

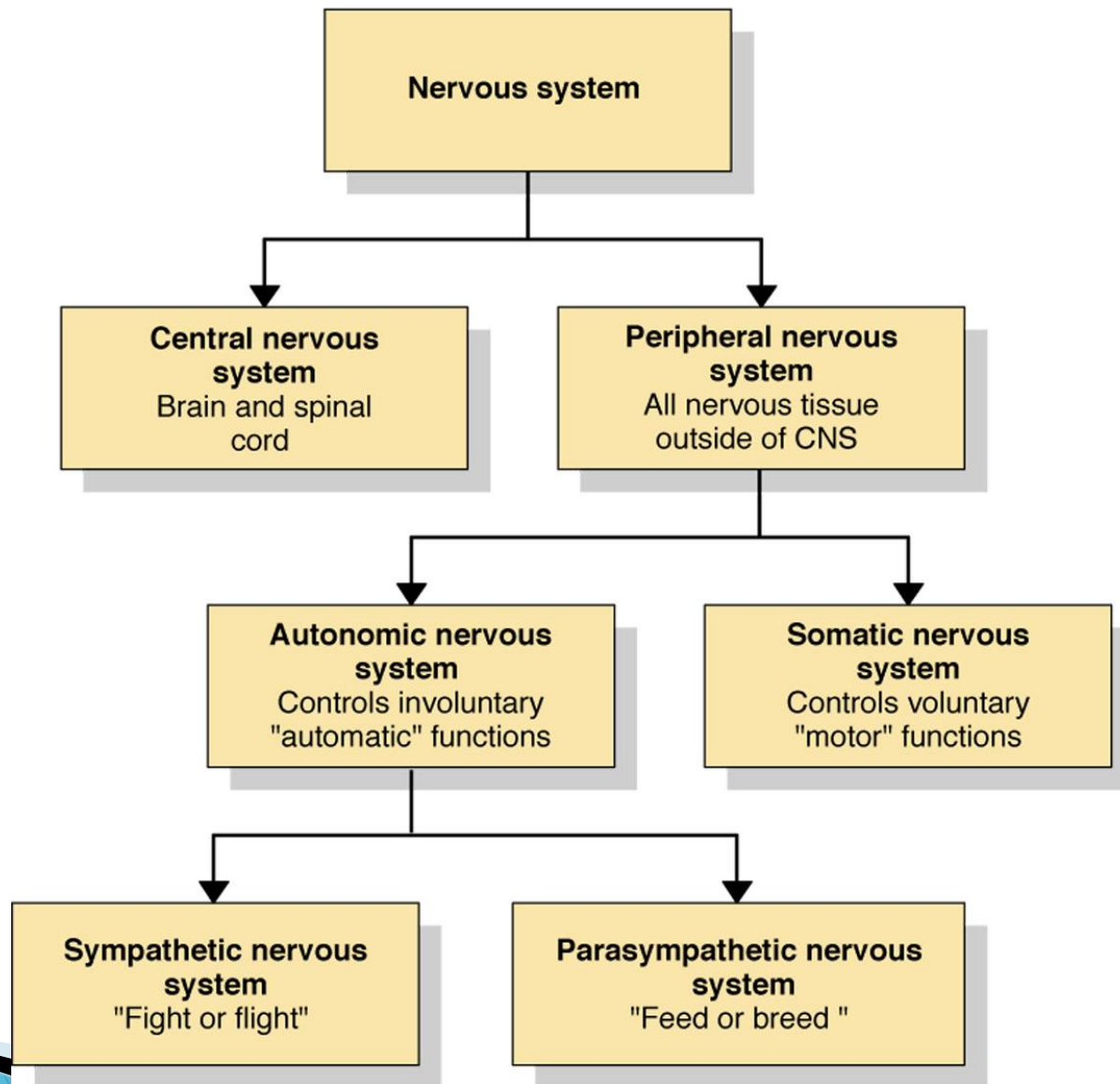
Drugs That Affect the Autonomic Nervous System

(Sympathetic Nervous System and Parasympathetic Nervous System)

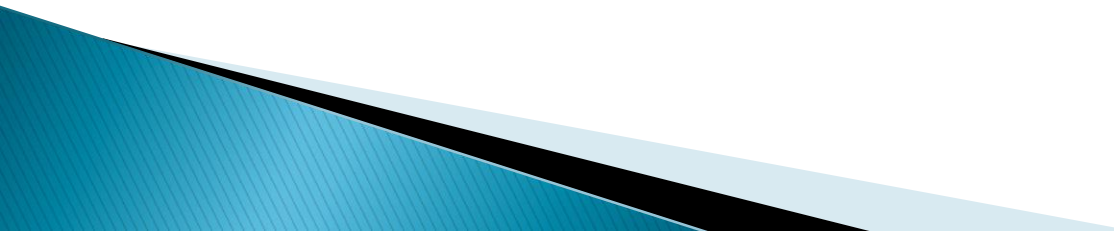
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Overview of the ANS

- ▶ Consists of the sympathetic and parasympathetic nervous system.
 - ▶ Drugs that stimulate the sympathetic nervous system are called adrenergics.
 - ▶ Adrenergics are also called adrenergic agonists or sympathomimetics because they mimic the effects of the SNS neurotransmitters norepinephrine and epinephrine (catecholamines).
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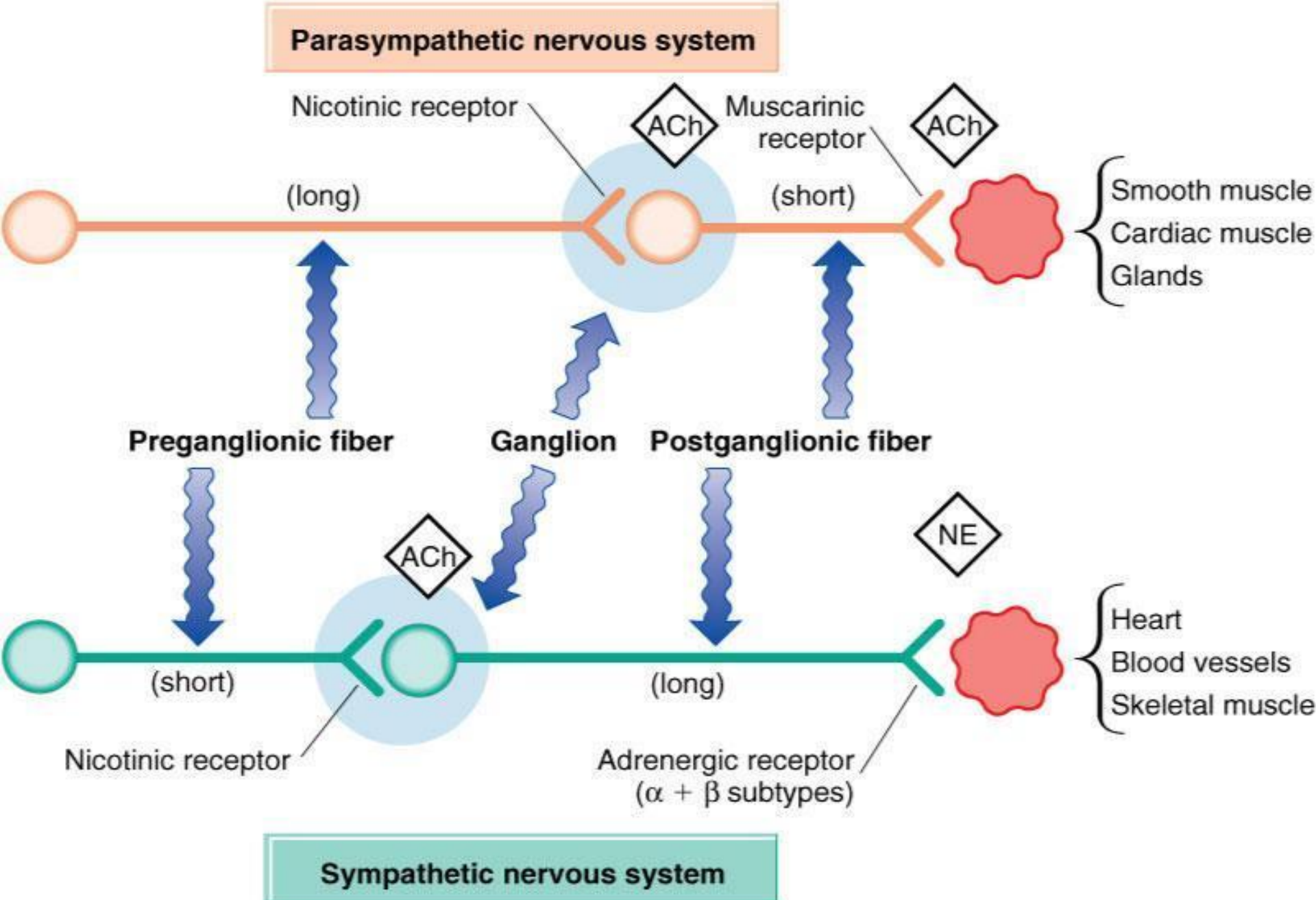


Fig. 19-1. The parasympathetic and sympathetic nervous systems and their relationship to one another. *ACh*, Acetylcholine; *NE*, norepinephrine.

Summary of sympathetic neurons and synapses

Preganglionic neurons

- ▶ Short
- ▶ Synapse with postganglionic neurons near spinal cord
- ▶ Release acetylcholine (ACH) to activate nicotinic receptors on postganglionic neurons

Postganglionic neurons


- ▶ Long
 - ▶ Synapse on the target organ
 - ▶ Release norepinephrine to activate adrenergic receptors on target organs
- 

Summary of parasympathetic neurons and synapses


Preganglionic neurons

- ▶ Long
- ▶ Synapse with postganglionic neurons at or near organ
- ▶ Release acetylcholine (ACH) to activate nicotinic receptors on postganglionic neurons

Postganglionic neurons

- ▶ Short
 - ▶ Synapse on the target organ
 - ▶ Release acetylcholine (ACH) to activate muscarinic receptors on the target organ
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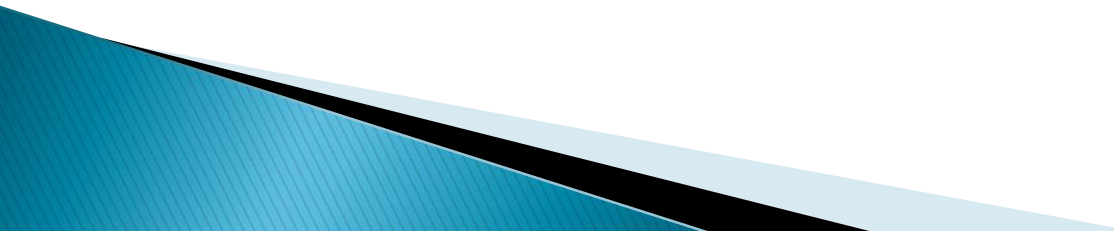
Adrenergic Receptors

- ▶ Adrenergic receptors are the sites where adrenergic drugs bind and produce their effects.
 - ▶ Adrenergic receptors are divided into alpha-adrenergic and beta-adrenergic receptors depending on whether they respond to norepinephrine or epinephrine.
 - ▶ Both alpha- and beta-adrenergic receptors have subtypes designated 1 and 2.
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Alpha Receptors

- ▶ Alpha₁-adrenergic receptors are located on the postsynaptic effector cells.
- ▶ Alpha₂-adrenergic receptors are located on the presynaptic nerve terminals.










Beta Receptors

- ▶ Both beta-adrenergic receptors are located on the postsynaptic effector cells.
 - ▶ Beta₁-adrenergic receptors are primarily located in the heart.
 - ▶ Beta₂-adrenergic receptors are primarily located in the smooth muscle of bronchioles, arterioles, and visceral organs.
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Dopaminergic Receptors

- ▶ Dopaminergic receptors are only stimulated by dopamine which causes the vessels of renal, mesenteric, coronary, and cerebral arteries to dilate and the flow of blood to increase.

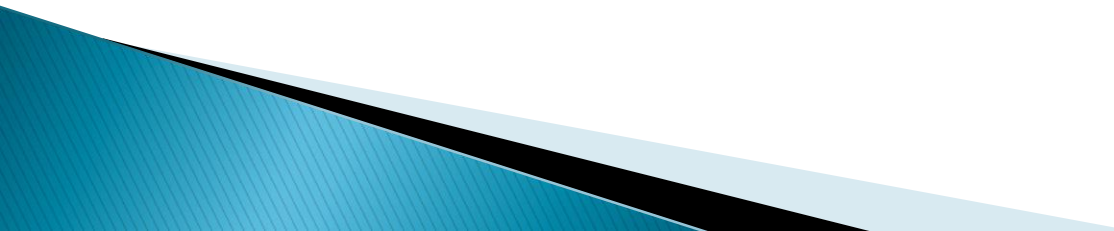
Adrenergic Receptor Specificity

Drug	α_1	α_2	β_1	β_2	Dopaminergic
Epinephrine					
Ephedrine					
Norepinephrine					
Phenylephrine					
Isoproterenol					
Dopamine					
Dobutamine					
terbutaline					

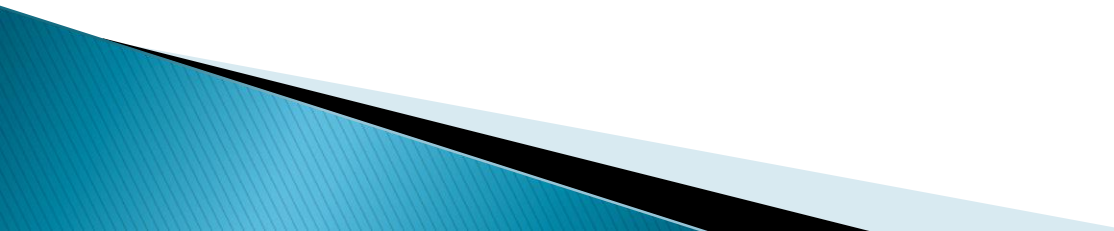
Adrenergic Blockers

- ▶ Adrenergic blockers, also called adrenergic antagonists or sympatholytics, have the opposite effect of adrenergics.
- ▶ Alpha-blockers and beta-blockers bind to the receptor sites for norepinephrine and epinephrine blocking the stimulation of the SNS.

Cholinergics

- ▶ Drugs that stimulate the parasympathetic nervous system are called cholinergics.
 - ▶ Sometimes called cholinergic agonists or parasympathomimetics, these drugs mimic the effect of acetylcholine, which is the neurotransmitter responsible for the transmission of nerve impulses to effector cells in the PSNS.
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Cholinergic Receptors

- ▶ The receptors that bind the acetylcholine and mediate its actions are called cholinergic receptors.
 - ▶ These receptors consist of nicotinic receptors and muscarinic receptors.
 - ▶ Nicotinic receptors are located in the ganglia of the PSNS and SNS and are stimulated by nicotine.
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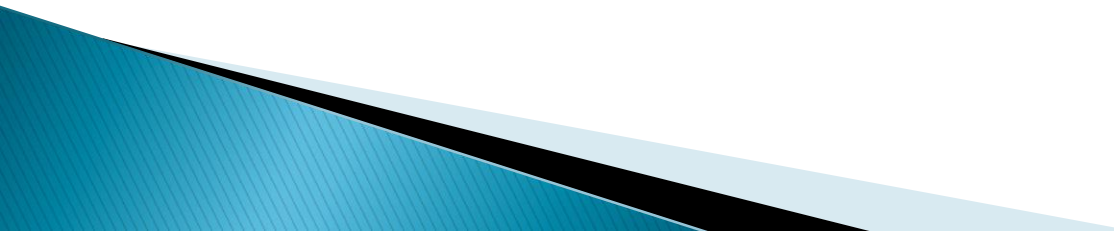
Muscarinic Receptors

- ▶ Muscarinic receptors are located postsynaptically in the smooth muscle, cardiac muscle, and glands.
- ▶ These receptors are stimulated by muscarine (found in mushrooms).

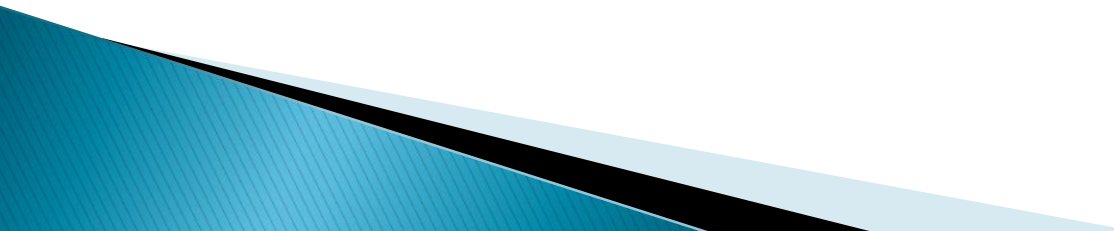
Cholinergic Drugs

- ▶ Cholinergic drugs can be direct-acting (bind to and activate cholinergic receptors) or indirect-acting (inhibit cholinesterase which is the enzyme responsible for breaking down acetylcholine).

Cholinergic Blockers

- ▶ Cholinergic blockers, anticholinergics, parasympatholytics, and antimuscarinic agents are all terms for the class of drugs that block the actions of acetylcholine in the PSNS.
 - ▶ Cholinergic blockers allow the SNS to dominate and, therefore, have many of the same effects as the adrenergics.
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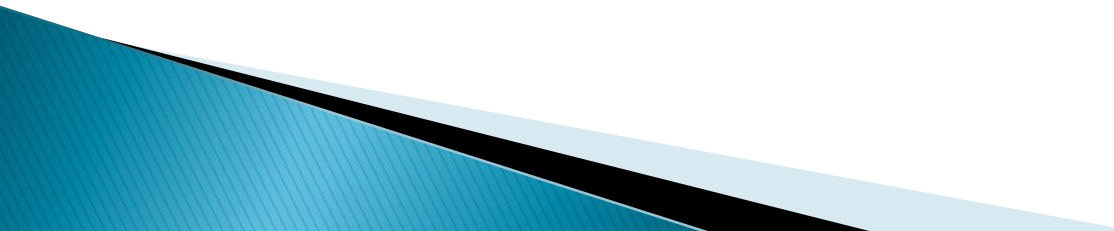
Cholinergic Blockers

- ▶ Cholinergic blockers are competitive antagonists that compete with acetylcholine for binding at the muscarinic receptors of the PSNS, inhibiting nerve transmission.
 - ▶ This effect occurs at the neuroeffector junctions of smooth muscle, cardiac muscle, and exocrine glands.
 - ▶ Have little effect at the nicotinic receptors.
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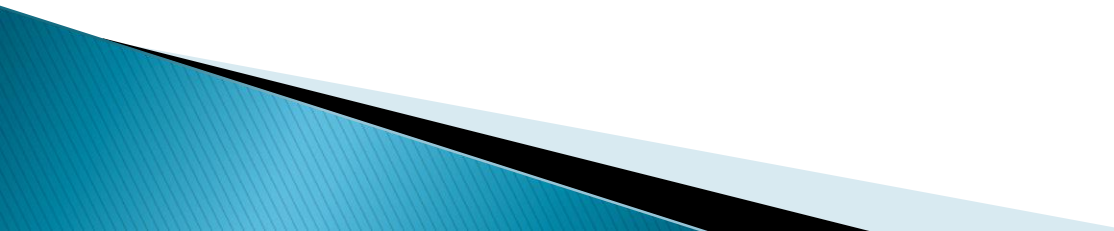
Autonomic Nervous System Medications

- ▶ Drugs Affecting the Sympathetic System:
 - Adrenergic Receptors
 - Adrenergic Agonists
 - Adrenergic Antagonists
 - Skeletal Muscle Relaxants

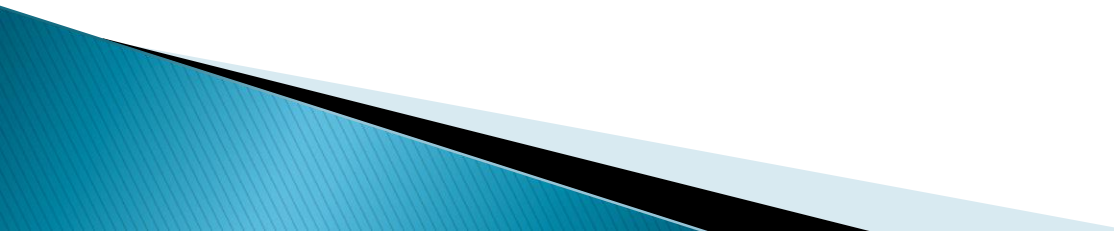
Adrenergic Drugs

- ▶ Also called sympathomimetics because they produce effects similar to those produced by the sympathetic nervous system.
 - ▶ Classified into two groups – catecholamines and noncatecholamines.
 - ▶ Also classified according to their action – direct-acting, indirect-acting, and dual-acting.
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Adrenergic Drugs

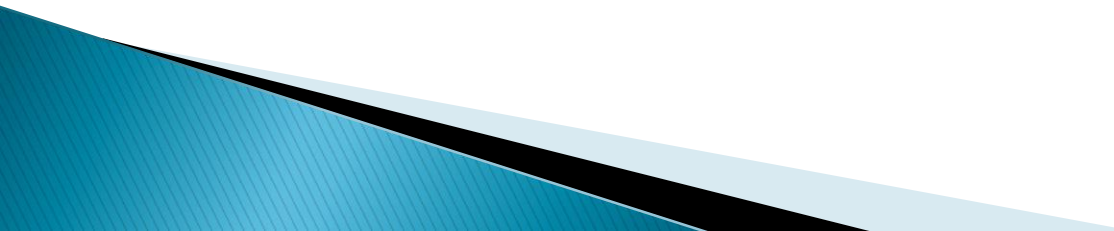
- ▶ Therapeutic uses depend on which receptors they stimulate and to what degree – alpha–adrenergic, beta–adrenergic, and dopamine receptors.
 - ▶ Most adrenergic drugs stimulate alpha and beta receptors mimicking the action of norepinephrine and epinephrine.
 - ▶ Dopaminergic drugs act primarily on SNS receptors stimulated by dopamine.
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Catecholamines

- ▶ Stimulate the nervous system, constrict peripheral blood vessels, increase heart rate, and dilate the bronchi.
 - ▶ Can be natural or synthetic and include: dobutamine, dopamine, epinephrine, norepinephrine, and isoproterenol.
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Catecholamines

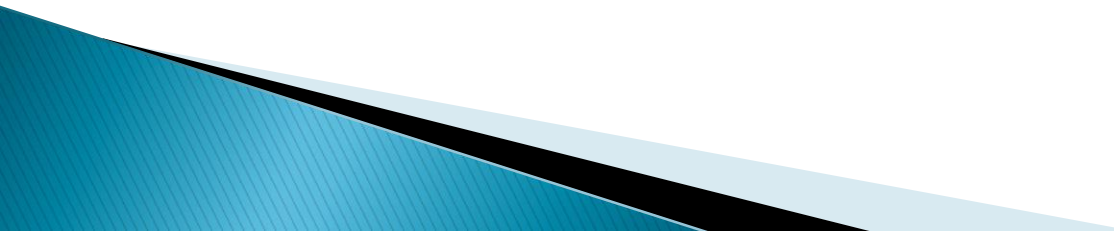
Pharmacokinetics:

- ▶ Not administered orally; when administered sublingually are absorbed rapidly through the mucous membranes; when administered SC absorption is slowed due to vasoconstriction around the injection site; when administered IM absorption is more rapid.
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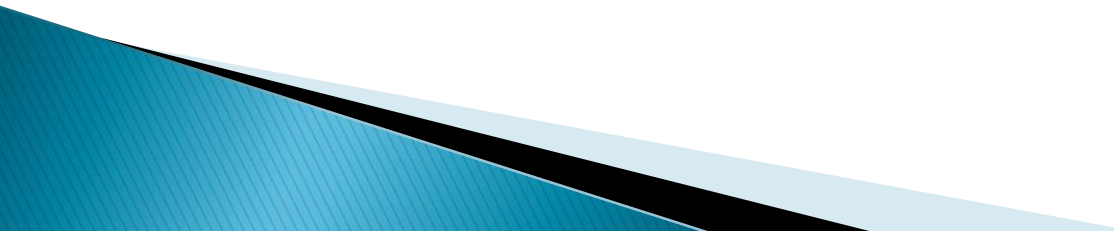
Catecholamines

- ▶ Widely distributed throughout the body; predominantly metabolized by the liver; excreted primarily in the urine.

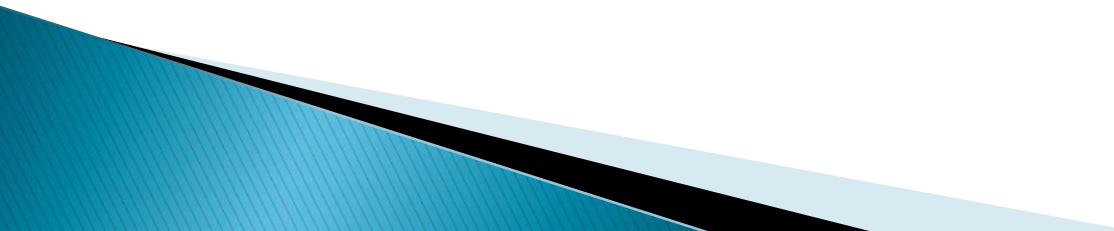
Pharmacodynamics:

- ▶ Are primarily direct-acting.
 - ▶ Activation of alpha receptors generates an excitatory response except for intestinal relaxation.
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Catecholamines

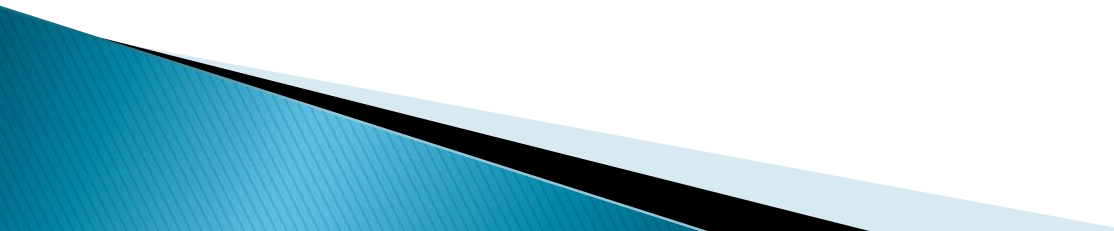
- ▶ Activation of the beta receptors mostly produces an inhibitory response except in the heart cells where norepinephrine produces excitatory effects.
 - ▶ The clinical effects of catecholamines depend on the dosage and route of administration.
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Catecholamines

- ▶ Positive inotropic effects – heart contracts more forcefully.
 - ▶ Positive chronotropic effects – heart beats faster.
 - ▶ Positive dromotropic effects – increased conduction through the AV node.
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Catecholamines

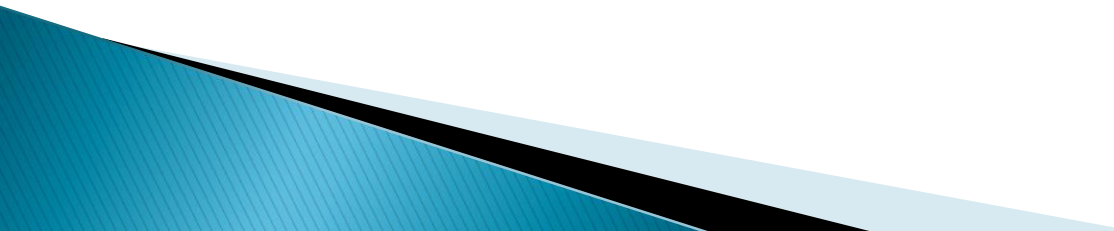
Pharmacotherapeutics:

- ▶ Use depends on the particular receptor site that is activated.
 - ▶ Norepinephrine – alpha activity.
 - ▶ Dobutamine and isoproterenol – beta activity.
 - ▶ Epinephrine – alpha and beta activity.
 - ▶ Dopamine – dopaminergic, beta, and alpha activity.
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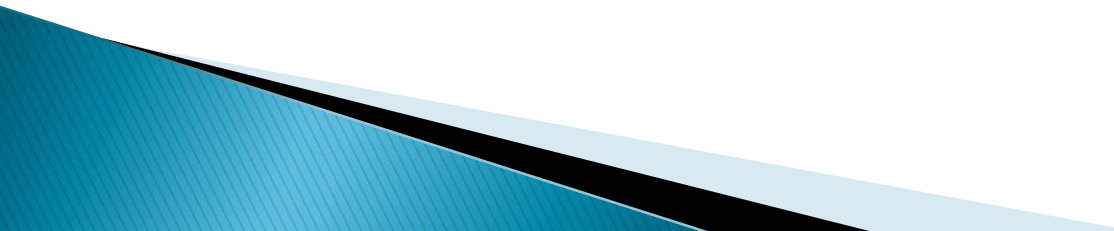
Catecholamines

- ▶ Catecholamines that stimulate alpha receptors are used to treat hypotension caused by a loss of vasomotor tone or hemorrhage.
- ▶ Catecholamines that stimulate beta₁–receptors are used to treat bradycardia, heart block, low cardiac output, paroxysmal atrial or junctional tachycardia, ventricular fibrillation, asystole, and cardiac arrest.

Catecholamines

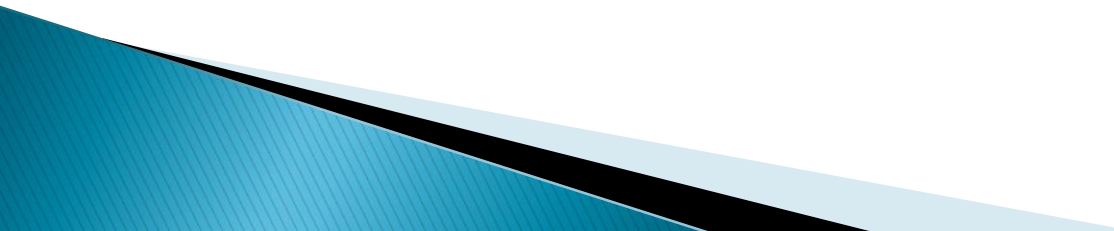
- ▶ Catecholamines that stimulate beta₂-receptors are used to treat acute and chronic bronchial asthma, emphysema, bronchitis, and acute hypersensitivity reactions to drugs.
 - ▶ Dopamine that stimulates dopaminergic receptors is used to improve blood flow to kidneys.
- 

Catecholamines

- ▶ Synthetic catecholamines have a short duration of action which can limit their therapeutic usefulness.
 - ▶ Drug interactions/adverse reactions:
 - ▶ Can be serious including hyper and hypotension, arrhythmias, seizures, and hyperglycemia.
- 

Non-catecholamines

Uses include:

- ▶ local or systemic constriction of blood vessels – phenylephrine (Neo-Synephrine).
 - ▶ nasal and eye decongestion and dilation of bronchioles – albuterol (Proventil/Ventolin).
 - ▶ smooth muscle relaxation – terbutaline sulfate (Brethine, Bricanyl).
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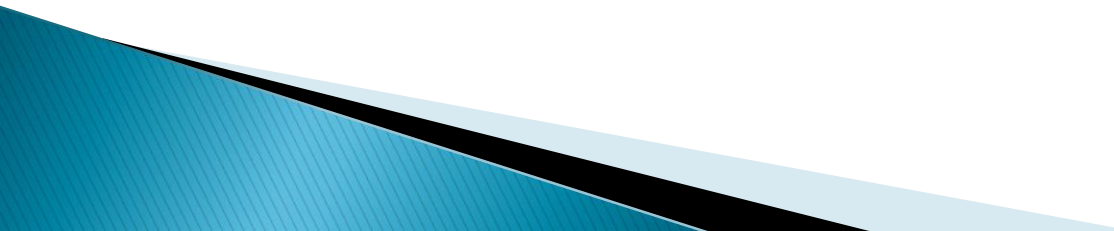
Non-catecholamines

Pharmacokinetics:

- ▶ Since the drugs have different routes of administration, absorption and distribution vary; can be administered orally; metabolized primarily by the liver; excreted primarily in the urine.

Non-catecholamines

Pharmacodynamics:

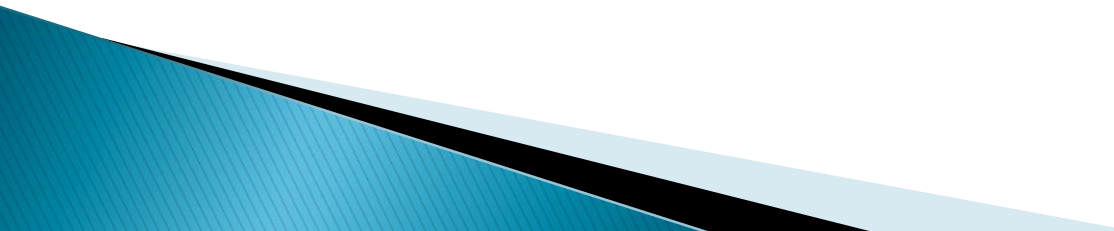
- ▶ Direct-acting noncatecholamines that stimulate alpha activity include phenylephrine (Neo-Synephrine).
 - ▶ Direct-acting noncatecholamines that stimulate beta2 activity include albuterol (Proventil/Ventolin) and terbutaline (Brethine).
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Non-catecholamines

- ▶ Indirect-acting – phenylpropanolamine (Acutrim).
- ▶ Dual-acting – ephedrine.

Non-catecholamines

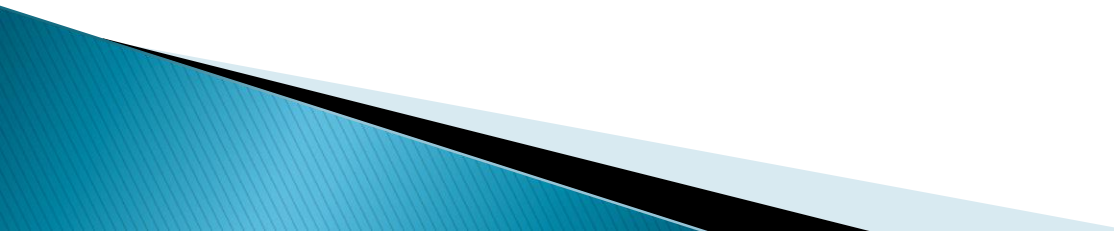
Pharmacotherapeutics:

- ▶ Stimulate the sympathetic nervous system and produce a variety of effects in the body.
 - ▶ Example – ritodrine (Yutopar) – used to stop pre-term labor.
 - ▶ Drug interactions/adverse reactions:
 - ▶ Taken with monoamine oxidase inhibitors can cause severe hypertension and death
- 

Alpha₁ Agonists

- ▶ Profound vasoconstriction
 - Increases afterload & blood pressure when given systemically
 - Decreases drug absorption & bleeding when given topically

Adrenergic Blocking Drugs

- ▶ Called sympatholytic drugs.
 - ▶ Used to disrupt SNS function by blocking impulse transmission at adrenergic receptor sites.
 - ▶ Classified according to their site of action: alpha-adrenergic blockers and beta-adrenergic blockers.
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Alpha₁ Antagonism

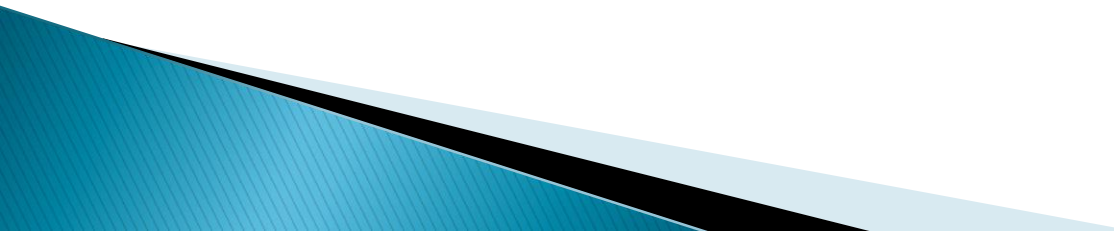
- ▶ Inhibits peripheral vasoconstriction
 - Used for hypertension
 - prazosin (Minipress[®])
 - doxazosin (Cardura[®])
 - phentolamine (Regitine[®])
 - Blocks alpha_{1&2} receptors

Alpha-Adrenergic Blockers

- ▶ Work by interrupting the actions of the catecholamines norepinephrine and epinephrine at the alpha receptors resulting in: relaxation of the smooth muscle in the blood vessels; increased dilation of blood vessels; and decreased blood pressure.
- ▶ Prototype drug – prazosin (Minipress)

Alpha-Adrenergic Blockers

Pharmacokinetics:

- ▶ The action of alpha blockers in the body isn't well understood.
 - ▶ Pharmacodynamics:
 - ▶ Block the synthesis, storage, release, and uptake of norepinephrine by neurons.
 - ▶ Antagonize epinephrine and norepinephrine at alpha receptor sites.
- 

Alpha-Adrenergic Blockers

- ▶ Do not discriminate alpha1 and alpha2 receptors.
- ▶ Occupy alpha receptor sites on the smooth muscle of blood vessels resulting in vasodilation, decreased peripheral vascular resistance, and decreased blood pressure.

Alpha-Adrenergic Blockers

- ▶ Pharmacotherapeutics:
- ▶ Used to treat: hypertension; peripheral vascular disorders, and pheochromocytoma (a catecholamine-secreting tumor causing severe hypertension).

Alpha-Adrenergic Blockers

Drug interactions/adverse reactions:

- ▶ Many drugs interact producing synergistic effects such as orthostatic hypotension, severe hypotension and vascular collapse.

Beta Antagonists (β Blockers)

- ▶ Frequently used
- ▶ Lower Blood Pressure
- ▶ Negative chronotropes & inotropes

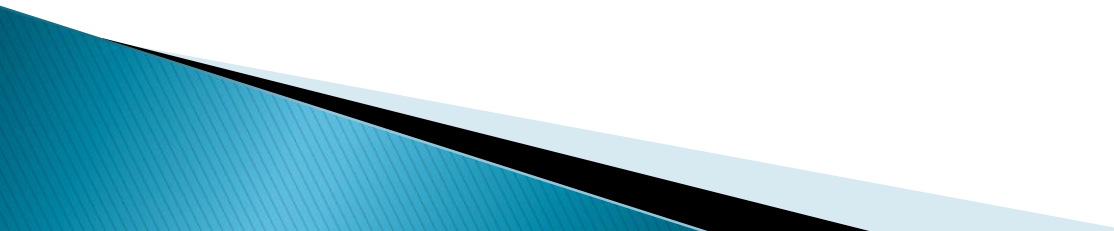
Beta₁ Selective Blockade

- atenolol (Tenormin[®])
- esmolol (Brevibloc[®])
- metoprolol (Lopressor[®])

Nonselective

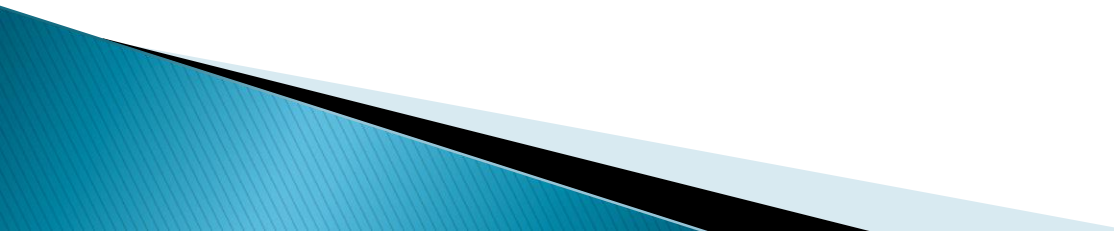
- propranolol (Inderal[®])
- labetalol (Normodyne[®], Trandate[®])
- sotalol (Betapace[®])

Beta-Adrenergic Blockers

- ▶ Prevent stimulation of the sympathetic nervous system by inhibiting the action of catecholamines at the beta-adrenergic receptors (beta-blockers).
 - ▶ Are selective or nonselective.
 - ▶ Nonselective beta-blockers affect beta1 receptor sites located mainly in the heart and beta2 receptor sites located in the bronchi, blood vessels, and uterus.
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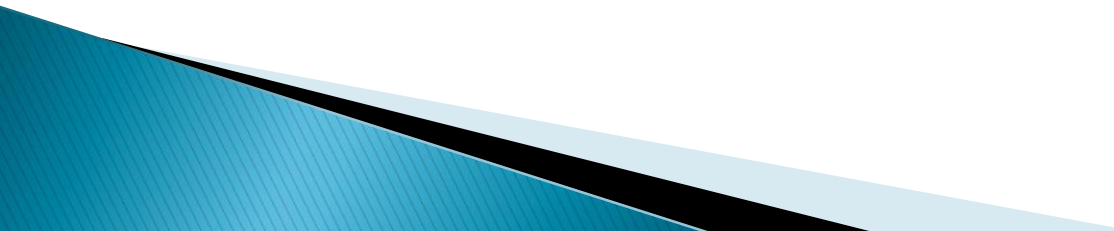
Beta-Adrenergic Blockers

Pharmacokinetics:

- ▶ Absorbed rapidly and are protein-bound; the onset of action is primarily dose and drug-dependent; distributed widely with the highest concentrations in the heart, lungs, and liver; metabolized primarily in the liver; excreted primarily in the urine.
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Beta-Adrenergic Blockers

Pharmacodynamics:

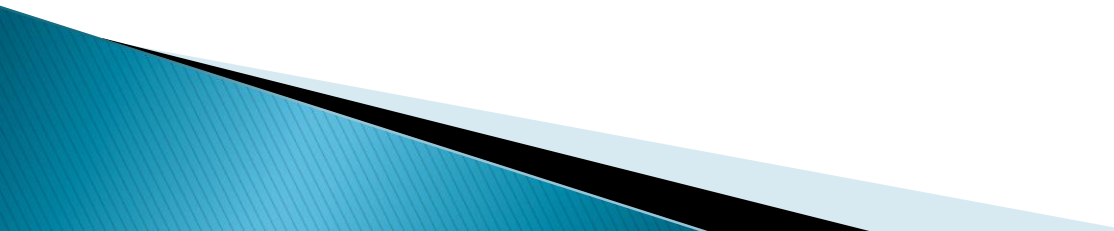
- ▶ Effect adrenergic nerve endings as well as the adrenal medulla.
 - ▶ Effects on the heart include: decreased peripheral vascular resistance; decreased blood pressure; decreased force of heart contractions; decreased oxygen consumption; slowed impulse conduction; and decreased cardiac output.
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Beta-Adrenergic Blockers

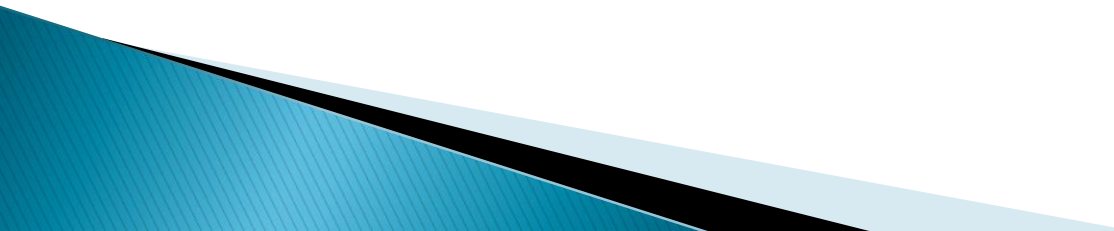
- ▶ Selective β_1 -blockers reduce stimulation of the heart (also called cardioselective beta-adrenergic blockers).
- ▶ Nonselective β_1 and β_2 -blockers not only reduce stimulation of the heart but can also cause the bronchioles of the lungs to constrict.

Beta-Adrenergic Blockers

Pharmacotherapeutics:

- ▶ Clinical usefulness is based largely upon how they affect the heart.
 - ▶ Used to treat heart attacks, angina, hypertension, hypertrophic cardiomyopathy, and supraventricular arrhythmias.
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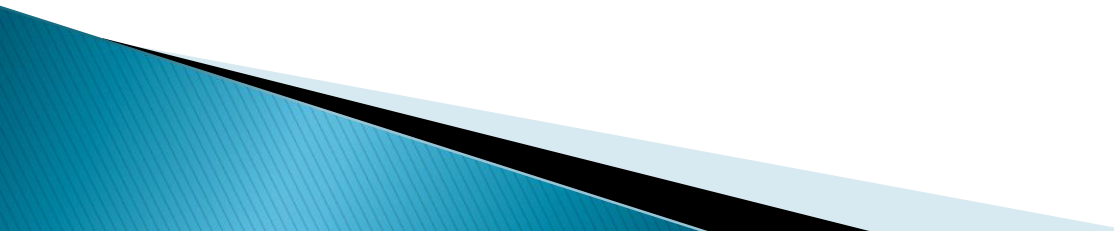
Beta-Adrenergic Blockers

- ▶ Also used to treat anxiety, cardiovascular symptoms associated with thyrotoxicosis, essential tremor, migraine headaches, open-angle glaucoma, and pheochromocytoma.
 - ▶ Drug interactions/adverse reactions:
 - ▶ Many causing cardiac and respiratory depression, arrhythmia, severe bronchospasm, and severe hypotension.
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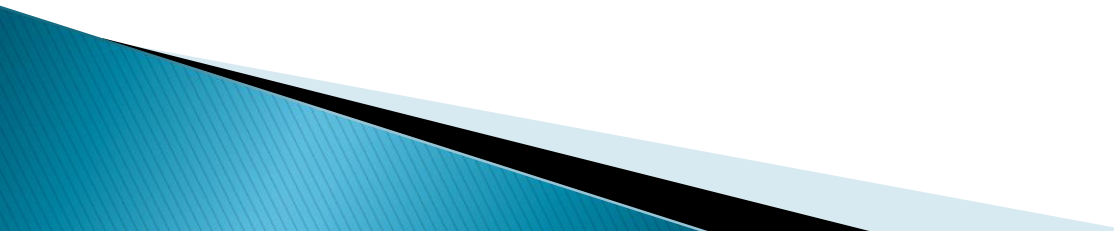
Autonomic Nervous System Medications (1 of 2)

- ▶ Drugs Affecting the Parasympathetic System:
 - Cholinergics
 - Anticholinergics
 - Ganglionic Blocking Agents
 - Neuromuscular Blocking Agents
 - Ganglionic Stimulating Agents

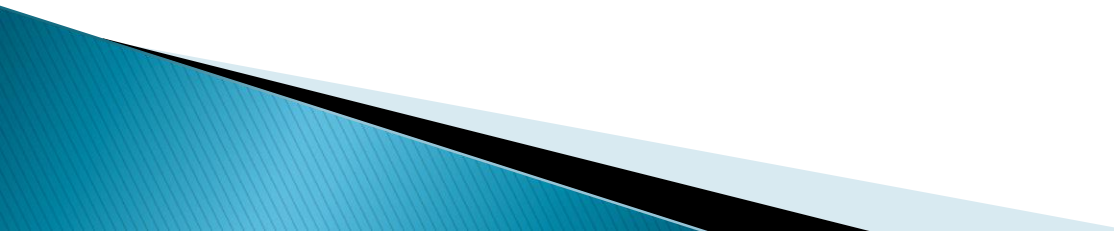
Cholinergic Drugs

- ▶ Promote the action of the neurotransmitter acetylcholine.
 - ▶ Also called parasympathomimetic drugs because they produce the effects that mimic parasympathetic nerve stimulation.
 - ▶ Two major classes of cholinergic drugs: cholinergic agonists and anticholinesterase drugs.
- 

Cholinergic Drugs

- ▶ Cholinergic agonists mimic the action of the neurotransmitter acetylcholine.
 - ▶ Anticholinesterase drugs inhibit the destruction of acetylcholine at the cholinergic receptor sites.
- 

Cholinergic Agonists

- ▶ Mimic the action of acetylcholine.
 - ▶ Include the drugs acetylcholine (rarely used), bethanechol (Urocholine), carbachol (Miostat), and pilocarpine.
 - ▶ Pharmacokinetics:
 - ▶ Administered topically (eye), orally, and subcutaneously; metabolized by cholinesterases; excreted by the kidneys.
- 

Cholinergic Agonists

Pharmacodynamics:

- ▶ Mimic the action of acetylcholine on the neurons of target organs producing: salivation, bradycardia, vasodilation, constriction of bronchioles, increased GI activity, increased tone and contraction of the bladder muscles, and constriction of pupils.

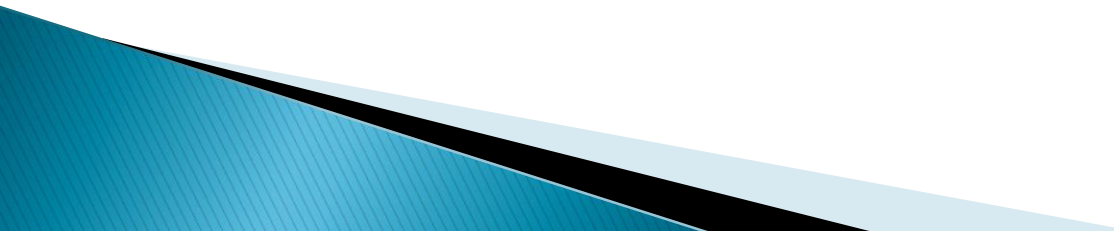
Cholinergic Agonists

Pharmacotherapeutics:

- ▶ Used to treat: atonic bladder conditions and post-operative and postpartum urinary retention; GI disorders such as post-operative abdominal distention and GI atony; reduce eye pressure in glaucoma patients and during eye surgery; and salivary hypofunction.

Cholinergic Agonists

Drug interactions/adverse reactions:

- ▶ Taken with other cholinergic drugs can increase the effects.
 - ▶ Taken with cholinergic blocking drugs can reduce the effects.
 - ▶ Can produce adverse effects in any organ innervated by the parasympathetic nerves.
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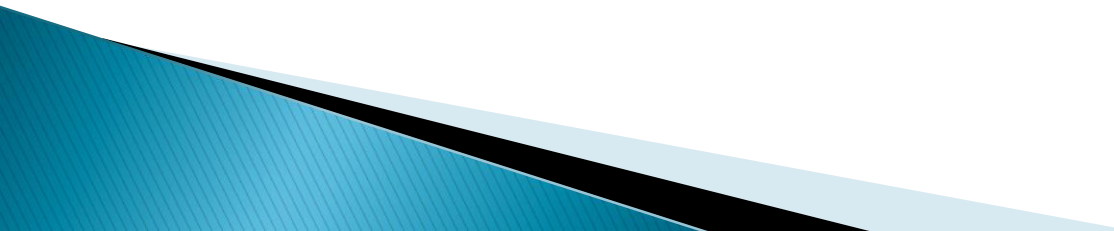
Cholinergic Agonists

*Cholinergic agents
cause SLUDGE!*

*These effects are
predictable by knowing
PNS physiology*

Salivation
Lacrimation
Urination
Defecation
Gastric motility
Emesis

Anticholinesterase Drugs

- ▶ Block the action of the enzyme acetylcholinesterase, which breaks down acetylcholine, at the cholinergic receptor sites.
 - ▶ Divided into two categories – reversible and irreversible.
 - ▶ Reversible have a short duration and include: donepezil (Aricept) and edrophonium (Tensilon).
- 

Reversible ChE Inhibitors

- ▶ neostigmine (Prostigmine[®])
 - Myasthenia Gravis at nicotinic_M receptors
 - Can reverse nondepolarizing neuromuscular blockade
- ▶ physostigmine (Antilirium[®])
 - Shorter onset of action
 - Used for iatrogenic atropine overdoses at muscarinic receptors

Anticholinesterase Drugs

- ▶ Irreversible anticholinesterase drugs have long-lasting effects.
- ▶ Used primarily as toxic insecticides and pesticides or as a nerve gas in chemical warfare.

Irreversible ChE Inhibitors

- ▶ Very rarely used clinically
- ▶ Very common in insecticides & chemical weapons
 - VX and Sarin gas
 - Cause SLUDGE dammit and paralysis
- ▶ Tx: atropine and pralidoxime (2-PAM®)
 - Anticholinergics

Anticholinesterase Drugs

Pharmacokinetics:

- ▶ Most are readily absorbed from the GI tract, SC, and mucous membranes; distribution varies among drugs; metabolized by enzymes in the plasma; excreted in the urine.

Anticholinesterase Drugs

Pharmacodynamics:

- ▶ Depending on the site, dosage, and duration of action, stimulant or depressant effects can be produced.

Anticholinesterase Drugs

Pharmacotherapeutics:

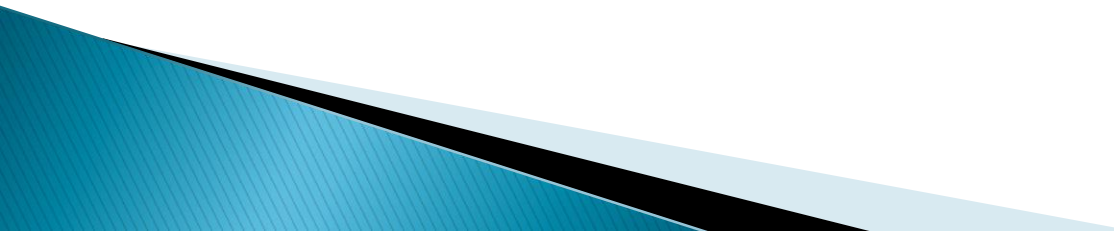
- ▶ Therapeutic uses include: reduce eye pressure; increase bladder tone; improve GI tone and peristalsis; promote muscular contraction; diagnose myasthenia gravis; an antidote to cholinergic blocking drugs; treat dementia due to Alzheimer's.

Anticholinesterase Drugs

Drug interactions/adverse reactions:

- ▶ Taken with other cholinergic drugs can increase the risk of toxicity.
- ▶ Nausea, vomiting, diarrhea, respiratory distress, and seizures.

Cholinergic Blocking Drugs

- ▶ Interrupt parasympathetic nerve impulses in the central and autonomic nervous systems.
 - ▶ Also referred to as anticholinergic drugs because they prevent acetylcholine from stimulating the muscarinic cholinergic receptors.
 - ▶ Drugs include the belladonna alkaloids– the prototype is atropine.
- 

Cholinergic Blocking Drugs

Pharmacokinetics:

- ▶ Absorbed from the eyes, GI tract, mucous membranes, and skin; when given IV atropine works immediately; distributed widely; cross the BBB; moderate protein-binding; metabolized by the liver; excreted by the kidneys.

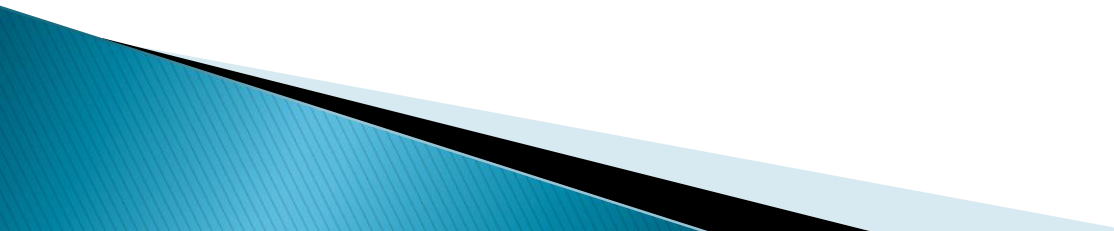
Cholinergic Blocking Drugs

Pharmacodynamics:

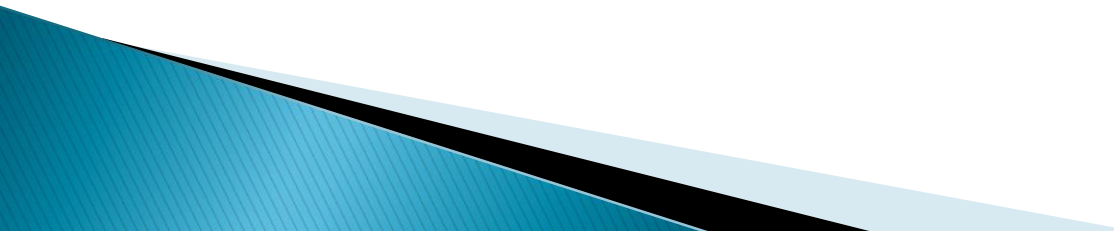
- ▶ Can produce a stimulating or depressing effects depending on the target organ.
- ▶ In the brain low drug levels stimulate and high drug levels depress.

Cholinergic Blocking Drugs

Pharmacotherapeutics:

- ▶ Often used to treat GI disorders and complications.
 - ▶ Atropine is administered pre-operative to reduce GI and respiratory secretions and prevent bradycardia caused by vagal nerve stimulation during anesthesia.
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Cholinergic Blocking Drugs

- ▶ Other uses include treatment of motion sickness, Parkinson's, bradycardia, arrhythmias, pupil dilation, and organophosphate pesticide poisoning.
 - ▶ Drug interactions/adverse reactions:
 - ▶ Many drugs increase the effects: cholinergic agonists and anticholinesterase drugs decrease the effects.
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Cholinergic Blocking Drugs

- ▶ Dry mouth, reduced bronchial secretions, increased heart rate, and decreased sweating can occur.

Anticholinergics

- ▶ Muscarinic antagonists
 - Atropine
- ▶ Ganglionic antagonists
 - block nicotinic_N receptors
 - *Turns off the ANS!*
 - trimethaphan (Arfonad®)
 - Hypertensive crisis
- ▶ Atropine Overdose
 - Dry mouth, blurred vision, anhidrosis