

Knowledge Objectives for Dr. Kozasa's Lectures

- Know general characteristics of signal-transducing receptors
 - Bind to a ligand (drug or endogenous molecule)
 - Participate in a signaling cascade

Distinguish from non-receptor-mediated drug action

Graded or Dose-Response effects (vs. all-or-none)
- Understand “occupational theory” of drug action
 - Molecular basis (ligand-receptor interaction)
 - Mathematical description
 - Occupational theory: $\text{Response} = \text{Max Response} * [D]/(K_d + [D])$
 - Shapes of dose-response curves
 - Significance of K_d
 - ligand dissociation constant
 - half-max binding when $[D] = K_d$
 - Understand the difference between Potency and Efficacy
 - Know the general mechanism of drug-receptor interaction, and recognize dose-response curves for:
 - Agonists
 - Antagonists
 - Competitive
 - Non-competitive
 - Partial Agonists
 - Inverse Agonists
- Biochemical Classification of Receptors: Know the general characteristics and mechanism of action for:
 - Membrane-bound receptors
 - G protein-coupled
 - Ligand-regulated ion channels
 - Tyrosine Kinase-linked
 - Guanyl cyclase-linked

(Know some specific examples of each type)
 - Cytosolic/nuclear “soluble” receptors
- Understand basic mechanisms of receptor regulation
 - Desensitization, homologous or heterologous
 - Spare receptors

Knowledge Objectives for Autonomic Drugs

1) Understand the pharmacological (not anatomical) Division of PNS: Cholinergic vs. Adrenergic

Cholinergic: All preganglionic and parasympathetic postganglionic Acetylcholine is the neurotransmitter at ganglia, nmj, and muscarinic tissue synapses

Adrenergic: Postganglionic sympathetic neurons (most). Norepinephrine is the transmitter

Exceptions:

Cholinergic transmission in sympathetic system - all ganglia, adrenal medulla, sweat glands (muscarinic)

Dopaminergic innervation in sympathetic system - renal blood vessels

2) Know the important steps of Neurotransmission: Synthesis, storage, release, recognition, and metabolism.

Know where drugs can intervene, and what are the differences between cholinergic and adrenergic systems in terms of these 5 steps.

Cholinergic Neurons: Rate limiting step is choline transport into neurons. Most important mechanism of degradation is AchE

Adrenergic Neurons: Know the enzymes involved in synthesis and degradation. Use of VMA in 24-hr urine for diagnosis of pheochromocytoma (how does it work). Uptake is one of the many mechanisms for removal of released NE. Negative feedback by an autoreceptor (what is this).

3) Know the physiological consequences of drug/receptor interactions in the ANS

Agonistic vs antagonistic

Direct-acting vs. indirect-acting (e.g. inhibition of AchE has same effect as Ach overdose)

Know for major organ systems which type of innervation predominates and what its effect is. If both types are present, know their opposite effects. 1) Eye 2) Heart 3) Vascular smooth muscle 4) Bronchial smooth muscle 5) GI tract 6) Genitourinary tract 7) Glands (sweat, salivary) [remember: "Flight or Fight" vs. "Rest and Digest"]

If you know the predominant innervation of the systems above, you will be able to predict the physiological consequences resulting from pharmacological activation or blockade of adrenergic or cholinergic receptors.

"Functional types" of cholinergic synapse/receptors: Muscarinic receptors at end organ (G-protein linked receptors) Nicotinic receptors at nmj, ganglia (ion-channel linked receptors)

Activation of Muscarinic receptors causes DUMBELS syndrome: Defecation, Urination, Miosis, Bronchoconstriction, Emesis, Lacrimation, Salivation

Activation of adrenergic receptors causes different effects: Relative potency of Epi, NE, and Isoproterenol. Know the major difference between $\alpha 1$ and $\alpha 2$ receptors. Know how different tissue distribution results in different effects: $\beta 1$ (heart), $\beta 2$ (blood vessels), and $\beta 3$ (adipose tissue).

4) Specific topics for Cholinergic Neurons

Acetylcholine is the transmitter; know its synthesis and breakdown

Activity terminated by hydrolysis of transmitter by AchE

Know the 2 “functional types” of cholinergic synapse/receptors

Muscarinic receptors at end organ (G-protein linked receptors)

Nicotinic receptors at nmj, ganglia (ion-channel linked receptors)

Both types activated by acetylcholine and its stable ester analogs

(bethanachol, carbachol)

(Why is Ach not an effective drug?)

Know the physiological consequences of activation of Muscarinic receptors

Drop in blood pressure due to activation of non-innervated muscarinic receptors causing NOS release and relaxation in vascular smooth muscle

often accompanied by reflex tachycardia

Useful muscarinic agonists - pilocarpine (glaucoma), bethanechol (bladder or gi atony)

Inhibition of AchE has the same effect as Ach “overdose” (prolongs its action at the synapse)

types of Ach inhibitors - reversible (eg Neostigmine, Physostigmine)

irreversible (organophosphate pesticides and nerve gasses)

Effects - primarily muscarinic (dumbels syndrome); nicotinic effects (ganglionic and nmj) only at high doses

Death can be caused by respiratory insufficiency (bronchoconstriction, secretion, central depression, depolarizing ganglionic blockade)

Antidotes - Atropine -blocks muscarinic end-organ effects

Pralidoxime - reactivates AchE

Clinical uses of AchE inhibitors (reversible): glaucoma, myasthenia gravis, atropine poisoning, Alzheimers disease (semi-experimental)

Muscarinic Antagonists: Atropine, scopolamine

autonomic effects: tachycardia, pupil dilation, cycloplegia, loss of secretion, bronchodilation (once used as antiasthmatic) vasodilation, decreased gut motility

central effects: hallucination, delirium, treat motion sickness (scopolamine)

Antidote to atropine poisoning: Physostigmine (penetrates CNS)

Atropine useful in treating poisoning due to AchE inhibition

Ganglionic Blockers (Antinicotinic)

Competitive inhibitors - Mecamylamine and Trimethaphan

These do not affect muscarinic or NMJ nicotinic receptors

Originally used vs hypertension (vasodilation due to interruption of sympathetic vascular tone), Trimethaphan used in extreme emergency (dissecting Aortic aneurism), but not otherwise useful due to multiple, often unpredictable side effects (global ganglionic blockade)

Nicotine will initially stimulate postsynaptic ganglionic nicotinic receptors (agonism), producing sympathetic effects in the cardiovascular system and parasympathetic effects in the gut; however, it is not hydrolyzed by AchE and a depolarizing ganglionic blockade (antagonism) results with complex effects

Neuromuscular Blockers (Antinicotinic) act at NMJ

Competitive (non-depolarizing) blockers: Tubocurarine, pancuronium, vecuronium

Useful for producing skeletal muscular paralysis during surgery

Have some antiganglionic and antivagal (muscarinic) side effects

Depolarizing blocker: succinylcholine

activates nicotinic receptor (initial fasciculations), then repolarization is inhibited and blockade results

Also useful in surgery due to rapid onset; beware of genetic defect in serum esterase (greatly prolonged paralysis)

5) Specific Topics for Adrenergic Neurons

Norepinephrine is the main transmitter; epinephrine is a “long distance” transmitter
also dopamine

Know important steps in adrenergic transmitter (catecholamine) metabolism:

Synthesis, vesicular uptake and storage, triggering of release, release, activation of postsynaptic receptors, activation of presynaptic receptors, uptake, catabolism

Know examples of drugs that can affect each of these steps

Subtypes of postsynaptic (and presynaptic) receptors: alpha 1 and 2, beta 1 and 2 (and 3), dopaminergic;

Important sites of alpha 1 receptors - vascular smooth muscle, iris radial muscle, piloerector muscle

alpha 2 - presynaptic terminals (feedback) Platelets

beta 1 - heart

beta 2 - bronchial smooth muscle, uterus, liver (glycogenolysis)

dopaminergic - renal vascular smooth muscle

Know relative selectivity of drugs (adrenergic agonists and antagonists) for alpha and beta receptors

for beta agonists and antagonists, know relative selectivity for beta 1 and beta 2

Know effects of alpha and beta activation and blockade on following systems:

Vascular smooth muscle, peripheral resistance

Heart, cardiac output (also reflex- know this pathway)

Bronchial smooth muscle

Eye (adrenergic, radial muscle, Dilation, myDriasis)

Uterus

Indirect Acting Drugs:

Acting on Metabolism: Metyrosine, Tyramine, Phenelzine, alpha methyl dopa

Acting on release: Amphetamine, guanethidine, bretylium

Acting on vesicular transport and storage: reserpine

Acting on uptake: Cocaine, imipramine

alpha 2 agonists: clonidine