Drugs Acting at Synaptic and Neuroeffector Junctional Sites Autonomic and Neuromuscular Pharmacology

Subcommittee:

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Drugs acting at synaptic and neuroeffector junctional sites autonomic and neuromuscular pharmacology
Recommended Curriculum Equivalent: 1.0 hr
Introduction and History
Neuronal Drugs
BOTULINUM TOXIN COCAINE entacapone metyrosine reserpine
Learning Objectives
Physiology and pathophysiology Describe the anatomical projections of the sympathetic and parasympathetic autonomic nervous system. Describe the evidence for the development of the concept of neurotransmitters, co-transmitters and end-organ specificity. Describe homeostasis, fight-or-flight, and rest-and-repair with regard to the autonomic nervous system. Describe the central control of the autonomic nervous system. List and describe the responses of end organs to activation of each division of the autonomic nervous system. Describe the concept of dominant tone.
Mechanisms of action Explain the mechanism and drugs that block uptake of choline into cholinergic neurons List drugs that Inhibit Catechol-o-methyl transferase peripherally List drugs that block storage vesicle transport systems Describe the mechanism by which drugs Inhibit reuptake of NE into adrenergic neurons Describe the mechanism by which drugs deplete NE by interfering with synthesis
Notes Define words containing the suffixes, -ergic, -mimetic, - lytic, and –ceptive.

Clinical Pharmacology Botulinum toxin only marginally effective for prophylaxis against chronic migraine headache. Not approved for treatment of episodic migraine headache.	
Relevance	
USMLE topic Central and peripheral nervous system	**Principles of therapeutics** Botulinum toxin Drugs affecting the autonomic nervous system Treatment for substance abuse disorders Antiparkinsonian drugs
AAMC Medical School Objectives Project Report X Patient Safety-Table 1	**Topic C** Drug treatment of common conditions

Drugs acting at synaptic and neuroeffector junctional sites autonomic and neuromuscular pharmacology			
Recommended Curriculum Equivalent: 3.0 hr			
Drug Classes and Drugs to consider			
Direct Acting Cholinergic Ester-Agonists	Direct Acting Cholinergic Alkaloid Agonists	Cholinergic Indirect Acting	Related Drugs
ACETYLCHOLINE BETHANECHOL	PILOCARPINE	ECHOTHIOPHATE EDROPHONIUM NEOSTIGMINE malathion parathion physostimine pyridostigmine	PRALIDOXIME obidoxime sarin VX series

Learning Objectives

Physiology and pathophysiology

Describe synthesis, storage, release, and inactivation of cholinergic agonists.

List the steps in the synthesis, storage, release and inactivation of acetylcholine, and drugs that interface with those processes.

List the location of nicotinic and muscarinic receptors and their subtypes.

Compare the two major cholinesterases: acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) as to anatomical locations, sites of synthesis and function.

Mechanism of action

Explain the mechanism of actions, including 2nd messenger systems of acetylcholine and related drugs.

Explain the differences in onset and duration of action and route of administration for different groups of anticholinesterases.

Explain the chemical makeup of the active site of AChE (anionic and esteratic) as to attraction, attachment and rates of breakdown of various substrates and inhibitors.

Distinguish the mechanism by which pralidoxime reactivates phosphorylated AChE.

Actions on organ systems

Describe the responses to activation of these receptors.

Explain the reason why anticholinesterases classified as reversible or irreversible.

Pharmacokinetics

Describe the variations of pharmacokinetics of cholinergic drugs.

Relate the onset of action of anticholinesterases, routes of administration, and the duration of action of anticholinesterases with sites and type of attachment to the enzyme.

Explain why anticholinesterases are reversible or irreversible, and indicate which anticholinesterases are in each category.

Explain the role of cholinesterase “aging” in the enzyme-inhibitor interaction.

Adverse effects, drug interactions and contraindications

List the adverse effects of cholinergic drugs.

List and describe the rationale for contraindications of cholinergic drugs.

Describe the adverse effects, and their relevance, of the two classes of neuromuscular blocking drugs.

Therapeutic uses

List the therapeutic uses of cholinergic agonists.

Describe the effects of accumulated acetylcholine at muscarinic and nicotinic receptors in the periphery and the central nervous system.

List therapeutic uses for and adverse side effects of anticholinesterases.

Explain why anticholinesterase agents can be used as insecticides (malathion, parathion) and chemical warfare agents (sarin, VX series).

Explain why pralidoxime is not effective reactivating all phosphorylated AChE.

Explain the concept of differential toxicity of malathion and parathion in different species.

Notes

Clinical Pharmacology

Pilocarpine may cause mental impairment when used topically, especially in the elderly.

Relevance

USMLE topic	**Principles of therapeutics**
Central and peripheral nervous system Pharmacodynamic and pharmacokinetic processes	Drugs affecting the autonomic nervous system Neuromuscular junction agonists Antiglaucoma drugs Mechanisms of toxicology
AAMC Medical School Objectives **Project Report X Patient Safety**-Table 1	**Topic C** Drug treatment of common conditions

Drugs acting at synaptic and neuroeffector junctional sites autonomic and neuromuscular pharmacology		
Recommended Curriculum Equivalent: 2.0 hr		
Drug Classes and Drugs to consider		
Antagonists at Muscarinic Receptors	Antagonists at Nicotinic Receptors	Drugs Acting at Autonomic Ganglia
ATROPINE ipratropium scopolamine tolterodine	MIVACURIUM nicotine SUCCINYLCHOLINE TUBOCURARINE	mecamylamine

Learning Objectives

Physiology and pathophysiology

List the locations of and the differences between muscarinic and nicotinic receptors.

Explain the rationale for historical uses in treatment of hypertension and autonomic hyperreflexia.

Mechanism of action

Describe nicotine's agonist and antagonist properties.

Actions on organ systems

Contrast and compare the depolarizing and the competitive Neuromuscular Junction blocking drugs.

Adverse effects, drug interactions and contraindications

Explain why muscarinic antagonists cause xerostomia, blurred vision, photophobia, tachycardia, anhidrosis, difficulty in micturition, hyperthermia, glaucoma and mental confusion in the elderly.

Explain why muscarinic antagonists are contraindicated in glaucoma, obstructive disease of the gastrointestinal tract or urinary tract, intestinal atony.

List the adverse side effects of drug acting at autonomic ganglia.

List the adverse side effects and drug interactions at the NMJ.

Therapeutic uses

Explain the rationale for the therapeutic use of muscarinic antagonists in diseases such as bronchoconstriction, excessive salivation, and motion sickness. Explain the rationale for the therapeutic use to produce mydriasis and cycloplegia.

Explain why nicotine is not used clinically (except as a smoking deterrent), and its historical, social and toxicological significance.

Explain the differential uses of competitive versus depolarizing Neuromuscular Blocking Drugs and their limitations.

Notes

Clinical Pharmacology

All anticholinergic drugs relatively contraindicated in the elderly due to risk of increased mental impairment.

Relevance

USMLE topic Central and Peripheral Nervous System	**Principles of therapeutics** Mechanisms of action and use of drugs for treatment of disorders of the nervous system – neuromuscular junction agonist and antagonists Drugs affecting the autonomic nervous system
AAMC Medical School Objectives Project Report X Patient Safety- Table 1	**Topic C** Drug treatment of common conditions, and diseases using frequently prescribed drugs for the treatment and prevention of disease

Drugs acting at synaptic and neuroeffector junctional sites autonomic and neuromuscular pharmacology		
Recommended Curriculum Equivalent: 3.5 hr		
Drug Classes and Drugs to consider		
Nonselective Alpha Adrenergic Agonists	Selective $Alpha_2$ Adrenergic Agonists	
DOPAMINE EPINEPHRINE NOREPINEPHRINE phenylephrine pseudoephedrine	BRIMONIDINE CLONIDINE METHYLDOPA	
Nonselective $Alpha_1$ $Alpha_2$ Antagonists	Selective $Alpha_1$ Adrenergic Antagonists	Indirect and Mixed Acting Agents
phenoxybenzamine phentolamine	PRAZOSIN tamsulosin terazosin	AMPHETAMINE ephedrine methamphetamine tyramine
Learning Objectives		
Physiology and pathophysiology List steps in the synthesis, storage, release and inactivation of norepinephrine and epinephrine. Describe types and subtypes of adrenergic receptors, their locations, and physiologic response to activation. Describe receptor selectivity of norepinephrine and epinephrine. Describe the differences between direct and indirect acting adrenergic drugs.		

Mechanism of action

Describe the property of intrinsic activity as a characteristic of Direct Agonists binding to receptors.

Describe the mechanism by which Indirect Agonists release neurotransmitters from neuron.

Describe the importance of Antagonists binding to receptors without intrinsic activity

Actions on organ systems

Explain why alpha-1 adrenergic antagonists are used to treat hypertension and benign prostatic hypertrophy.

Explain why alpha-1 adrenergic agonists are important in the treatment of nasal congestion, hypotension, paroxysmal atrial tachycardia, and are used to cause mydriasis and vasoconstriction (with local anesthetics).

Explain the mechanism for the use of alpha-2 adrenergic agonists in the treatment of hypertension, and for topical treatment of glaucoma.

Adverse effects, drug interactions and contraindications

List the adverse side effects of alpha1 and alpha2 agonists.

Explain drug interactions with oxytocic drugs and monamine oxidase inhibitors.

List the contraindications for alpha1 adrenergic agonists.

List the adverse side effects of nonselective alpha and selective alpha adrenergic antagonists.

Therapeutic uses

Explain why alpha-1 adrenergic agonists are important in the treatment of nasal congestion, hypotension, paroxysmal atrial tachycardia, and are used to cause mydriasis and vasoconstriction (with local anesthetics).

Explain the mechanism for the use of alpha-2 adrenergic agonists in the treatment of hypertension, and for the topical treatment of glaucoma.

Explain the limitations of the use of nonselective alpha-1, alpha-2 adrenergic antagonists in the treatment of hypertension.

Notes

Clinical Pharmacology

A recent trend to use a combination of methylphenidate and modified release clodidine to treat ADHD in older children. However, this should not be considered a first-line drug regimen. Caution in that clonidine should not be discontinued abruptly due to risk of rebound hypertension. Clonidine use is sometimes associated with adverse CNS activity including depression and psychosis. Adverse CNS events have also been observed in patients prescribed methyldopa.

Relevance

USMLE topic	**Principles of therapeutics**
Central and peripheral nervous system	Mechanisms of action and use of drugs for treatment of disorders of the nervous system Autonomic drugs Stimulants, amphetamines

AAMC Medical School Objectives Project Report X Patient Safety-Table 1	**Topic C** Drug treatment of common conditions, and diseases using frequently prescribed drugs for the treatment and prevention of disease

Drugs acting at synaptic and neuroeffector junctional sites autonomic and neuromuscular pharmacology		
Recommended Curriculum Equivalent: 1.5 hr		
Drug Classes and Drugs to consider		
Nonselective Beta Adrenergic Agonists	Selective Beta Adrenergic Agonists	
Isoproterenol	ALBUTEROL	
Nonselective Alpha$_1$ Alpha$_2$ Antagonists	Selective Alpha$_1$ Adrenergic Antagonists	Indirect and Mixed Acting Agents
phenoxybenzamine phentolamine	PRAZOSIN tamsulosin terazosin	AMPHETAMINE ephedrine methamphetamine tyramine
Learning Objectives		
Mechanism of action Compare and contrast the pharmacology of the nonselective beta-adrenergic agonists, epinephrine and isoproterenol. Compare and contrast the pharmacology of the beta selective adrenergic agonists, isoproterenol, albuterol, salmeterol, and dobutamine. Compare and contrast the pharmacology of the beta-adrenergic antagonists, propranolol, metoprolol, and atenolol. Compare and contrast the pharmacology of the nonselective alpha and beta blocking drug labetalol, with selective beta blocking drugs.		
Adverse effects, drug interactions and contraindications List the adverse side effects of beta$_2$ adrenergic agonists. List the adverse side effects of beta adrenergic antagonists.		
Therapeutic uses Explain the mechanisms for the use of selective beta-adrenergic agonists in diseases such as cardiac decompensation, asthma, premature labor, bronchospasm and emphysema.		
Notes		
Clinical Pharmacology There is no beta adrenergic blocking drug that has not been associated with reactive bronchconstriction. Thus caution is advised in adult patients with a history of pediatric asthma. Use of these agonists as effective tocolytics in humans is not supported by good clinical evidence.		
Relevance		
USMLE topic Central and peripheral nervous system	**Principles of therapeutics** Mechanisms of action and use of drugs for treatment of disorders of the nervous system Autonomic drugs Stimulants, amphetamines	

AAMC Medical School Objectives Project Report X Patient Safety-Table 1	**Topic C** Drug treatment of common conditions, and diseases using frequently prescribed drugs for the treatment and prevention of disease