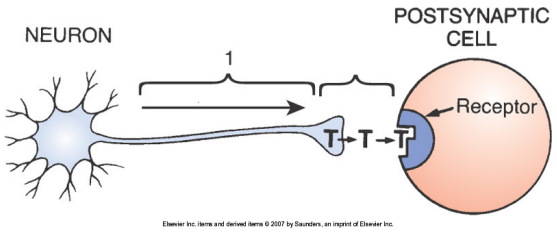
Introduction to Neuropharmacology

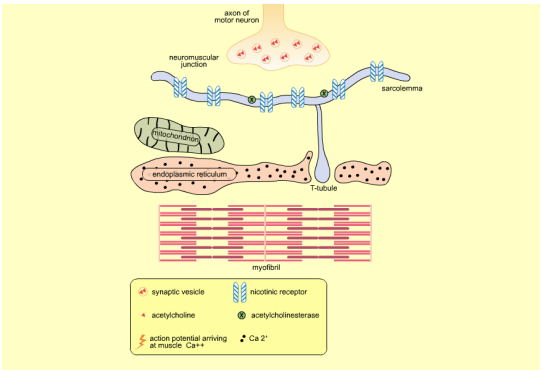
Neuropharmacology

- Study of drugs that alter processes controlled by the nervous system
- Division of neuropharmacological agents
  - Peripheral Nervous system drugs
  - Central Nervous system drugs

How Neurons Regulate Physiology

- General process
  - Transmission of impulse down axon
  - Release of neurotransmitter from axon terminal
  - Binding of neurotransmitter to receptor on post-synaptic cell
  - Post-synaptic cell changes action
    - Muscle relaxes or contracts
    - Glands secrete or stop secreting
    - Neurons fire more often or less often





Ways we can interfere

- Alter axonal conduction
  - Local anesthetics
- Alter synaptic Transmission
- Affect receptors

- If drug causes same effect as natural process: receptor activation
- If drug reduces or causes opposite: receptor deactivation

Steps of Synaptic Transmission

- Transmitter synthesis
- Transmitter Storage (vesicles)
- Release of Transmitter
  - Only small number of vesicles release
- Receptor Binding (reversible)
- Termination of Transmission
  - Reuptake
  - Enzymatic degradation
  - Diffusion(slow, usually doesn't happen in vivo)

Transmitter Synthesis

- Drugs can
  - Increase transmitter synthesis
  - Decrease transmitter synthesis
  - Cause synthesis of different transmitter that is more effective than the natural
  - Theoretical: cause synthesis of ineffective transmitter

Storage and Release

- Storage: drugs can interfere with storage
  - Less transmitter stored → less released
- Transmitter release: drugs can
  - Promote release
  - Inhibit release

Receptor Binding

- Drug can
  - Bind directly to receptors and activate them
    - Agonists
  - Bind to receptors and block them
    - Antagonists
  - Bind to receptor and enhance activation by natural transmitter
    - No special name

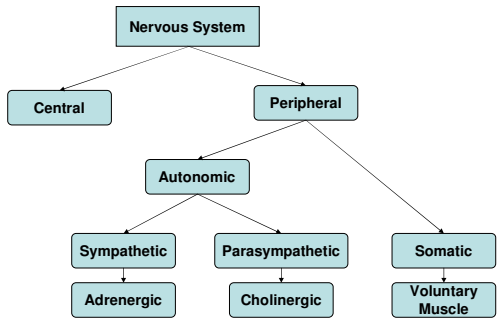
Termination of Transmitter

- Block Reuptake
  - Reuptake inhibitors
- Inhibition of enzymatic degradation
- Both cause more increased transmitter action

Receptor types and Selectivity

- Drug Selectivity: selectivity of drug for effected receptor
  - Does drug bind to only α1 receptors or does it also bind to β1 and β2 receptors?
- Physiologic Selectivity: does the receptor do more than one thing? (Is it present in multiple tissues?)
  - β1 receptors control heart rate, conductivity, and contraction as well as renin release from kidney

Physiology of Peripheral Nervous System



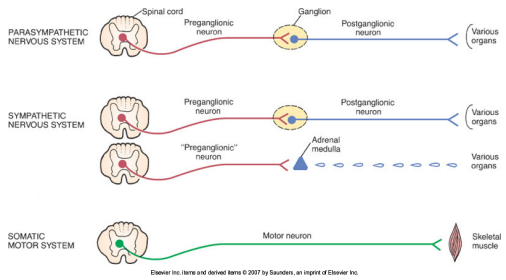
Peripheral Neurotransmitters

- Acetylcholine
- Epinephrine
- Norepinephrine
- Dopamine (kind of)

Peripheral Receptors

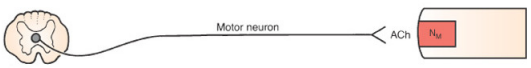
- Cholinergic Receptors
  - All receptors that mediate responses to acetylcholine
    - Muscarinic, Nicotinic-M, Nicotinic-N
- Adrenergic Receptors
  - All receptors that mediate responses to epinephrine and norepinephrine
    - Alpha-1, alpha-2, beta-1, beta-2

Peripheral Pathways (Memorize Fig 13-4, pg 102)

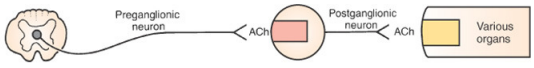


Peripheral Pathways (Memorize Fig 13-4, pg 102)

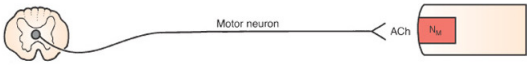
- Somatic
  - Muscle movement
  - No ganglia
  - Transmitter: Acetylcholine
  - Receptor: Nicotinic-M ("M" for muscle)



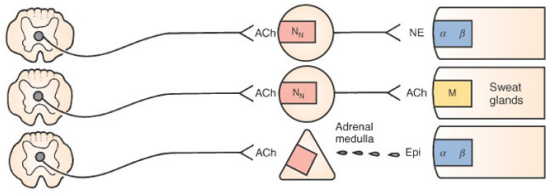
Parasympathetic



Somatic



Sympathetic Neurotransmitters



Overview of Autonomic Functions

- Regulation of Heart
- Regulation of glands
  - Salivary
  - Gastric
  - Sweat
  - Bronchial
- Regulation of smooth muscle
  - Bronchi, blood vessels, urogenital
  - GI tract

Parasympathetic Functions

- Slow heart
- Increase gastric secretion and motility
- Emptying Bowel
- Focusing eye for near vision
- Constriction of pupil
- Contraction of bronchial smooth muscle

- Most cholinergic drugs affect: GI, bladder, eye

Sympathetic Functions

- Cardiovascular system
- Body temperature
- Stress: Fight or Flight
  - Increase HR and BP
  - Shunt blood from skin & viscera to muscles
  - Dilation of bronchi
  - Dilation of pupils
  - Mobilization of stored energy: glucose, fatty acids

Control Mechanisms

- Innervation by both where effects are opposed
  - Heart rate
- Innervation by both where effects are complementary
  - Male reproductive processes
- Innervation by only one
  - Blood vessels

Autonomic Tone

- Steady day-to-day influence exerted by the autonomic system
  - Usually only one division provide tone
  - Parasympathetic system usually provides the basal tone

Peripheral Receptor Subtypes

- Cholinergic
  - Nicotinic-N (“n” for neuronal)
  - Nicotinic-M (“m” for muscle)
  - Muscarinic
- Adrenergic
  - Alpha-1
  - Alpha-2
  - Beta-1
  - Beta-2
  - (Dopamine receptors)

Cholinergic Receptors

Subtypes and Normal Physiology

- Acetylcholine activates all cholinergic subtypes, so…Why do we have subtypes at all?
  - Maybe we are evolving and will soon produce endogenous nicotine?
  - Maybe God designed it that way so we could discover medicine?
  - Other reasons?
- Some cholinergic receptors are not attached to any nerve.

Cholinergic Receptor Function

- Nicotinic-N: promotes ganglionic transmission at all ganglia
- Nicotinic-M: causes skeletal muscle contraction
- Muscarinic:
  - Increased gland secretion
  - Contraction of smooth muscle (bronchi, bladder, GI)
  - Slow heart rate
  - Contraction of iris (miosis) and ciliary (focus)

Adrenergic Receptor Function

- Alpha-1
  - Ocular: mydriasis
  - Blood vessels: vasoconstriction
  - Male genitals: ejaculation
  - Bladder neck and prostate: contraction
- Alpha-2
  - Located on presynaptic terminal
  - Inhibits release of norepinephrine
  - Located in PNS and CNS

Adrenergic Receptor Function

- Beta-1
  - Heart: ↑inotropic, chronotropic, dromotropic
  - Kidney: stimulate release of renin
- Beta-2
  - Bronchi: dilation
  - Uterus: relaxation of uterine smooth muscle
  - Arterioles in heart, lungs, skeletal muscle: vasodilation
  - Glycogenolysis
  - Enhances skeletal muscle contraction

Dopamine Receptors

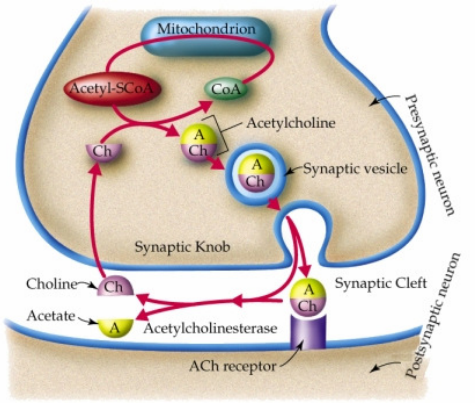
- Primarily in CNS, not PNS
- Only known function of PNS dopamine receptors is
  - Dilation of renal arteries → enhances renal perfusion

Selectivity of Adrenergic Neurotransmitters

Transmitter	Alpha 1	Alpha 2	Beta 1	Beta 2	Dopa
Epinephrine	+	+	+	+	0
Norepinephrine	+	+	+	0	0
Dopamine	+	0	+	0	+

Life Cycle of Acetylcholine

- Synthesized in presynaptic terminal from choline and Acetylcoenzyme A
- Stored in vesicles and released with AP
- Binds to receptors on postsynaptic cell
  - Dissociates
  - Is broken down by acetylcholinesterase on the post-synaptic cell membrane
  - Choline is re-absorbed by neuron to synthesize more ACh



Norepinephrine

- Synthesized in presynaptic terminal from a series of precursors, stored in vesicles
- Released after action potential
- Binds to receptors
  - Alpha-2 on the presynaptic neuron
  - Alpha1 or Beta1 on postsynaptic cell
- Reuptake by presynaptic neuron
  - Recycled…or
  - Broken down by MAO (monamine oxidase)

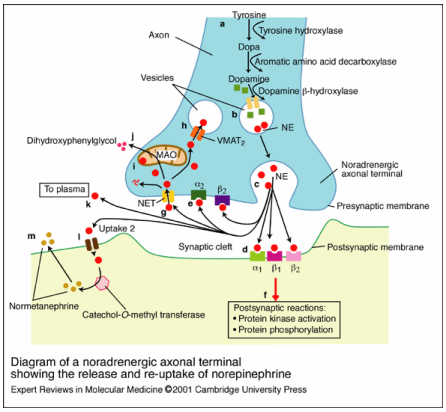


Diagram of a noradrenergic axonal terminal showing the release and re-uptake of norepinephrine

Lifecycle of Epinephrine

- Synthesized in adrenal medulla by making norepinephrine and then converting it
- Stored in vesicles in adrenal medulla
- Released into bloodstream after AP
  - Travels in blood throughout the body
  - Metabolized by the liver