

## *Autonomic Pharmacology: Sympathomimetics*

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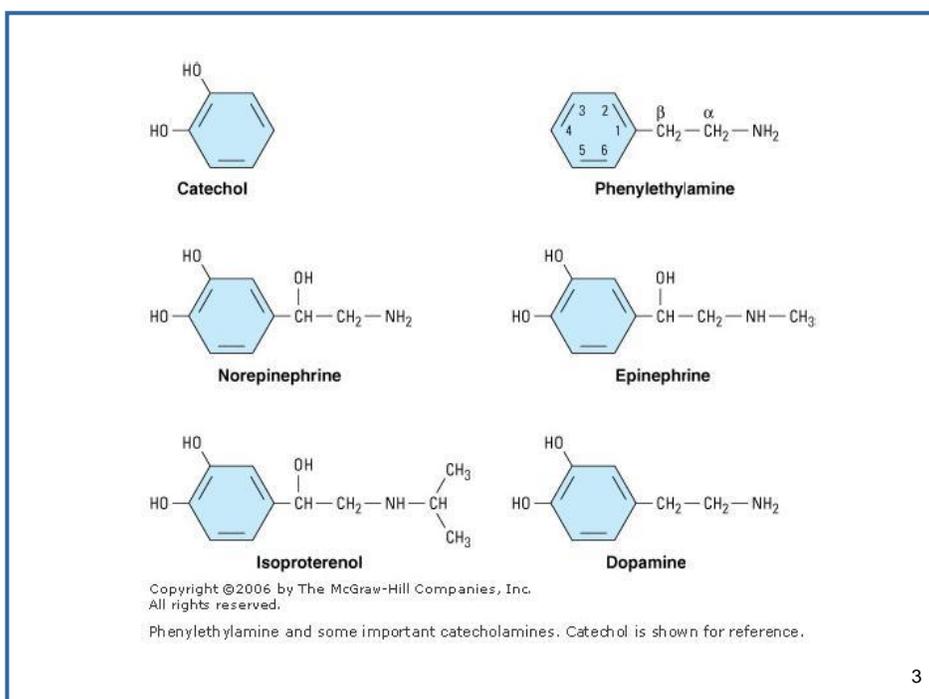
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## *Catecholamines*

- Epinephrine (adrenaline)
- Norepinephrine (levarterenol, noradrenaline)
- Isoproterenol (isoprenaline)
- Dopamine
- Fenoldopam
- Dobutamine

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## Epinephrine

- The rise in systolic blood pressure that occurs after epinephrine release or administration is caused by its positive inotropic and chronotropic actions on the heart (predominantly  $\beta_1$  receptors) and the vasoconstriction induced in many vascular beds ( $\alpha$  receptors). Epinephrine also activates  $\beta_2$  receptors in some vessels (eg, skeletal muscle vessels), leading vasodilation.
- Consequently, total peripheral resistance may actually fall, explaining the fall in diastolic pressure that is sometimes seen with epinephrine injection. Activation of  $\beta_2$  receptors in skeletal muscle contributes to blood flow increase during exercise.
- Under physiologic conditions, epinephrine functions largely as a hormone; after release from the adrenal medulla into the blood, it acts on distant cells.

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## *Norepinephrine*

- **Norepinephrine** and epinephrine have similar effects on  $\beta_1$  receptors in the heart and similar potency at receptors.
- Norepinephrine has relatively little effect on  $\beta_2$  receptors.
- Consequently, norepinephrine increases peripheral resistance and both diastolic and systolic blood pressure.
- Compensatory vagal reflexes tend to overcome the direct positive chronotropic effects of norepinephrine; however, the positive inotropic effects on the heart are maintained.

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## *Isoproterenol*

- **Isoproterenol** is a very potent  $\beta$ -receptor agonist and has little effect on  $\alpha$  receptors. The drug has positive chronotropic and inotropic actions; because isoproterenol activates  $\beta$  receptors almost exclusively, it is a potent vasodilator.
- These actions lead to a marked increase in cardiac output associated with a fall in diastolic and mean arterial pressure and a lesser decrease or a slight increase in systolic pressure.

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## *Dopamine*

- **Dopamine** activates D<sub>1</sub> receptors in several vascular beds, which leads to vasodilation. The effect this has on renal blood flow can be of clinical value.
- The activation of presynaptic D<sub>2</sub> receptors, which suppress norepinephrine release, contributes to these effects to an unknown extent.
- In addition, dopamine activates β<sub>1</sub> receptors in the heart. At low doses, peripheral resistance may decrease.
- At higher rates of infusion, dopamine activates vascular α receptors, leading to vasoconstriction, including in the renal vascular bed.
- Consequently, high rates of infusion of dopamine may mimic the actions of epinephrine.

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## *Fenoldopam*

- **Fenoldopam** is a D<sub>1</sub>-receptor agonist that selectively leads to peripheral vasodilation in some vascular beds.
- The primary indication for fenoldopam is in the intravenous treatment of severe hypertension. Continuous infusions of the drug have prompt effects on blood pressure.

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## *Dobutamine*

- **Dobutamine** is a relatively  $\beta_1$ -selective synthetic catecholamine.
- Dobutamine also activates  $\alpha_1$  receptors to some extent.

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## *Other Sympathomimetics*

- These agents are of interest because of pharmacokinetic features (oral activity, distribution to the central nervous system) or because of relative selectivity for specific receptor subclasses.

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## *Methoxamine*

- **Methoxamine** acts pharmacologically like phenylephrine, since it is predominantly a direct-acting  $\alpha_1$ -receptor agonist.
- It may cause a prolonged increase in blood pressure due to vasoconstriction; it also causes a vagally mediated bradycardia.
- Methoxamine is available for parenteral use, but clinical applications are rare and limited to hypotensive states.

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## *Midodrine*

- **Midodrine** is a prodrug that is enzymatically hydrolyzed to desglymidodrine, an  $\alpha_1$ -receptor-selective agonist. The peak concentration of desglymidodrine is achieved about 1 hour after midodrine is administered.
- The primary indication for midodrine is the treatment of postural hypotension, typically due to impaired autonomic nervous system function. Although the drug has efficacy in diminishing the fall of blood pressure when the patient is standing, it may cause hypertension when the subject is supine.

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## *Ephedrine (1/2)*

- **Ephedrine** occurs in various plants and has been used in China for over 2000 years; it was introduced into Western medicine in 1924 as the first orally active sympathomimetic drug.
- It is found in ma-huang, a popular herbal medication. Ma-huang contains multiple ephedrine-like alkaloids in addition to ephedrine. Because ephedrine is a noncatechol phenylisopropylamine, it has high bioavailability and a relatively long duration of action—hours rather than minutes.

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## *Ephedrine (2/2)*

- Ephedrine has not been extensively studied in humans in spite of its long history of use. Its ability to activate  $\beta$  receptors probably accounted for its earlier use in asthma.
- Because it gains access to the central nervous system, it is a mild stimulant. Ingestion of ephedrine alkaloids contained in ma-huang has raised important safety concerns.
- Pseudoephedrine, one of four ephedrine enantiomers, has been available over the counter as a component of many decongestant mixtures. However, the use of pseudoephedrine as a precursor in the illicit manufacture of methamphetamine has led to restrictions on its sale.

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### *Xylometazoline and oxymetazoline*

- **Xylometazoline** and **oxymetazoline** are direct  $\alpha$ -acting agonists. These drugs have been used as topical decongestants because of their ability to promote constriction of the nasal mucosa.
- When taken in large doses, oxymetazoline may cause hypotension, presumably because of a central clonidine-like effect. Oxymetazoline has significant affinity for  $\alpha_{2A}$  receptors.

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### *Amphetamine and its derivatives (1/2)*

- **Amphetamine** is a phenylisopropylamine that is important chiefly because of its use and misuse as a central nervous system stimulant. Its pharmacokinetics are similar to those of ephedrine; however, amphetamine even more readily enters the central nervous system, where it has marked stimulant effects on mood and alertness and a depressant effect on appetite.
- Its peripheral actions are mediated primarily through the release of catecholamines.

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## *Amphetamine and its derivatives (1/2)*

- **Methamphetamine** is very similar to amphetamine with an even higher ratio of central to peripheral actions.
- **Phenmetrazine** is a variant phenylisopropylamine with amphetamine-like effects. It has been promoted as an anorexiant and is also a popular drug of abuse.
- **Methylphenidate** is an amphetamine variant whose major pharmacologic effects and abuse potential is similar to those of amphetamine. It has efficacy in some children with attention deficit hyperactivity disorder.
- **Modafinil** is a new drug with both similarities to and differences from amphetamine. It has significant effects on central  $\alpha_{1B}$  receptors but in addition appears to affect GABAergic, glutaminergic, and serotonergic synapses. It can be used as CNS stimulant.

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## *Alpha<sub>2</sub>-selective agonists*

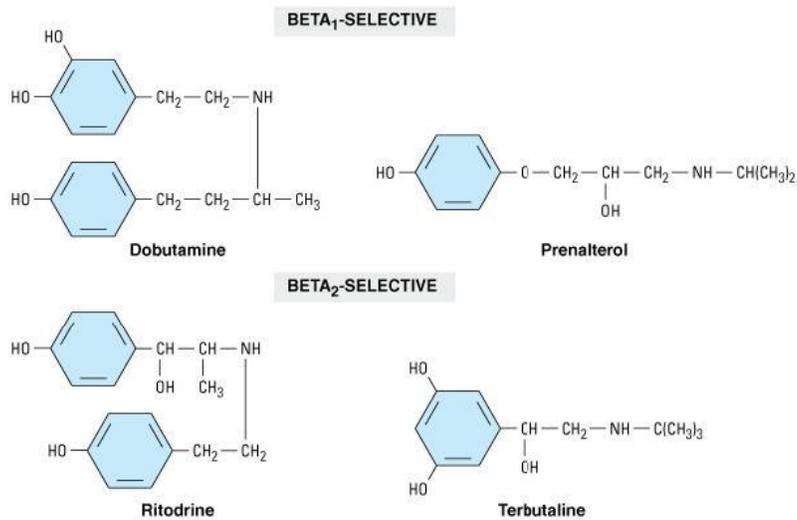
- **Alpha<sub>2</sub>-selective agonists** have an important ability to decrease blood pressure through actions in the central nervous system even though direct application to a blood vessel may cause vasoconstriction. Such drugs (eg, clonidine, methyldopa, guanfacine, guanabenz) are useful in the treatment of hypertension.
- **Dexmedetomidine** is a centrally acting  $\alpha_2$ -selective agonist that is indicated for sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting.

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## Beta-selective agonists

- **Beta-selective agonists** are very important because of the separation of  $\beta_1$  and  $\beta_2$  effects that has been achieved.
- Although this separation is incomplete, it is sufficient to reduce adverse effects in several clinical applications.

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Examples of  $\beta_1$ - and  $\beta_2$ -selective agonists.

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### ***Beta<sub>1</sub>-selective agonists***

- Beta<sub>1</sub>-selective agents include dobutamine and a partial agonist, prenalterol. Because they are less effective in activating vasodilator  $\beta_2$  receptors, they may increase cardiac output with less reflex tachycardia than occurs with nonselective agonists such as isoproterenol.
- A major limitation with these drugs—as with other direct-acting sympathomimetic agents—is that tolerance to their effects may develop with prolonged use and the likelihood that chronic cardiac stimulation in patients with heart failure may worsen long-term outcome.

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### ***Beta<sub>2</sub>-selective agonists***

- Beta<sub>2</sub>-selective agents have achieved an important place in the treatment of asthma (e.g. terbutaline).
- An additional application is to achieve uterine relaxation in premature labor (e.g. ritodrine).

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## Cocaine

- **Cocaine** is a local anesthetic with a peripheral sympathomimetic action that results from inhibition of transmitter reuptake at noradrenergic synapses.
- It readily enters the central nervous system and produces an amphetamine-like effect that is shorter lasting and more intense. The major action of cocaine in the central nervous system is to inhibit dopamine reuptake into neurons in the "pleasure centers" of the brain.
- These properties and the fact that it can be smoked, "snorted" into the nose, or injected for rapid onset of effect have made it a heavily abused drug.

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## Tyramine

- **Tyramine** is a normal by-product of tyrosine metabolism in the body and is also found in high concentrations in some fermented foods such as cheese.
- It is readily metabolized by MAO in the liver and is normally inactive when taken orally because of a very high first-pass effect, ie, low bioavailability. If administered parenterally, it has an indirect sympathomimetic action caused by the release of stored catecholamines.

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**Table 9–5. Foods Reputed to Have a High Content of Tyramine or Other Sympathomimetic Agents.**

<b>Food</b>	<b>Tyramine Content of an Average Serving</b>
Beer	(No data)
Broad beans, fava beans	Negligible (but contains dopamine)
Cheese, natural or aged	Nil to 130 mg (cheddar, Gruyère, and Stilton especially high)
Chicken liver	Nil to 9 mg
Chocolate	Negligible (but contains phenylethylamine)
Sausage, fermented (eg, salami, pepperoni, summer sausage)	Nil to 74 mg
Smoked or pickled fish (eg, pickled herring)	Nil to 198 mg
Snails	(No data)
Wine (red)	Nil to 3 mg
Yeast (eg, dietary brewer's yeast supplements)	2–68 mg

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## Indications of sympathomimetics (1/2)

- Acute allergy (adrenaline)
- Acute congestive heart failure (dobutamine, dopamine)
- Anaphylactic shock (adrenalin)
- Angioedema (adrenaline)
- Asthma and bronchospasm ( $\beta_2$ -agonists, ephedrine, pseudoephedrine)
- Diagnosis of familial Mediterranean fever (metaraminol)
- Glaucoma (adrenaline, dipivefrin, aproclonidine, brimonidine)
- Hypertension (clonidine)

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## Indications of sympathomimetics (2/2)

- Cardiac arrest (adrenaline)
- Chronic pain (clonidine)
- Local anesthetic (cocaine)
- Midriatic (phenylephrine)
- Nasal decongestant, vasoconstrictor (phenylephrine and other  $\alpha$ -agonists, ephedrine, pseudoephedrine, phnylpropanolamine)
- Opioid addiction (clonidine)
- Paroxysmal atrial tachycardia (metoxamine)
- Postural hypotension (midodrine)
- Tocolytic (terbutalin, ritodrin)

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## Contraindications of sympathomimetics

- Halothane anesthesia
- Hypertension
- Hyperthyroidism
- Congestive heart failure
- Coronary arterial disease
- Tachyarrhythmia

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PREPARATIONS AVAILABLE 1	
<p><b>Amphetamine, racemic mixture (generic)</b> (attention deficit hyperactivity disorder [ADHD], narcolepsy) Oral: 5, 10 mg tablets Oral (Adderall®) 1:1:1:1 mixtures of amphetamine sulfate, amphetamine aspartate, dextroamphetamine sulfate, and dextroamphetamine saccharate, formulated to contain a total of 5, 7.5, 10, 12.5, 15, 20, or 30 mg in tablets, or 10, 20, or 30 mg in capsules</p> <p><b>Apraclonidine (Iopidine)</b> (glaucoma) Topical: 0.5, 1%, ophthalmic solutions</p> <p><b>Armodafinil (Nuvigil)</b> (narcolepsy) Oral: 50, 150, 250 mg tablets</p> <p><b>Brimonidine (Alphagan)</b> (glaucoma) Topical: 0.15, 0.2% ophthalmic solution</p> <p><b>Dexmedetomidine (Precedex)</b> (sedation) Parenteral: 100 mcg/mL</p> <p><b>Dexamethylphenidate (Focalin)</b> (ADHD) Oral: 2.5, 5, 10 mg tablets Oral sustained release: 5, 10, 15, 20, 30 mg capsules</p> <p><b>Dextroamphetamine (generic, Dexedrine)</b> (ADHD, narcolepsy) Oral: 5, 10 mg tablets Oral sustained release: 5, 10, 15 mg capsules Oral mixtures with amphetamine: see Amphetamine (Adderall)</p> <p><b>Dobutamine (generic, Dobutrex)</b> (hypotension) Parenteral: 12.5 mg/mL in 20 mL vials for injection</p> <p><b>Dopamine (generic, Intropin)</b> (hypotension) Parenteral: 40, 80, 160 mg/mL for injection; 80, 160, 320 mg/100 mL in 5% D/W for injection</p> <p><b>Ephedrine (generic)</b> (hypotension, asthma) Oral: 25 mg capsules Parenteral: 50 mg/mL for injection</p> <p><b>Epinéphrine (generic, Adrenalin Chloride, others)</b> (anaphylaxis, hypotension, asthma) Parenteral: 1:1000 (1 mg/mL), 1:2000 (0.5 mg/mL), 1:10,000 (0.1 mg/mL), 1:100,000 (0.01 mg/mL) for injection Parenteral autoinjector (EpiPen®): 1:1000 (1 mg/mL), 1:2000 (0.5 mg/mL) Ophthalmic: 0.1, 0.5, 1, 2% drops Nasal: 0.1% drops and spray Aerosol for bronchospasm (Primatene Mist, Bronkaid Mist): 0.22 mg/spray Solution for nebulizer aerosol: 1:100</p> <p><b>Fenoldopam (Corlopam)</b> (hypertension) Parenteral: 10 mg/mL for IV infusion</p> <p><b>Hydroxyamphetamine (Paremyd)</b> (mydriatic) Ophthalmic: 1% drops (includes 0.25% tropicamide)</p>	<p><b>Isoproterenol (generic, Isuprel)</b> (bradycardia) Parenteral: 1:5000 (0.2 mg/mL), 1:50,000 (0.02 mg/mL) for injection</p> <p><b>Metaraminol (Aramine)</b> (hypotension) Parenteral: 10 mg/mL for injection</p> <p><b>Methamphetamine (Desoxyn)</b> (ADHD) Oral: 5 mg tablets</p> <p><b>Methylphenidate (generic, Ritalin, Ritalin-SR)</b> (ADHD, narcolepsy) Oral: 5, 10, 20 mg tablets Oral sustained release: 10, 18, 20, 27, 36, 54 mg tablets; 20, 30, 40 mg capsules</p> <p><b>Midodrine (ProAmatine)</b> (hypotension) Oral: 2.5, 5, 10 mg tablets</p> <p><b>Modafinil (Provigil)</b> (narcolepsy) Oral: 100, 200 mg tablets</p> <p><b>Naphazoline (generic, Privine)</b> (decongestant) Nasal: 0.05% drops and spray Ophthalmic: 0.012, 0.02, 0.03, 0.1% drops</p> <p><b>Norepinephrine (generic, Levophed)</b> (hypotension) Parenteral: 1 mg/mL for injection</p> <p><b>Oxymetazoline (generic, Afrin, Neo-Synephrine 12 Hour, Visine LR)</b> (decongestant) Nasal: 0.05% spray Ophthalmic: 0.025% drops</p> <p><b>Phenylephrine (generic, Neo-Synephrine)</b> (hypotension, decongestant) Oral: 10 mg chewable tablets Parenteral: 10 mg/mL for injection Nasal: 0.125, 0.16, 0.25, 0.3, 1% drops and spray Ophthalmic: 0.12, 2.5, 10% solution</p> <p><b>Pseudoephedrine (generic, Sudafed)</b> (decongestant) Oral: 30, 60 mg tablets; 30, 60 mg capsules; 15, 30 mg/5 mL syrup; 7.5 mg/0.8 mL drops Oral extended release: 120, 240 mg tablets, capsules</p> <p><b>Tetrahydrozoline (generic, Visine)</b> (decongestant) Nasal: 0.05, 0.1% drops Ophthalmic: 0.05% drops</p> <p><b>Tizanidine (Zanaflex)</b> (muscle relaxant) Oral: 2, 4, 6 mg capsules; 2, 4 mg tablets</p> <p><b>Xylometazoline (generic, Otrivin)</b> (decongestant) Nasal: 0.05, 0.1% drops</p>

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## Study questions

1. Make a chart showing different dosage or concentration for adrenaline for different indications.
2. Make a table giving examples of sympathomimetics for different administration routes.

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*Thank you...*