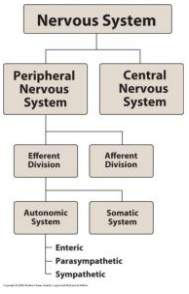
Autonomic Pharmacology

Drugs Affecting the Autonomic Nervous System

Objectives

- Recognize & understand the functional organization of the nervous system
- Identify & understand differences between sympathetic & parasympathetic divisions
- Describe effects of sympathetic & parasympathetic stimulation on various organs
- Describe steps in synthesis, storage, release, and & termination of major autonomic neurotransmitters
- Name major types of receptors found on autonomic effector tissues
- Understand pharmacologic manipulations of cholinergic & adrenergic systems

The Autonomic Nervous System



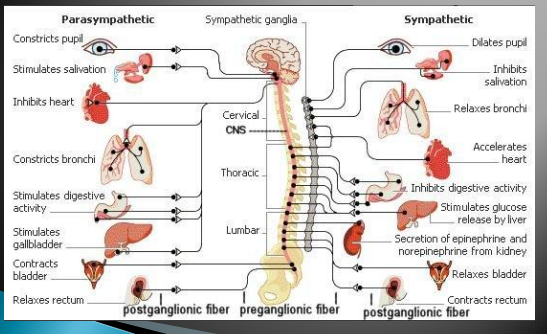
The Autonomic Nervous System

- Autonomic = Independent
  - Involuntary organ control
- Innervates
  - Smooth muscle (blood vessels, bladder, respiratory tract)
  - Cardiac muscle
  - Glands

Anatomy of the ANS

- Efferent neurons
  - Two types: Preganglionic and Postganglionic
  - From the Brain to the Body
- Afferent neurons
  - Reflex regulation
- Sympathetic neurons
- Parasympathetic neurons
- Enteric neurons
  - "Brain of the Gut"

Parasympathetic vs. Sympathetic

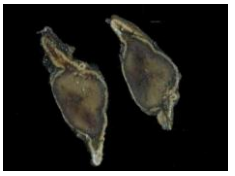


Parasympathetic vs. Sympathetic

- Parasympathetic
  - "SLUD" – salivation, lacrimation, urination, and defecation
  - "D" - digestion, defecation, diuresis
- Sympathetic
  - "E" situations - exercise, excitement, emergency, embarrassment

Innervation

- Most organs receive dual innervation
- Sympathetic innervation:
  - Adrenal medulla
  - Kidney
  - Pilomotor muscles
  - Sweat Glands

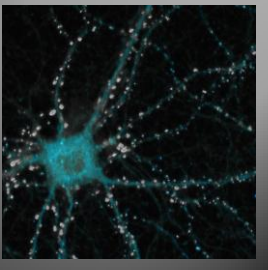


Special Cases

- Sexual intercourse
  - parasympathetic promotes erection while sympathetic produces ejaculation
- Eye
  - sympathetic response is dilation and relaxation of the ciliary muscle for far vision
  - parasympathetic does opposite
- Urination:
  - parasympathetic system relaxes sphincter muscle & promotes contraction of muscles of the bladder wall
  - sympathetic blocks urination
- Defecation
  - parasympathetic system causes relaxation of the anal sphincter and stimulates colon & rectum to contract
  - sympathetic blocks defecation

Chemical Signaling

- Local Mediators
  - Histamine
- Hormones
  - Thyroid
- Neurotransmitters
  - Acetylcholine
  - Norepinephrine
  - Epinephrine



Chemical Signaling

- **<u>Neurotransmission = COMMUNICATION</u>**
  - No actual physical connection exists
  - Between two nerve cells
  - Between a nerve and the organ it innervates
- Synapse
  - Space between nerve cells
  - Where communication between neurons occurs

Chemical Signaling

- Neurotransmitters
  - Membrane receptors
- Receptors
  - Special sensory neurons in sense organs that receive stimuli from the external environment
  - LOCK & KEY

Autonomic Neurotransmission

- Neurotransmitters
  - Over fifty identified
- ANS chemical signaling
  - Acetylcholine (ACh)
  - Norepinephrine (NE)
- Cholinergic
  - Release ACh
- Adrenergic
  - Release NE

Key Terms

- Agonist
  - Substance which binds to receptor and triggers a response
- Antagonist
  - Substance that inhibits the normal physiological function of a receptor
  - "Blocker"
- Direct-acting
  - Drugs which effect receptors
- Indirect-acting
  - Drugs which effect neurotransmission

Cholinergic Drugs

Cholinergic Agonists

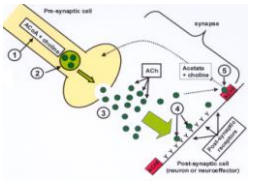
- Indirect Acting:
  - Donezepil
  - Edrophonium
  - Neostigmine
  - Physostigmine
  - Tacrine
- Direct Acting:
  - Acetylcholine
  - Bethanechol
  - Carbachol
  - Pilocarpine
- Indirect Acting (irreversible):
  - Echothiophate

Neurotransmission at Cholinergic Neurons

- Synthesis
- Storage
- Release
- Binding
  - Muscarinic
  - Nicotinic
- Degradation
- Recycling

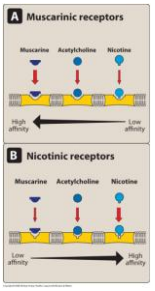
Cholinergic Neurotransmission

1. Synthesis of ACh from acetyl CoA and choline
2. Storage of ACh in synaptic vesicles
3. Release of Ach
4. Action of ACh by binding to and activating receptors
5. Inactivation by enzymatic breakdown of Ach by AChE located in the synapse



http://www.muhealth.org/~pharm204/PNS1.jpg

Cholinergic Receptors (Cholinoreceptors)



Cholinergic Receptors

- Stimulated by acetylcholine (ACh)
- Nicotinic
  - Recognize nicotine
  - Autonomic ganglia (both sympathetic and parasympathetic)
  - Neuromuscular junctions
- Muscarinic
  - Recognize muscarine
  - Ganglia of peripheral nervous system and autonomic effector glands
  - Stimulated by the mushroom poison, muscarine

Direct-Acting Cholinergic Agonists

- Parasympathomimetics
- Bind and Activate cholinergic receptors
- Two groups
  - Choline Esters
    - Carbachol and Bethanechol
  - Plant Alkaloids
    - Pilocarpine

Direct-Acting Cholinergic Agonists

- Acetylcholine
  - Decrease in Heart Rate and Cardiac Output
  - Decrease in Blood Pressure
  - Increases salivation
  - Increases intestinal secretions and motility
  - Increases bronchiolar secretions
  - Miosis
  - Muscarinic/nicotinic receptors
    - Intraocular administration: miosis during opthalmic surgery
    - Intracoronary administration: coronary angiography

Direct-Acting Cholinergic Agonists

- Bethanechol
  - Muscarinic receptors
  - Oral/SC administration: stimulates bladder and GI muscles
- Carbachol
  - Muscarinic/nicotinic receptors
  - Intraocular administration: miosis during opthalmic surgery
  - Topical ocular administration: glaucoma

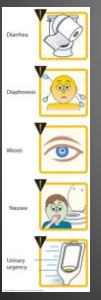
Direct-Acting Cholinergic Agonists

- Pilocarpine
  - Less potent
  - Muscarinic receptors
- Glaucoma
  - Administered topically to the cornea
  - Lowers intraocular pressure by increasing outflow of aqueous humor
- Xerostomia
  - Administered orally to stimulate salivary gland secretion

Direct-Acting Agonists: Plant Alkaloids

- Muscarine
  - Muscarinic receptors
  - No clinical use
- Nicotine
  - Nicotinic receptors
  - Smoking cessation – gum, patches, nasal spray, & inhaler

Direct-Acting Cholinergic Agonists



- Common Side Effects/Adverse Effects
  - Diarrhea
  - Diaphoresis
  - Miosis
  - Nausea
  - Urinary Urgency
  - Urine Increase

Indirect-Acting Cholinergic Agonists

- Anticholinesterases
- Prevent break down of ACh at cholinergic synapses
- Reversible cholinesterase inhibitors
  - Shorter-acting
- Irreversible cholinesterase inhibitors
  - Longer-acting

Indirect-Acting Cholinergic Agonists

- Neostigmine
  - Counteract curariform toxicity
  - Post-op urinary retention & abdominal distention
- Physostigmine
  - Glaucoma
  - Antidote for atropine poisoning
- Pyridostigmine
  - Myasthenia gravis
  - Other
  - Myasthenia gravis, diplopia, blurred vision

Indirect-Acting Cholinergic Agonists

- Edrophonium
  - MOA
    - Prevents hydrolysis of Ach
  - Indications
    - Differential diagnosis of

- Myasthenia gravis
  - Muscle weakness due to Ach deficiency
  - Edrophonium can improve neuromuscular transmission

Indirect-Acting Cholinergic Agonists

- Donepezil/Galantamine/Rivastigmine/Tacrine
  - Indications
    - Alzheimer disease
  - Central Acting
    - Cross Blood Brain Barrier
    - Increase ACh concentration
  - Improves cholinergic function

Indirect-Acting Cholinergic Agonists Irreversible

- Echothiophate
  - Organophosphate
- MOA
  - Form covalent bond with catalytic site of cholinesterase
  - Long duration of action
    - Slowly hydrolyzed
    - Aging
- Indications
  - Ocular conditions: chronic treatment of open-angle glaucoma

Cholinergic Antagonists

- Antimuscarinic Agents
  - Atropine
  - Cyclopentolate
  - Ipratropium
  - Scopolamine
  - Tropicamide
- Ganglionic Blockers
  - Nicotine
- Neuromuscular Blockers
  - Pancuronium
  - Rocuronium
  - Succinylcholine
  - Vecuronium

Muscarinic Receptor Antagonist

- Antimuscarinics
- Compete with ACh
- Inhibits effects of parasympathetic nerve stimulation
- Belladonna Alkaloids
  - Atropine, scopolamine, hyoscyamine
- Semisynthetic/Synthetic
  - Ipratropium, dicyclomine, oxybutynin, flavoxate, tolterodine, tropicamide

Atropine/Scopolamine

- Prototype
  - *Atropa belladonna* (deadly nightshade)
  - Belladonna – "fair lady"
    - Pupillary dilation
- Atropine
  - Relax smooth muscle
  - Increase heart rate and condution
  - Inhibit exocrine gland secretion
  - Scopolamine

Atropine

- Blocks parasympathetic stimulation
- Action is dose-dependent
  - 0.5mg - Dry mouth, ↓ sweating
  - 1mg - ↑HR, very dry mouth, thirst
  - 2mg – Blurred vision, tachycardia, palpitations
  - 5mg – urinary retention, hot/dry skin, restlessness, fatigue
  - 10mg – rapid/weak pulse, hallucinations, delirium, coma

Atropine Poisoning

- Mad as a hatter
- Blind as a bat
- Dry as a bone
- Red as a beet
- Hot as a pistol

Organophosphate Poisoning

Ipratropium

- Administered via inhalation
- Used in obstructive lung diseases
  - Emphysema
  - Chronic bronchitis

Ganglionic Blockers

- Nicotine
  - Cigarettes, patches, gum, chewing tobacco, Skoal, Snuff
  - Depolarizes autonomic ganglia
  - Clinical use:
    - Smoking cessation

Neuromuscular Blocking Drugs

- Inhibit neurotransmission at skeletal neuromuscular junctions
- Results in muscle weakness and paralysis
- Nondepolarizing agents
  - Curariform drugs
- Depolarizing agents
  - Succinylcholine

Neuromuscular Blocking Drugs

- MOA: competitive antagonists of Ach at Nicotinic receptors in skeletal muscle
- Sequence of paralysis
  - Small & rapidly moving muscles
  - Larger muscles
  - Intercostal muscles & diaphragm
- Clinical Use:
  - Muscle relaxation during surgery
  - Facilitate intubation/endoscopic procedures

Neuromuscular Blocking Drugs

- NONDEPOLARIZING or COMPETITIVE
- Curare: “arrow poison”
- Low doses
- High doses
- IV
- Do Not Cross Blood Brain Barrier
- Selection based on duration of action

Neuromuscular Blocking Drugs

- Depolarizing
- Succinylcholine
  - MOA: Binds to N receptors causing persistent depolarization of the motor end plate
  - Fasciculations followed by sustained paralysis
  - Hydrolyzed by plasma cholinesterases
    - Short duration of action
  - Indications:
    - Muscle relaxation during surgery
  - No pharmacological antidote

Adrenergic Pharmacology

Adrenergic Receptors

- Stimulated by norepinephrine (NE) or epinephrine (E)
- Alpha-adrenergic receptors
  - Excitatory
- Beta-adrenergic receptors
  - Excitatory or inhibitory

Adrenergic receptors

- Alpha 1
  - Smooth muscle of most arterioles
  - Sphincter muscles of the GI tract & bladder
  - Smooth muscle contraction
- Alpha 2
  - Presynaptic nerves and parts of the GI tract

Adrenergic receptors

- Beta 1
  - Dominant type in the heart and other locations
  - Cardiac stimulation
- Beta 2
  - Bronchioles of the lung, the wall muscles of the bladder and other locations
  - Smooth muscle relaxation

Adrenergic Receptors

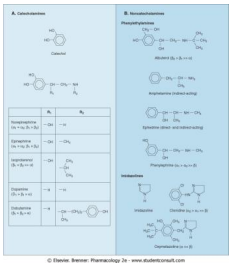
- Alpha
  - $Alpha_1$ – mediates contraction of smooth muscle
  - $Alpha_2$ - mediates ↑ in NE release, platelet aggregation, inhibition of insulin secretion, ↓ in aqueous humor secretion, CNS effects
- Beta
  - $Beta_1$ – cardiac stimulation
  - $Beta_2$ – relaxation of bronchial, smooth, and uterine muscle

Direct-Acting Adrenergic Agonists: Catecholamines

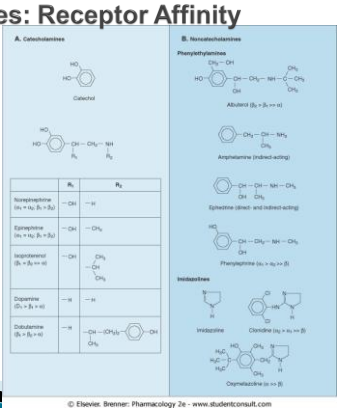
- Norepinephrine
  - Endogenous sympathetic neurotransmitter
- Epinephrine
  - Principal hormone of adrenal medulla
- Dopamine
  - Precursor to norepinephrine and epinephrine
- Isoproterenol and dobutamine

Catecholamines: Chemistry and Pharmacokinetics

- Catechol moiety & ethylamine side chain
- Rapidly inactivated
- Administered parenterally – Why?



Catecholamines: Receptor Affinity



Catecholamines: Cardiovascular Effects

- Norepinephrine
  - Alpha 1 adrenergic receptors
  - Vasoconstriction, ↑ PVR
    - Increased BP
- Epinephrine
  - ↑SBP and ↑ or ↓ DBP
  - Lower doses = $ß_2$ stimulation > $α_1$
  - Higher doses = α > ß

Catecholamines: Cardiovascular Effects

- Isoproterenol: beta 1 & 2
  - Vasodilation & cardiac stimulation
- Dobutamine
  - ↑ myocardial contractility & stroke volume
  - Produces smaller increase in heart rate
- Dopamine
  - Low doses vs. high doses

Catecholamines Effects

- Respiratory
  - Bronchodilators
- Adverse effects
  - Excessive vasoconstriction
  - Reduced blood flow to vital organs
  - Excessive cardiac stimulation
  - Hyperglycemia (beta agonists)

Catecholamines: Specific Drugs

- Dopamine
  - Septic and cardiogenic shock
  - Dose titrated to achieve desired BP
- Norepinephrine
  - Septic shock
  - Cardiogenic shock

Catecholamines: Specific Drugs

- Epinephrine
  - Indications:
    - Anaphylactic shock
    - Vasoconstrictor
    - Cardiac stimulant
- Dobutamine
  - Cardiac stimulant

Direct-Acting Adrenergic Agonists: Noncatecholamines

- No catechol moiety
- Phenylephrine
- Midodrine
- Albuterol and related drugs
- Imidazolines

Phenylephrine

- Selective α_1 adrenergic receptor agonist
- Produces vasoconstriction via smooth muscle contraction
- Indications:
  - Nasal decongestant
  - Ocular decongestant
  - Facilitates ophthalmic examination
  - Hypotension/shock
  - BP maintenance during surgery

Noncatecholamines: Albuterol, Terbutaline

- Selective β_2 adrenergic receptor agonist
- Smooth muscle relaxation
- Indications
  - Albuterol: Asthma/COPD
    - Bronchodilation
  - Terbutaline: premature labor
    - Relaxes uterus
- Adverse Effects:
  - Tachycardia, muscle tremor, nervousness

Noncatecholamines: Imidazolines

- Activate α-adrenergic & imidazoline receptors
- Oxymetazoline
  - Vasoconstriction via α_1 receptors
  - Topical nasal and ocular decongestants
- Clonidine
  - Activate α_2 & imidazoline receptors in CNS
  - Chronic hypertension
- Adverse Effects
  - Sedative
  - Cardiovascular depression

Indirect-Acting Agonists

- Amphetamine
  - High lipid solubility
  - ↑ synaptic concentrations of norepinephrine
  - Effects: vasoconstriction, cardiac stimulation, CNS stimulation, ↑BP
- Cocaine
  - Stimulates sympathetic nervous system
  - Effects: vasoconstriction, cardiac stimulation, ↑BP
  - Indications: local anesthesia

Mixed-Acting Adrenergic Receptor Agonists

- Ephedrine/Pseudoephedrine
  - Activate α and β receptors
  - Nasal decongestants: α_1 receptors
  - Side Effects:
    - Tachycardia
    - ↑BP
    - Urinary retention
    - CNS stimulation/Insomnia

Adrenergic Receptor Antagonists

- Sympatholytics
  - Drugs which reduce sympathetic stimulation
- Therapeutic effects
  - Blockade of α_1 or β_1 receptors
- Adverse effects
  - Blockade of α_2 or β_2 receptors

Nonselective α-Blockers

- Phenoxybenzamine
  - Forms covalent bond with α receptor
  - Chemical sympathectomy
    - ↓PVR, ↑ blood flow
    - Relaxes smooth muscle in bladder neck & prostate
  - Hypertensive episodes:
    - Pheochromocytoma

Nonselective α-Blockers Phentolamine

- Competitive receptor antagonists
  - Vasodilation, ↓PVR, ↓BP
- Dermal necrosis & ischemia
  - i.e. accidental injection of epinephrine into finger
- Adverse Effects
  - Dizziness, headache, nasal congestion

Selective α_1-Antagonists

- MOA:
  - Relax vascular & smooth muscles including urinary and prostate
- Indications
  - Hypertension
  - Urinary retention
- Adverse Effects
  - 1st dose syncope

Selective α_1-Antagonists

- Prazosin, doxazosin & terazosin
- Alfuzosin and Tamsulosin
  - Uroselective α_1 blockers
  - Indication: urinary retention in males with BPH

B-Adrenergic Receptor Antagonists

- Blockade of β_1-receptors
  - Heart: negative chronotropic, inotropic, and dromotropic effect
  - Kidneys: reduces secretion of renin
  - Eye: ↓ aqueous humor secretion and intraocular pressure

B-Adrenergic Receptor Antagonists

- Blockade of β_2-receptors
  - Lungs: bronchoconstriction
  - Liver: slows recovery of blood glucose after hypoglycemic event
  - Masks signs/symptoms of hypoglycemia

B-Adrenergic Receptor Antagonists

- Nonselective
  - Nadolol
  - Pindolol
  - Propanolol
  - Timolol
- Selective
  - Acebutolol
  - Atenolol
  - Esmolol
  - Metoprolol

Nonselective Beta Blockers

- Propanolol
  - High lipid solubility
  - Hypertension
  - Essential tremor, migraine headaches, acute thyrotoxicosis, acute myocardial infarction, pheochromocytoma
- Timolol
  - Glaucoma

Selective Beta Blockers

- Cardioselective
  - $\beta_1 > \beta_2$
- Selectivity is not absolute
- Use with caution in asthmatics
- Metoprolol

α- and β–Adrenergic Receptor Antagonists

- Carvedilol
  - MOA: vasodilation, ↓HR & BP, ↑ cardiac output
  - Clinical use: hypertension & heart failure
- Labetalol
  - MOA: vasodilation, ↓HR & BP
  - Clinical use: hypertension

The END!!!!!