

DRUGS ACTING AT SYNAPTIC AND NEUROEFFECTOR JUNCTIONAL SITES AUTONOMIC AND NEUROMUSCULAR PHARMACOLOGY (11)

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In general, medical students enter medical pharmacology courses with a sound background in the anatomy of the ANS, but a somewhat inadequate grasp of its physiology. Therefore, we need to spend considerable time on the latter and little time on the former in ANS pharmacology. The importance of autonomic pharmacology is greater than that of its collective therapeutic agents. It is the foundation for understanding other areas such as cardiovascular pharmacology and pharmacology of the central nervous system. Autonomic nerves and/or their effector cells are the sites of action responsible for the side effects of many drugs whose primary sites of action are elsewhere.

I. Introduction to the autonomic nervous system (1)

A. History

1. Describe the anatomical projections of the sympathetic and parasympathetic autonomic nervous system.
2. Describe the evidence for development of the concept of neurotransmitters, cotransmitters, and end-organ receptor specificity.

B. Define words containing the suffixes, -ergic, -mimetic, -lytic and -ceptive.

C. Describe homeostasis, fight-or-flight and rest-and-repair with regard to sympathetic and parasympathetic activity.

D. Describe the central control of the autonomic nervous system.

E. List and describe the responses of end organs to activation of the sympathetic and parasympathetic nervous systems.

F. Describe the concept of predominant tone.

II. Cholinergic neurotransmission and muscarinic agonists (1)

A. List the steps in the synthesis, storage, release and inactivation of acetylcholine, and drugs that interface with those processes. Explain their mechanisms. Describe the types of receptors, nicotinic and muscarinic. Describe and explain the site and mechanism of action of drugs that interfere with these steps, such as botulinum toxin.

B. Acetylcholine-muscarinic and nicotinic receptor sites

1. List the locations of and the differences between muscarinic and nicotinic receptors.
2. List the therapeutic uses of muscarinic agonists.
3. List the adverse side effects of muscarinic agonists
4. Important or prototypic drugs: acetylcholine, bethanechol, and pilocarpine.

III. Anticholinesterases (1)

- A. Compare the two major cholinesterases: acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) as to anatomical locations, sites of synthesis and function.
- B. 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.
- C. 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.
- D. Explain why anticholinesterases are reversible or irreversible, and indicate which anticholinesterases are in each category.
- E. Describe the effects of accumulated acetylcholine at muscarinic and nicotinic receptors in the periphery and the central nervous system.
- F. List therapeutic uses for and adverse side effects of anticholinesterases.
- G. Distinguish the mechanism by which pralidoxime reactivates phosphorylated AChE.
- H. Explain the role of enzyme aging in the enzyme-inhibitor interaction.
- I. 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.
- J. Important or prototypic drugs: physostigmine, neostigmine, edrophonium, pyridostigmine, echothiophate and pralidoxime.

IV. Antagonists at muscarinic receptor sites (1)

- A. Describe the mechanism of action.
- B. Explain the rationale for the therapeutic use in diseases such as bronchoconstriction, excessive salivation, and motion sickness. Explain the rationale for the therapeutic use to produce mydriasis and cycloplegia.
- C. Explain why muscarinic antagonists cause xerostomia, blurred vision, photophobia, tachycardia, anhidrosis, difficulty in micturition, hyperthermia, glaucoma and mental confusion in the elderly.
- D. Explain why muscarinic antagonists are contraindicated in glaucoma, obstructive disease of the gastrointestinal tract or urinary tract, intestinal atony.
- E. Important or prototypic drugs: atropine, scopolamine, tolterodine and ipratropium.

V. Drugs acting at autonomic ganglia (0.5)

- A. Nicotine
 1. Describe nicotine's agonist and antagonist properties.
 2. Explain why it is not used clinically (except as a smoking deterrent), and its historical, social and toxicological significance.
- B. Antagonists acting at ganglionic nicotinic receptor sites
 1. Describe the pharmacological effects, and understand the role of predominant tone.
 2. Explain rationale for original uses in treatment of hypertension and autonomic hyperreflexia.
 3. List the adverse side effects.
 4. Important drug: trimethaphan

VI. Antagonists at nicotinic receptor sites in the skeletal neuromuscular junction (NMJ) (0.5)

- A. Describe the selectivity of drugs between ganglionic and neuromuscular nicotinic receptors.
- B. Describe the physiology and pathophysiology of transmission at NMJ.
- C. Classes of neuromuscular antagonists
 1. Depolarizing agent
Explain the uses and limitations.
 2. Competitive antagonists at NMJ
List the adverse side effects.
 3. Important-prototypic drugs: succinylcholine, tubocurarine, mivacurium.

4. Contrast and compare the depolarizing and competitive NMJ blocking drugs.
- D. Explain the rationale for the combination use of antimuscarinic and anticholinesterase agents in reversal of neuromuscular blockade.

VII. Sympathetic neurotransmission, and the adrenal medulla (1)

- A. List the steps in the synthesis, storage, release and inactivation of norepinephrine and epinephrine, and the drugs that interfere with those processes. Explain their mechanisms.
- B. Describe the types and subtypes of adrenergic receptors, their locations, and physiologic response to activation.
- C. Describe the receptor selectivity of norepinephrine and epinephrine.
- D. Important or prototypic drugs: epinephrine, norepinephrine, monoamine oxidase inhibitors, metyrosine, reserpine, and entacapone.

VIII. Indirectly acting sympathomimetic agents (1)

- A. Describe the difference between actions of direct and indirect adrenergic drugs.
- B. Explain the mechanism of indirect acting adrenergic drugs.
- C. List the therapeutic uses.
- D. Important or prototypic drugs: tyramine, ephedrine, pseudoephedrine, cocaine, amphetamine, and methamphetamine.

IX. Alpha adrenergic agents (1.5)

- A. Alpha-1 Adrenergic Agonists
 1. 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).
 2. List the adverse side effects.
 3. Explain drug interactions with oxytocic drugs and monoamine oxidase inhibitors.
 4. List the contraindications.
 5. Important-prototypic drugs: epinephrine, norepinephrine, and phenylephrine.
- B. Alpha-2 adrenergic agonists
 1. Explain the mechanism for the use of alpha-2 adrenergic agonists in the treatment of hypertension, and for the topical treatment of glaucoma.
 2. List the adverse side effects.
 3. Important or prototypic drugs: clonidine and brimonidine
- C. Nonselective alpha-1, alpha-2 adrenergic antagonists
 1. Explain the limitations of the use of nonselective alpha-1, alpha-2 adrenergic antagonists in the treatment of hypertension.
 2. List the adverse side effects.
 3. Important or prototypic drugs: phentolamine, phenoxybenzamine.
- D. Alpha-1 adrenergic antagonists
 1. Explain why alpha-1 adrenergic antagonists are used to treat hypertension and benign prostatic hypertrophy.
 2. List the adverse side effects.
 3. Important or prototypic drugs: prazosin, terazosin, tamsulosin

X. Beta adrenergic agents (1.5)

- A. Nonselective beta adrenergic agonists

Compare and contrast the pharmacology of epinephrine and isoproterenol.
- B. Selective beta adrenergic agonists
 1. Compare and contrast the pharmacology of beta selective adrenergic agonists isoproterenol, albuterol, salmeterol, and dobutamine.
 2. Explain the mechanisms for the use of these drugs in diseases such as cardiac

decompensation, asthma, premature labor, bronchospasm and emphysema.

3. List the adverse side effects.

C. Beta adrenergic antagonists

1. Compare and contrast the pharmacology of propranolol, metoprolol and atenolol.

2. List the adverse side effects.

3. Important or prototypic drugs: propranolol, metoprolol, timolol and atenolol.

D. Compare and contrast the pharmacology of the nonselective alpha and beta blocking drug labetalol, with selective beta blocking drugs.

Minimum list of drugs in autonomic and neuromuscular pharmacology (+ indicates a top 200 prescribed drug in 2003)

ACETYLCHOLINE	labetalol	PRALIDOXIME
ALBUTEROL+	malathion	PRAZOSIN
AMPHETAMINE +	mecamylamine	PROPRANOLOL+
ATENOLOL+	methamphetamine	pyridostigmine
ATROPINE	methyldopa	reserpine
BETHANECHOL	METOPROLOL+	salmeterol
Botulinum toxin	metyrosine	sarin
brimonidine	mivacurium	scopolamine
CLONIDINE+	NEOSTIGMINE	SUCCINYLCHOLINE
COCAINE	NICOTINE	tamsulosin+
dobutamine	NOREPINEPHRINE	terazosin+
DOPAMINE	parathion	timolol
EDROPHONIUM	phenoxybenzamine	tolterodine+
entacapone	PHEHTOLAMINE	TUBOCURARINE
EPHEDRINE	phenylephrine	TYRAMINE
EPINEPHRINE	physostigmine	VX series
ipratropium+	pilocarpine	
ISOPROTERENOL	pseudoephedrine	

PRIMARY DRUGS - All uppercase letters

Secondary drugs - lowercase letters