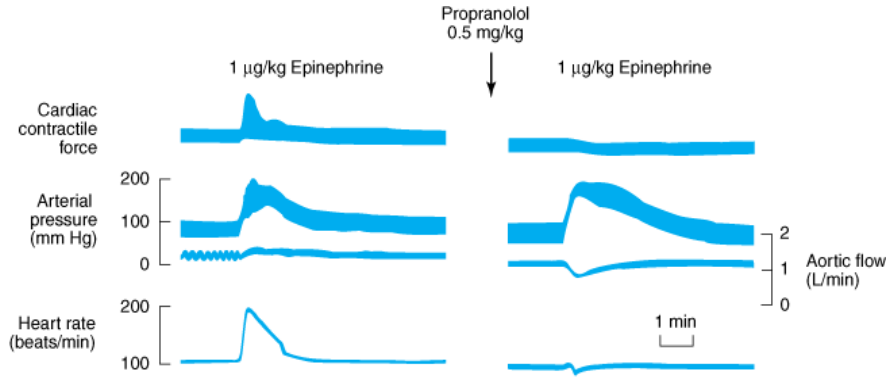
Effects of propranolol



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Properties of Several Beta-Receptor-Blocking Drugs

	Selectivity	Partial Agonist Activity	Local Anesthetic Action	Lipid Solubility	Elimination Half-Life	Approximate Bioavailability
Acebutolol	β_1	Yes	Yes	Low	3–4 hours	50
Atenolol	β_1	No	No	Low	6–9 hours	40
Betaxolol	β_1	No	Slight	Low	14–22 hours	90
Bisoprolol	β_1	No	No	Low	9–12 hours	80
Carteolol	None	Yes	No	Low	6 hours	85
Carvedilol[1]	None	No	No	High	7–10 hours	25–35
Celiprolol	β_1	Yes	No	Low	4–5 hours	70
Esmolol	β_1	No	No	Low	10 minutes	0
Labetalol[1]	None	Yes	Yes	Moderate	5 hours	30
Metoprolol	β_1	No	Yes	Moderate	3–4 hours	50
Nadolol	None	No	No	Low	14–24 hours	33
Penbutolol	None	Yes	No	High	5 hours	>90
Pindolol	None	Yes	Yes	Moderate	3–4 hours	90
Propranolol	None	No	Yes	High	3.5–6 hours	30[2]
Sotalol	None	No	No	Low	12 hours	90
Timolol	None	No	No	Moderate	4–5 hours	50

[1]Carvedilol and labetalol also cause α_1 adrenoceptor blockade.

[2]Bioavailability is dose-dependent.

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Indications of beta blockers

- Angina pectoris, myocardial infarction, hypertension, arrhythmia (systemic applications)
- Congestive heart failure and hypertrophic obstructive cardiomyopathy (bisoprolol, carvedilol, metoprolol)
- Glaucoma (timolol, betaksolol, karteolol, levobunolol, metipranolol)
- Anxiety, excitement
- Tremor (propranolol)
- Hyperthyroidism (propranolol)
- Migraine prophylaxis (propranolol, atenolol)
- Prophylaxis of hemorrhage in patients with portal hypertension (nadolol)

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Contrindications of beta blockers

- Asthma
- Cardiogenic shock
- Severe unstable decompensated heart failure
- Second or third degree heart block
- Hypoglycemia
- Severe hemorrhage
- Metabolic acidosis

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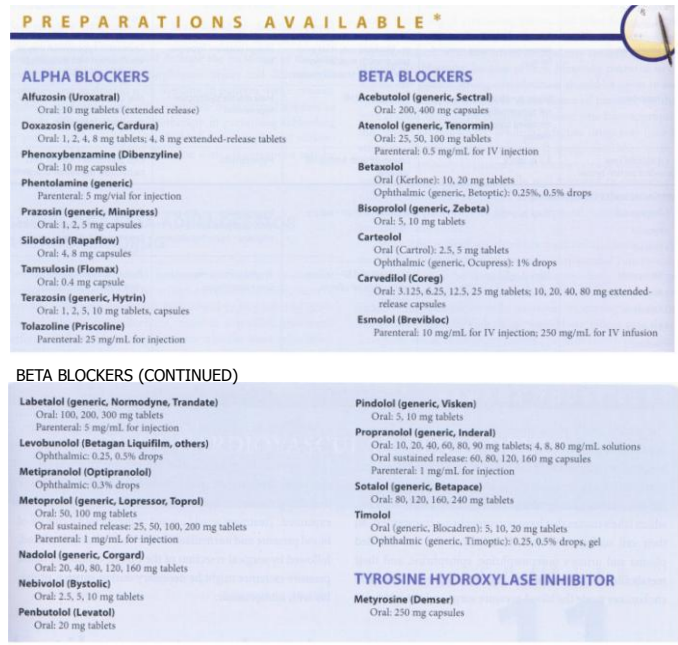

PREPARATIONS AVAILABLE*

ALPHA BLOCKERS

Alfuzosin (Uroxatral)
Oral: 10 mg tablets (extended release)

Doxazosin (generic, Cardura)
Oral: 1, 2, 4, 8 mg tablets; 4, 8 mg extended-release tablets

Phenoxybenzamine (Dibenzyline)
Oral: 10 mg capsules

Phentolamine (generic)
Parenteral: 5 mg/vial for injection

Prazosin (generic, Minipress)
Oral: 1, 2, 5 mg capsules

Silodosin (Rapaflow)
Oral: 4, 8 mg capsules

Tamsulosin (Flomax)
Oral: 0.4 mg capsule

Terazosin (generic, Hytrin)
Oral: 1, 2, 5, 10 mg tablets, capsules

Tolazoline (Priscoline)
Parenteral: 25 mg/mL for injection

BETA BLOCKERS

Acebutolol (generic, Sectral)
Oral: 200, 400 mg capsules

Atenolol (generic, Tenormin)
Oral: 25, 50, 100 mg tablets
Parenteral: 0.5 mg/mL for IV injection

Betaxolol
Oral (Kerlone): 10, 20 mg tablets
Ophthalmic (generic, Betoptic): 0.25%, 0.5% drops

Bisoprolol (generic, Zebeta)
Oral: 5, 10 mg tablets

Carteolol
Oral (Cartrol): 2.5, 5 mg tablets
Ophthalmic (generic, Ocupress): 1% drops

Carvedilol (Coreg)
Oral: 3.125, 6.25, 12.5, 25 mg tablets; 10, 20, 40, 80 mg extended-release capsules

Esmolol (Brevibloc)
Parenteral: 10 mg/mL for IV injection; 250 mg/mL for IV infusion

BETA BLOCKERS (CONTINUED)

Labetalol (generic, Normodyne, Trandate)
Oral: 100, 200, 300 mg tablets
Parenteral: 5 mg/mL for injection

Levobunolol (Betagan Liquifilm, others)
Ophthalmic: 0.25, 0.5% drops

Metipranolol (Optipranolol)
Ophthalmic: 0.3% drops

Metoprolol (generic, Lopressor, Toprol)
Oral: 50, 100 mg tablets
Oral sustained release: 25, 50, 100, 200 mg tablets
Parenteral: 1 mg/mL for injection

Nadolol (generic, Corgard)
Oral: 20, 40, 80, 120, 160 mg tablets

Nebivolol (Bystolic)
Oral: 2.5, 5, 10 mg tablets

Penbutolol (Levatol)
Oral: 20 mg tablets

Pindolol (generic, Visken)
Oral: 5, 10 mg tablets

Propranolol (generic, Inderal)
Oral: 10, 20, 40, 60, 80, 90 mg tablets; 4, 8, 80 mg/mL solutions
Oral sustained release: 60, 80, 120, 160 mg capsules
Parenteral: 1 mg/mL for injection

Sotalol (generic, Betapace)
Oral: 80, 120, 160, 240 mg tablets

Timolol
Oral (generic, Blocadren): 5, 10, 20 mg tablets
Ophthalmic (generic, Timoptic): 0.25, 0.5% drops, gel

TYROSINE HYDROXYLASE INHIBITOR

Metyrosine (Demser)
Oral: 250 mg capsules

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Study questions

1. Find additional properties of certain beta blockers (i.e. NO donor, K channel blocker…).
2. Discuss other sympathetic system inhibition possibilities other than alpha and beta receptor blockage.

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Thank you...

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