Autonomic (ANS) Pharmacology

• Sympathetic Nervous System
Autonomic and Somatic Innervation

- Skeletal muscle is innervated by somatic nerves, controlling voluntary actions.
- All other innervated structures are supplied by the autonomic or involuntary system.
- Somatic system: No ganglia present.
- Autonomic nervous system (ANS) has ganglia.
- These ganglia are sites at which preganglionic fibers form synaptic connections with postganglionic neurons.
- These ganglia are located outside the cerebrospinal axis.
Other differences between Somatic and Autonomic Innervation:

- Motor nerves to skeletal muscle: myelinated
- Postganglionic autonomic nerves are nonmyelinated
- Denervation of skeletal muscle results in paralysis and atrophy
- Denervated smooth muscle or glands retain some activity
**Red = sympathetic actions**

**Blue = parasympathetic actions**

**EYE**
- Contraction of iris radial muscle (pupil dilates)
- Contraction of iris sphincter muscle (pupil contracts)
- Contraction of ciliary muscle (lens accommodates for near vision)

**TRACHEA AND BRONCHIOLES**
- Dilates
- Constricts, increases secretions

**ADRENAL MEDULLA**
- Epinephrine and norepinephrine secreted

**KIDNEY**
- Secretion of renin ($\beta_1$ increases; $\alpha_1$ decreases)

**URETERS AND BLADDER**
- Relaxes detrusor; contraction of trigone and sphincter
- Contraction of detrusor; relaxation of trigone and sphincter

**GENITALIA (male)**
- Stimulates ejaculation
- Stimulates erection

**GENITALIA (female)**
- Relaxation of uterus

**GASTROINTESTINAL**
- Decrease in muscle motility and tone; contraction of sphincters
- Increased muscle motility and tone

**BLOOD VESSELS**
- (skeletal muscle) Dilation
- (skin, mucous membranes, and splanchnic area) Constriction

**Lacrimal Glands**
- Stimulates tears

**Salivary Glands**
- Thick, viscous secretion
- Copious, watery secretion

**Heart**
- Increased rate; increased contractility
- Decreased rate; decreased contractility

**Blood Vessels**
- (skeletal muscle) Dilation
- (skin, mucous membranes, and splanchnic area) Constriction
Characteristics of Autonomic Organ Innervation

– Usually, parasympathetic and sympathetic systems are physiological antagonists; that is, if one system facilitates or augments a process the other system inhibits the process.
– Since most visceral organs are innervated by both system, the activity of the organ is influenced by both, even though one system may be dominant.

– The general pattern of antagonism between sympathetic and parasympathetic systems is not always applicable. The interaction between sympathetic and parasympathetic systems may be independent or interdependent.
Examples of Antagonistic Interactions between Sympathetic and Parasympathetic Systems

- Actions of sympathetic and parasympathetic influences on the heart.
- Actions of sympathetic and parasympathetic influences on the iris.
Interdependent or Complementary Sympathetic and Parasympathetic Effects

• Actions of sympathetic and parasympathetic systems on male sexual organs are complementary.
Independent Effects

- Vascular resistance is mainly controlled by sympathetic tone.
Homeostasis is a dynamic balance between parasympathetic and sympathetic activity. The diagram illustrates the transition between rest-and-digest and fight-or-flight states, with parasympathetic activity on the left and sympathetic activity on the right.
Fight or Flight: General Functions of the Autonomic Nervous System

- ANS regulates organs/processes not under conscious control including:
  - circulation
  - digestion
  - respiration
  - temperature
  - sweating
  - metabolism
  - some endocrine gland secretions
– Sympathetic system is most active when the body needs to react to changes in the internal or external environment: The requirement for sympathetic activity is most critical for:
  • temperature regulation
  • regulation of glucose levels
  • rapid vascular response to hemorrhage
  • reacting to oxygen deficiency

– During rage or fright, the sympathetic system can discharge as a unit—affecting multiorgan systems.
Sympathetic Responses

- heart rate increases.
  - blood pressure increases.
  - blood is shunted to skeletal muscles.
  - blood glucose increase.
  - bronchioles dilate.
    - pupils dilate
Parasympathetic responses

• slows heart rate.
• protects retina from excessive light.
• lowers blood pressure.
• empties the bowel and bladder.
• increases gastrointestinal motility.
• promotes absorption of nutrients.
Neurotransmitters and the Autonomic Nervous System

• Neurotransmitter Criteria: To support the idea that a chemical is a neurotransmitter, several conditions must be satisfied---
  – The chemical should be found in the appropriate anatomical location (e.g. synaptic terminal)
  – Enzymes that are involved in "transmitter" synthesis should also be present.
Neurotransmission Steps

• Axonal conduction
  – Depolarization of the axonal membrane potential results in an action potential.
  – The up stoke of the action potential is a sodium current flowing through voltage-activated sodium channels
– As the membrane potential decreases, activation occurs of an outgoing potassium current, which opposes further depolarization and initiates repolarization.

– Longitudinal spread of local depolarizing sodium currents results in progressive, longitudinal activation of sodium channels and new sites of depolarization. The rate of conduction is dependent on the number and synchrony of sodium channel activation.

– Number and synchrony of sodium channel activation is membrane potential dependent.
• As the resting membrane potential decrease (towards 0), fewer sodium channels will be activated by a depolarizing influence and conduction velocity slows.
1. An action potential depolarizes the axon terminal.

2. The depolarization opens voltage-gated Ca^{2+} channels and Ca^{2+} enters the cell.

3. Calcium entry triggers exocytosis of synaptic vesicle contents.

4. Neurotransmitter diffuses across the synaptic cleft and binds with receptors on the postsynaptic cell.
Many chemical can inhibit norepinephrine or acetylcholine release through receptor interactions at the appropriate terminal. Examples:

- Norepinephrine + presynaptic alpha 2-adrenergic receptor (autoreceptor) inhibits norepinephrine release
- Alpha\textsubscript{2} receptor antagonists increase release of norepinephrine
- Neurally-mediated acetylcholine release from cholinergic neurons is inhibited by alpha\textsubscript{2}-adrenergic receptor agonists
- Stimulation of presynaptic beta\textsubscript{2} adrenergic receptors increases slightly norepinephrine release
• These agents Inhibit neurally-mediated norepinephrine released by interacting with presynaptic receptors
  – Adenosine
  – Acetylcholine
  – Dopamine
  – Prostaglandins
  – Enkephalins

• Neurotransmitter + Post-Junctional Receptors Interactions Lead to Physiological Response
Termination of Transmitter Action

– Cholinergic: Termination of action of acetylcholine is acetylcholine hydrolysis. (acetylcholinesterase-catalyzed)
  • If acetylcholinesterase is inhibited, the duration of cholinergic effect is increased.

– Adrenergic: Termination of action of adrenergic neurotransmitters is by reuptake and diffusion away from receptors.
Cholinergic Neurotransmission

1. **Synthesis of Acetylcholine**
   - Transport of choline is inhibited by hemicholinium.

2. **Uptake into Storage Vesicles**
   - Acetylcholine is protected from degradation in the vesicle.

3. **Release of Neurotransmitter**
   - Release is blocked by botulinum toxin.
   - Spider venom causes release of acetylcholine.

4. **Binding to the Receptor**
   - Postsynaptic receptor is activated by binding of the neurotransmitter.

5. **Degradation of Acetylcholine**
   - Acetylcholine is rapidly hydrolyzed by acetylcholinesterase in the synaptic cleft.

6. **Recycling of Choline**
   - Choline is taken up by the neuron.
Transmitter Synthesis and Degradation

- Acetylcholine is synthesized from the immediate precursors acetyl coenzyme A and choline in a reaction catalyzed by choline acetyltransferase (choline acetylase).
Acetylcholinesterase

- Rapid inactivation of acetylcholine is mediated by acetylcholinesterase.
- Acetylcholinesterase is present at ganglia, visceral neuroeffector junctions, and neuromuscular junctional endplates.
- Another type of cholinesterase, called pseudo-cholinesterase or butyrylcholinesterase has limited presence in neurons, but is present in glia. Most pseudo-cholinesterase activity is found in plasma and liver.
- Pharmacological effects of anti-cholinesterase drugs are due to inhibition of acetylcholinesterase
Cholinergic Transmission: Site Differences

- **Skeletal Muscle**
  - Neurotransmitter: Acetylcholine
  - Receptor Type: Nicotinic
  - Sectioning and degeneration of motor and post-ganglionic nerve fibers results in:
    - an enhanced post-synaptic responsiveness, denervation hypersensitivity.
      - Denervation hypersensitivity in skeletal muscle is due to
        - increased expression of nicotinic cholinergic receptors
        - and their spread to regions away from the endplate.
Autonomic Effectors

- Neurotransmitter: Acetylcholine
- Receptor type: Muscarinic
- Effector coupled to receptor by a G protein
- In smooth muscle and in the cardiac conduction system, intrinsic electrical activity and mechanism activity is present, modifiable by autonomic tone.
  - Activities include propagated slow waves of depolarization:
    - Examples: intestinal motility and spontaneous depolarizations of cardiac SA nodal pacemakers.

- Acetylcholine decreases heart rate by decreases SA nodal pacemaker phase 4 depolarization
Autonomic Ganglia

- Neurotransmitter: Acetylcholine
- Receptor type: Nicotinic
- Generally similar to skeletal muscle site: initial depolarization is due to receptor activation. The receptor is a ligand-gated channel.
Blood vessels

– Choline ester administration results in blood vessel dilatation as a result of effects on prejunctional inhibitory synapses of sympathetic fibers and inhibitory cholinergic (non-innervated receptors).

– In isolated blood vessel preparations, acetycholine's vasodilator effects are mediated by activation of muscarinic receptors which cause release of nitric oxide, which produces relaxation.
Signal Transduction

- **Nicotinic Receptors**
  - Ligand-gated ion channels
  - Agonist effects blocked by tubocurarine
  - Receptor activation results in:
    - rapid increases of Na$^+$ and Ca$^{2+}$ conductance
    - deplorization
    - excitation
  - Subtypes based on differing subunit composition:
    Muscle and Neuronal Classification
Muscarinic Receptors

- G-protein coupled receptor system
- Slower responses
- Agonist effects blocked by atropine
- At least five receptor subtypes have been described by molecular cloning. Variants have distinct anatomical locations and differing molecular specificities
Acetate

Choline

Acetylcholine

Echothiophate
Edrophonium
Neostigmine
Physostigmine

INCREASED INTRACELLULAR RESPONSE
Autonomic

Sympathetic innervation of adrenal medulla
- Preganglionic neuron
- Ganglionic transmitter
- Acetylcholine
- Nicotinic receptor
- Epinephrine released into the blood
- Adrenergic receptor
- Striated muscle

Sympathetic
- Acetylcholine
- Nicotinic receptor
- Norepinephrine
- Adrenergic receptor
- Striated muscle

Parasympathetic
- Acetylcholine
- Muscarinic receptor

Somatic
- No ganglia
- Striated muscle

Sites of action of ganglionic blockers
- Nicotinic receptor

Sites of action of neuro-muscular blockers
- Nicotinic receptor

Site of action of antimuscarinic drugs
- Muscarinic receptor

Effector organs
Adrenergic Neurotransmission

• Introduction to the Neurotransmitters
• Norepinephrine: transmitter released at most postganglionic sympathetic terminals
• Dopamine: major CNS neurotransmitter of mammalian extrapyramidal system and some mesocortical and mesolimbic neuronal pathways.
• Epinephrine: most important hormone of the adrenal medulla
Catecholamine Synthesis, Storage, and Release

1. **SYNTHESIS OF NOREPINEPHRINE**
   - Hydroxylation of tyrosine is the rate-limiting step.

2. **UPTAKE INTO STORAGE VESICLES**
   - Dopamine enters a vesicle and is converted to norepinephrine.
   - Norepinephrine is protected from degradation in the vesicle.
   - Transport into the vesicle is inhibited by reserpine.

3. **RELEASE OF NEUROTRANSMITTER**
   - Influx of calcium causes fusion of the vesicle with the cell membrane in a process known as exocytosis.
   - Release is blocked by guanethidine and bretylium.

4. **BINDING TO RECEPTOR**
   - Postsynaptic receptor is activated by the binding of neurotransmitter.

5. **REMOVAL OF NOREPINEPHRINE**
   - Released norepinephrine is rapidly taken into the neuron.
   - Reuptake is inhibited by cocaine and imipramine.

6. **METABOLISM**
   - Norepinephrine is methylated by COMT and oxidized by MAO.

**SYNAPTIC SPACE**

**INTRACELLULAR RESPONSE**
**A** α Adrenoceptors

- Epinephrine
- Norepinephrine
- Isoproterenol

α Receptor

High affinity ➔ Low affinity

**B** β Adrenoceptors

- Isoproterenol
- Epinephrine
- Norepinephrine

β Receptor

High affinity ➔ Low affinity
**β-adrenergic receptors**

- Order of agonist potency
  - Isoproterenol > epinephrine > norepinephrine
- **β-receptors** are divided into two major categories: β1 and β2.
  - β1 receptors myocardium.
  - β2 receptors smooth muscle and most other sites.
- The subdivision of beta receptors followed from the observation that in the heart norepinephrine and epinephrine were equipotent, whereas epinephrine was many fold (10 - 50) more potent at smooth muscle.
A β3 receptor has been found that is strongly activated by norepinephrine compared to epinephrine and may explain "atypical" pharmacological properties of adipose tissue.

The β3-receptor is not blocked by propranolol, classified as a non-selective beta-receptor blocker.

Activation of β1, β2 and β3 receptors increases adenylyl cyclase activity (Gs mediated) resulting in a rise of intracellular cAMP.
Cardiac inotropic effects result from increases in Ca2+ concentration, due to:

- phosphorylation of L-type Ca2+ channels
- phosphorylation of sarcolemmal Ca2+ pumps
- direct action Gs action on the L-type channel
  - Effects on the liver lead to activation of glycogen phosphorylation
- β2 receptor activation mediates relaxation of vascular smooth muscle
  - β2 receptor activation mediates relaxation of G.I. smooth muscle.
  - alpha2 adrenergic receptor activation acts presynaptically to reduce Ach release and promote G.I. smooth muscle relaxation.
  - The alpha2 receptor effect is the more important.
Alpha Adrenergic Receptors

• Order of agonist potency
  – epinephrine > norepinephrine >> isoproterenol
  – Multiple alpha receptor subtypes have been identified.
  – Multiple forms were suggested when, after administration of an alpha-receptor antagonist, repetitive nerve stimulation resulted in increasing amount of norepinephrine release.
– This findings suggested a presynaptic alpha-receptor binding site.
– Post-synaptic receptors alpha1.
– Pre-synaptic receptors alpha2.
– Alpha2 receptors are also present post-synaptically. This site is involved in the action of some centrally-acting antihypertensive agents, e.g. clonidine.
– Some drugs, such as clonidine are more active at alpha2 receptors.
Catecholamine Refractoriness

Following exposure to catecholamines, there is a progressive loss of the ability of the target site to respond to catecholamines. This phenomenon is termed tachyphylaxis, desensitization or refractoriness.

Regulation of catecholamine responsiveness occurs at several levels:

- Receptors
- G proteins
- Adenylyl cyclase
- Cyclic nucleotide phosphodiesterase

Stimulation of β-adrenergic receptors rapidly causes receptor phosphorylation and decreased responsiveness.

The phosphorylated receptor exhibits:

- decreased coupling to Gs and
- decreased stimulation of adenylyl cyclase.
INDIRECT-ACTING
Drug enhances release of norepinephrine from vesicles.

DIRECT-ACTING
Drug directly activates receptor.

MIXED-ACTING
Drug acts both directly and indirectly.
A  Agonists  
(for example, epinephrine)

- $\beta_1$ and $\beta_2$ receptor
- $\beta_1$ and $\beta_2$ receptors activated
- CELLULAR EFFECTS

B  Antagonists  
(for example, propranolol)

- Epinephrine
- $\beta_1$ and $\beta_2$ receptors blocked but not activated

C  Partial agonists  
(for example, pindolol and acebutolol)

- $\beta_1$ and $\beta_2$ receptors partially activated but unable to respond to more potent catecholamines
- DECREASED CELLULAR EFFECTS
## Predominant Sympathetic or Parasympathetic Tone

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<thead>
<tr>
<th>Antatomical Site</th>
<th>Predominant Autonomic Tone</th>
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</tr>
<tr>
<td>Sweat Glands</td>
<td>Sympathetic-cholinergic</td>
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Pharmacological Modification of Autonomic Function

Sites of Drug Action:
- Transmitter Synthesis (Site 1)
- Transmitter Release (Site 2)
- Receptor Interactions (Site 3)
- Termination of Transmitter Effects (Site 4)
Transmitter Synthesis: Site 1

– Cholinergic
  • **Hemicholinium** (HC-3) blocks the choline transport system into the nerve ending, thus limiting acetylcholine (ACh) synthesis.

– Adrenergic
  • **Alpha-methyltyrosine** inhibits tyrosine hydroxylase thus preventing synthesis of norepinephrine.
  • **Methyldopa** inhibits aromatic amino acid decarboxylase and is itself decarboxylated and hydroxylated to form the "false transmitter" alpha-methyl norepinephrine
Transmitter Release: Site 2

– Cholinergic
  • **Botulinum** toxin can be used clinically to treat ocular muscle spasms, muscle dystonias, and spasms.
  • **Botulinus** toxin binding at a presynaptic site blocks ACh release.
  • Vesamicol blocks ACh transport into storage vesicles, thus limiting release.
Adrenergic

- **Bretylium and guanethidine** prevent action-potential mediated norepinephrine release.
- Transient release may occur with these agents because they displace norepinephrine from storage sites.
- **Tyramine, amphetamine, and ephedrine** can produce a brief liberation of transmitter.
- **Reserpine**, by inhibiting vesicular uptake, produces a slow, depletion of norepinephrine, ultimately causing adrenergic blockade. Cytoplasmic MAO metabolizes the neurotransmitter.
- **Reserpine** similarly depletes dopamine and serotonin. Physiological effects of reserpine are due to depletion of many transmitters.
Receptor Interactions: Site 3

– Cholinergic
  
  • Tetraethylammonium, trimethaphan and hexamethonium are nicotinic ganglionic antagonists.
  
  • Decamethonium, a depolarizing drug, selectively causes neuromuscular blockade.
  
  • All classes of muscarinic receptors are blocked by atropine.
Adrenergic

- **Phenylephrine** (Neo-Synephrine): an alpha1 receptor agonist.
- **Clonidine** (Catapres): an alpha2 receptor agonist.
- **Prazosin** (Minipress): an example of an alpha1 receptor antagonist.
- **Yohimbine** (Yocon): an example of an alpha2 receptor antagonist.
- **Isoproterenol** (Isuprel): β1 and β2 receptor agonist.
- **Dobutamine** (Dobutrex): a relatively selective myocardial β1 receptor agonist.
- **Terbutaline** (Brethine): relatively selective β2 receptor agonist.
- **Propranolol** (Inderal): an example of a non-selective beta-adrenergic receptor blocker.

- **Metoprolol** (Lopressor): an example of a relatively selective β1 receptor antagonist
Termination of Transmitter Effects: Site 4

– **Cholinergic**
  
  • **Acetylcholinesterase** inhibitors prevent breakdown and inactivation of acetylcholine.
    – ACh accumulation at the neuromuscular junction causes flacid paralysis.
    – ACh accumulation at postganglionic muscarinic sites results in either excessive stimulation (contraction & secretion) or inhibition (hyperpolarization), depending on the site.
    – ACh accumulation at autonomic ganglia cause increased transmission.
Adrenergic

- Interference with neurotransmitter reuptake results in potentiation of catecholamine effects.
- **Cocaine and imipramine** are examples of drugs that inhibit the reuptake system.
- **Monoamine oxidase (MAO)** inhibitors potentiate actions of tyramine; whereas **catechol-O-methyl transferase (COMT)** inhibitors (pyrogallol and tropolone) only slightly increase catecholamine effects.