13. Drug Actions in Synaptic Transmission – Scrogin
15. Adrenergic Agonists and Antagonists II – Scrogin
16. Adrenergic Agonists and Antagonists III – Scrogin
17. Cholinergic Agonists & Antagonists – Scrogin
18. Neuromuscular Relaxants – Scrogin
19. Serotonin and Dopamine – Scrogin
20. Opioid Analgesics – Gentile
21. Local Anesthetics – Byram
22. General Anesthetics – Haske
23 & 24. NSAIDS 1 & II – Clipstone (Posted Later)
25. Using Acupuncture to Explore the Neuropharmacology of the Pain Pathway - Michelfelder
ADRENERGIC AGONISTS I AND II

LEARNING OBJECTIVES

1. Distinguish the anatomical and chemical characteristics of the sympathetic, parasympathetic and somatic motor systems (e.g., origin, pathway, neurotransmitters released from pre and post-ganglionic cells).

2. List the major visceral organs that are innervated by the sympathetic and parasympathetic systems (as discussed in lecture) and describe the functional responses of the organs to activation of either system.

3. Describe the basic distribution of the adrenergic receptor subtypes in the main visceral organs discussed in class, i.e., eye, heart, bronchiole smooth muscle, kidney, vascular smooth muscle, splanchnic vasculature.

4. List the 4 main subtypes of adrenergic receptors and recognize the most common second messenger system to which they are coupled, and how the second messenger mediates the typical functional response of the target organs discussed in lecture.

5. List the two adrenergic receptors that are expressed on the pre-synaptic membrane of both noradrenergic and non-noradrenergic nerve terminals and describe how their activation influences neurotransmitter release.

6. Arrange epinephrine, norepinephrine and the prototypical β-adrenergic receptor agonist, isoproterenol, in order of their affinity for the 4 main adrenergic receptors discussed in lecture.

7. Describe how the catecholamines influence cardiovascular and bronchiolar function and what receptors mediate these effects.

8. For the adrenergic receptor agonists discussed in class, categorize them according to their relative affinity for the different adrenergic receptors and describe how this relates to their ability to influence vascular tone, bronchiole smooth muscle relaxation and cardiac contractility.

9. List the most common toxic side effects of the endogenous and synthetic adrenergic agonists discussed in lecture (those bolded on slides) and describe the mechanisms by which they occur.

10. List the most important therapeutic uses for the endogenous and synthetic adrenergic agonists discussed in class. (all those discussed in lecture)

11. List 4 commonly used indirect acting sympathomimetics

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12. Describe the most important toxic side effects and most important therapeutic uses indirect acting sympathomimetic drugs.
SYNAPTIC TRANSMISSION: TARGETS OF DRUG ACTION

1. **Synaptic transmission** can be broken down into 5 main steps, each of which can be manipulated pharmacologically to alter physiological function.

   A. **Neurotransmitter Synthesis** (1) occurs inside the neuron, requires transport of specific precursor molecules across plasma membrane.

      1. Therapeutic drugs can inhibit enzymes involved in neurotransmitter production.

      2. Dietary intake of certain amino acids can influence precursor availability. Example: tryptophan. A diet low in tryptophan combined with high intake of amino acids that are taken up by the same amino acid transporter that takes up tryptophan can reduce serotonin production.

      3. **Precursor loading** can increase neurotransmission Ex: L-DOPA in Parkinson’s Disease

   B. **Vesicular Storage** (2)– All neurotransmitters (except for gases and some nucleosides) are stored in secretory vesicles

      1. Storage of neurotransmitters in synaptic vesicles protects them from degradation by cytosolic enzymes. Packaging of protein neurotransmitters in large vesicles at the cell body enables the transport of protein neurotransmitters down the axon to the nerve terminal.

      2. Neurotransmitters in the cytoplasm can be degraded when vesicular transport is inhibited resulting in neurotransmitter depletion.
C. **Synaptic Release (3)** - Depolarization of the nerve terminal results in the opening of calcium channels. Elevated intracellular calcium permits the fusion of synaptic vesicles with the plasma membrane. The interaction of vesicle-membrane bound SNAREs with plasma membrane bound SNAREs leads to fusion of the vesicle with the plasma membrane and rapid release of neurotransmitter into the synapse.

1. Toxins can degrade SNAREs and disrupt fusion of synaptic vesicles with the cell membrane. The pharmacological effect of such disruption depends upon the cell type that takes up the toxin

2. **Botulinum toxin** degrades SNAREs of the cholinergic neuromuscular junction resulting in skeletal muscle paralysis due to loss of acetylcholine release. Botulinum toxin is now used therapeutically to treat localized muscle spasms.

3. Tetanus toxin targets neurons that inhibit motor neurons resulting in excessive muscle tone. This occurs first in the masseter muscle resulting in “lockjaw”.

4. Some indirectly acting drugs (i.e., those that do not interact directly with a receptor) stimulate the release of neurotransmitters in a *calcium-independent* manner. Ex: **amphetamine** taken up by re-uptake transporters at the axon terminal (see description of reuptake transporters below under termination of neurotransmitter actions) and, once inside the cell, can activate signaling mechanisms that actually reverse the direction of neurotransmitter transport, resulting in the release of endogenous neurotransmitter back out to the extracellular side of the membrane without any membrane voltage change and calcium influx.
D. Binding of neurotransmitter to receptor (4) - Neurotransmitters bind to receptors localized on pre- and post-synaptic cell membranes.

1. **Drugs that bind directly to receptors provide the most selective manipulation of synaptic transmission.**

2. Drugs can act on pre-synaptic receptors to modulate neurotransmitter release by altering the influx of calcium following action potential generation. **Contributes to some side effects**, e.g., adrenergic receptor agonists used for asthma cause muscle tremor by stimulating acetylcholine release from motor neurons.

E. Termination of neurotransmitter action (5) – three major mechanisms account for termination of neurotransmitter action:

1. **Re-uptake of the neurotransmitter out of the synaptic cleft can occur at the pre-synaptic nerve terminal, the post-synaptic cell or the surrounding glial cells.** Primary reuptake site
is dependent on the location of reuptake protein expression.

2. Diffusion out of the synaptic cleft

3. Metabolic transformation and degradation.

Note: The action of different neurotransmitters is terminated by different mechanisms, (e.g., the action of monoamines: serotonin, norepinephrine and dopamine, are terminated by re-uptake into the pre-synaptic cell, while acetylcholine is degraded in the synaptic cleft).

2. Therapeutic examples: Targets of dopaminergic and adrenergic neurotransmission – dopaminergic, noradrenergic and adrenergic neurons release the catecholamines dopamine norepinephrine or epinephrine respectively. Dopaminergic neurons are found in the CNS. Noradrenergic and adrenergic neurons are found throughout the CNS as well as in the peripheral autonomic nervous system. Numerous drugs have been developed that target dopaminergic and noradrenergic neurotransmission because of their importance in motor and cardiovascular function as well as mood regulation and appetite.

A. Synthesis – dopaminergic and noradrenergic neurons transport tyrosine into the cell via an amino acid transporter. Several enzymatic steps eventually lead to tyrosine’s conversion to dopamine. Dopamine is the precursor to norepinephrine and epinephrine

1. Hydroxylation of tyrosine by tyrosine hydroxylase is the rate-limiting step in the production of catecholamines. Metyrosine binds to tyrosine hydroxylase, but cannot be transformed to DOPA, and thus decreases production of dopamine. Metyrosine is used in the treatment of hypertension by reducing norepinephrine production.

2. L-DOPA is a precursor of dopamine. It is used to treat Parkinson’s disease in which dopaminergic neurons in the brain are damaged. Since DOPA and dopamine are also precursors of norepinephrine. DOPA loading can have adverse effects on the cardiovascular system due to enhanced norepinephrine neurotransmission in the peripheral autonomic nerves.

3. Synthesis inhibition – carbidopa blocks the conversion of L-DOPA to dopamine. Carbidopa does not cross the blood brain barrier. It can be used to reduce the cardiovascular side effects of L-DOPA in peripheral adrenergic nerves, and preserve the beneficial effects of L-DOPA treatment for Parkinson’s disease within the CNS.
B. Storage- Dopamine is transported into synaptic vesicles by a vesicular transporter specific to monoamines, (i.e., serotonin, norepinephrine, histamine, and dopamine). Dopamine is transformed to norepinephrine by dopamine β-hydroxylase. The dopamine β-hydroxylase enzyme is expressed within the vesicle. This prevents the destruction of norepinephrine in the cytosol where oxidative enzymes rapidly degrade it. The vesicular monoamine transporter (VMAT) is blocked by reserpine which results in the depletion of monoamines (NE, DA, and serotonin). Reserpine can cross the blood brain barrier and block monoamine vesicular uptake in CNS neurons which can contribute to depression. Reserpine is now used safely and effectively at low doses that are combined with other antihypertensive drugs to treat refractory hypertension.

C. Release – calcium-dependent fusion of the synaptic vesicle with the pre-synaptic membrane leads to expulsion of the neurotransmitter.

1. Bretylium inhibits excitability of the nerve terminal membrane and Ca2+-dependent fusion of the synaptic vesicle with the plasma membrane thus reducing neurotransmitter release. Bretylium has affinity for, and is taken up by reuptake transporters proteins that normally take up norepinephrine. Thus bretylium has specific effects on adrenergic neurotransmission. This drug is used to reduce ventricular arrhythmia in a hospital setting.

D. Binding – Norepinephrine binds to 2 major types of receptors called α and β adrenergic receptors. Each type of "adrenergic" receptor has several subtypes that mediate different physiological functions depending upon the second messenger systems to which the receptor is coupled and the function of the cell type on which it is expressed

1. Post-synaptic receptor binding influences numerous cell functions that will be addressed in later lectures. Both agonists and antagonists of adrenergic
receptors are used in the treatment of cardiovascular and respiratory diseases as well as mood disorders.

2. Activation of pre-synaptic adrenergic receptors on nerve terminals influences neurotransmitter release, α–adrenergic receptors can inhibit, while β–adrenergic receptors can facilitate neurotransmitter release.

E. Termination of action – Termination of the action of norepinephrine released from noradrenergic nerve terminals is mediated primarily by re-uptake and to a lesser extent by diffusion and metabolic transformation. Termination of exogenously administered norepinephrine is mediated, in large part, by metabolism in plasma by catecholamine-O-methyltransferase (COMT). A second metabolic enzyme, monoamine oxidase (MAO), is present within the cell cytoplasm and rapidly oxidizes any norepinephrine and dopamine within the cytoplasm that is not transported into synaptic vesicles within time.

1. Re-uptake is the primary mode of terminating monoamine actions.
   Inhibitors of monoamine re-uptake have highly significant pharmacological effects. **Cocaine** inhibits re-uptake of monoamines including norepinephrine, dopamine and serotonin.
   Inhibitors of monoamine re-uptake are now widely used to combat depression and anxiety. **Tri-cyclic antidepressants** block re-uptake of several monoamines. As the name implies selective serotonin re-uptake inhibitors (SSRIs) provide a more selective inhibition of serotonin reuptake from the synapse of serotonergic neurons.
   Newer antidepressants now also target the norepinephrine transporter and some target both serotonin and norepinephrine transporters.
   Antidepressants must be able to cross the blood brain barrier to mediate their therapeutic effects. They can also
have significant systemic side effects, particularly in the cardiovascular system, which is richly innervated by noradrenergic neurons.

2. Metabolism is less important for termination of endogenously released catecholamine since re-uptake from the synapse is so efficient. Circulating catecholamines such as those released by the adrenal gland or those administered exogenously are subject to metabolism by COMT. The efficiency of this enzyme dramatically reduces the half-life of exogenously administered catecholamines. However, synthetic drugs designed to activate adrenergic receptors, e.g., phenylephrine, have been developed that are resistant to degradation by the enzyme and so have a longer half-life.

3. Metabolism also becomes a factor for catecholamines that have been taken back up into the cell. If they are not rapidly transported into the synaptic vesicle they become subject to rapid degradation by monoamine oxidase (MAO). MAO inhibitors lead to increased catecholamines in the cytoplasm. As norepinephrine accumulates in the cytoplasm, the transporter protein reverses direction leading to expulsion of norepinephrine into the synapse. Dietary sources of certain amino acids can produce adverse reactions when combined with MAO inhibitors. For example, tyramine can be taken up into noradrenergic cells. However, ingested tyramine is normally subject to significant first pass metabolism by MAO's in the liver. When MAOs are inhibited, such as during treatment for depression, ingested tyramine accumulates and is transported into adrenergic cells where it competes with norepinephrine for transport into synaptic vesicles resulting in even higher levels of cytoplasmic norepinephrine than with MAO inhibitors alone. The cytoplasmic accumulation of norepinephrine can reverse the concentration gradient across the plasma membrane and cause the reversal of the reuptake transporter. The resulting excessive release of norepinephrine can lead to a hypertensive crisis due to excessive vasoconstriction by norepinephrine in the periphery. Older MAOIs were irreversible and non-selective (block both MAO-A and MAO-B). Newer selective drugs can block MAO-A leaving MAO-B intact, allowing for tyramine degradation in gut, but still provides inhibition of serotonin, NE and DA breakdown in brain.
3. **Neuropeptide transmission.** Neuropeptides have distinct features that set them apart from other neurotransmitters. Consequently, additional issues must be considered when targeting peptidergic neurotransmission.

A. **Synthesis** – Neuropeptide synthesis requires the production of specific mRNAs within the nucleus. The mRNAs are transported from the nucleus and translated into pre-propeptide in the endoplasmic reticulum. Various cleavage processes mediated by peptidases ensue that lead to the production of active neuropeptide.

1. Peptidase inhibitors can be used to block the cleavage of pre-peptides thus preventing them from forming active neurotransmitter or hormones. But peptidases commonly target multiple proteins so their inhibition can lead to accumulation of lots of different proteins and non-specific effect. However, there several clinical trials ongoing.

B. **Storage into vesicle** – in contrast to other neurotransmitters, the neuropeptides are packaged into large “dense core vesicles”. This packaging occurs at the endoplasmic reticulum and so is difficult to target selectively. The vesicles are transported to the nerve terminal.

C. **Release** – Dense core vesicles reside farther away from the pre-synaptic membrane than do small synaptic vesicles. Consequently, increases in intracellular calcium concentration of longer duration are required to stimulate peptide release. Neuropeptides are often produced within other neuronal types and are co-released when the nerve terminal is activated. Therefore, drugs that target membrane ion channels to influence release of classic neurotransmitters, e.g., bretylium, will also influence neuropeptide release as well.

D. **Binding of neurotransmitter** – peptide neurotransmitters travel much farther distances to reach their receptor than do other neurotransmitters. Peptide molecules are also much larger than other classic neurotransmitters. Consequently, the interaction of peptides with their receptor is much more complex and not well understood. Nevertheless, peptidergic analogs have been developed for pharmaceutical use. However, they are unsuitable for use in the modification of neurotransmission in the CNS because they cannot cross the blood brain barrier. Therefore, many non-
peptidergic receptor agonists and antagonists have been developed to allow for penetration into the CNS. To date relatively few specific agonists and antagonists of neuropeptide receptors have been developed. Though several examples do exist.

1. Non-peptide opioid receptor antagonists have been developed and are highly efficient. **Naloxone** is a small lipophilic molecule widely used to reverse opioid overdose. **Naltrexone** has a longer duration of action and is used in the treatment of opiate addiction and alcoholism.

E. Termination of action - Neuropeptides are not taken up into the nerve terminal. The major mechanism of neuropeptide inactivation is by cleaving via peptidases. However, peptidases usually have multiple targets, therefore, their inhibition can lead to side effects. As yet, peptidases have not been a major target of pharmacotherapy of neurotransmission.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metyrosine</td>
<td>Hypertension</td>
<td>Competitive inhibition of tyrosine hydroxylase</td>
</tr>
<tr>
<td>Reserpine</td>
<td>Hypertension</td>
<td>Inhibits VMAT uptake of monoamines</td>
</tr>
<tr>
<td>Bretylium</td>
<td>Ventricular Arrhythmia</td>
<td>Inhibit action potential generation and calcium dependent synaptic vesicle fusion</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Analgesia in surgery</td>
<td>Blocks monoamine reuptake</td>
</tr>
<tr>
<td>Amphetamine or Ephedrine</td>
<td>Narcolepsy, ADHD</td>
<td>Reverse monoamine reuptake transporters</td>
</tr>
<tr>
<td>Naloxone, Naltrexone</td>
<td>Opioid overdose or dependence</td>
<td>Non-peptide blockers of opioid receptors in CNS</td>
</tr>
<tr>
<td>SSRIs</td>
<td>Depression/anxiety</td>
<td>Selective inhibition of serotonin reuptake transporter</td>
</tr>
<tr>
<td>ACE inhibitors e.g., lisinopril</td>
<td>Hypertension</td>
<td>Inhibits peptide cleavage of Angiotensin I to Angiotensin II</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>Hypotension during surgery</td>
<td>Direct agonist of adrenergic receptor</td>
</tr>
<tr>
<td>MAO inhibitors</td>
<td>Depression</td>
<td>Blockade of cytoplasmic metabolism of monoamines</td>
</tr>
<tr>
<td>L-DOPA</td>
<td>Parkinson's Disease</td>
<td>Precursor of dopamine, stimulates dopamine production</td>
</tr>
<tr>
<td>Carbidopa</td>
<td>Parkinson's Disease</td>
<td>Blocks L-DOPA conversion to dopamine, does not cross BBB, so protects peripheral adrenergic neurons from producing too much dopamine and norepinephrine</td>
</tr>
<tr>
<td>Tyramine</td>
<td>Ingested in diet, not therapeutic</td>
<td>Competes with NE for transport into synaptic vesicle</td>
</tr>
</tbody>
</table>
ADRENERGIC AGONISTS I AND II

LEARNING OBJECTIVES

1. Distinguish the anatomical and chemical characteristics of the sympathetic, parasympathetic and somatic motor systems (e.g., origin, pathway, neurotransmitters released from pre and post-ganglionic cells).

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11. List 4 commonly used indirect acting sympathomimetics
12. Describe the most important toxic side effects and most important therapeutic uses indirect acting sympathomimetic drugs.
ADRENERGIC AGONISTS & ANTAGONISTS

GENERAL COMMENTS

The next three lectures will focus on therapeutic agents that activate (sympathomimetics) and inhibit the sympathetic nervous system. These drugs act directly or indirectly on the receptors that mediate sympathetic function. These receptors are known collectively as "adrenergic" or "adreno" receptors. Emphasis will be placed on mechanisms and site of drug action, clinical utility, major side effects and important contraindications for use of these therapeutic agents. Subsequent lectures will focus on drugs that influence the parasympathetic side of the autonomic system. Therefore, the present lecture material will briefly cover some basic concepts in general autonomic function. But the emphasis of these lectures will be on the sympathetic system. Facts that are underlined should be the main focus of learning.

I. Anatomy

A. Autonomic Nervous System – is defined as an involuntary motor system. It is composed of sympathetic (thoracolumbar division), parasympathetic (craniosacral) and enteric nervous systems. The sympathetic and parasympathetic systems are comprised of two sets of fibers arranged in series with the exception of the adrenal gland. Pre-ganglionic cells arise from the intermediolateral cell column of the spinal cord and project to clusters of cell bodies, or “ganglia” that give rise to post-ganglionic cells that innervate the effector organ. The adrenal gland acts like a ganglion but releases hormone into the circulation.


1. Sympathetic - thoracolumbar division (short pre-ganglionic cells and long-post ganglionic cells)

2. Parasympathetic - craniosacral division (long pre-ganglionic cells and short post-ganglionic cells)
3. Enteric nervous system

The enteric nervous system (ENS) innervates the gastrointestinal tract, pancreas and gallbladder. The ENS can function autonomously, but its activity is modified by both the sympathetic and parasympathetic autonomic nervous systems. Innervation from the sympathetic and parasympathetic systems provides:

1) a second level of control over digestion
2) over-ride of the intrinsic enteric activity in times of emergency or stress (e.g., fight or flight).


II. Neurochemistry of the Autonomic Nervous system

A. Pre-ganglionic fibers release acetylcholine

B. Post-ganglionic parasympathetic fibers release acetylcholine

C. Post-ganglionic sympathetic fibers release norepinephrine (NE) (NE = noradrenaline; hence “adrenergic”)  

D. Adrenal medulla releases epinephrine (EPI) and NE (to a lesser extent) into the circulation

E. Exceptions: Post-ganglionic sympathetic fibers that innervate sweat glands and some skeletal muscle blood vessels that release acetylcholine.

III. Functional Organization of the Autonomic System – Some organs receive dual innervation, while other systems do not.

A. Parasympathetic - “Rest and digest”, or “rest and recovery”.

Eye – innervation of circular (or sphincter) muscles of pupil - constriction (miosis)
Heart – innervates sinoatrial node to reduce heart rate, and AV node to slow conduction.

Bronchioles – innervates smooth muscle of bronchi – causes constriction

GI tract – innervates all portions of the GI tract to promote secretions and motility

Bladder – innervates detrusor muscle, when activated causes bladder emptying

**B. Sympathetic** - “Fight or Flight”, major effects:

Eye – innervates radial (or dilator) muscle causes mydriasis, innervates ciliary body to stimulate production of aqueous humor

Heart - accelerated sinoatrial node pacemaker depolarization (increased heart rate).

Three currents contribute to sinoatrial node membrane potential,

1) inward calcium current
2) a hyperpolarization-induced inward current or "funny current" (mediated by hyperpolarization activated cyclic nucleotide gated channel, a non-selective cation channel)
3) outward K+ current.

Sympathetic activation increases inward calcium current and the funny current to promote faster spontaneous depolarization during phase 4 of sinoatrial node action potential and lower threshold for activation. Sympathetic activation also stimulates greater calcium influx into myocytes during depolarization culminating in greater contractile force of the heart.

Bronchioles – relaxation of smooth muscle lining the bronchioles

Blood vessels - contraction and relaxation - dependent on receptor population expressed in targeted vascular bed (e.g., alpha1 vs. beta2), as well as the ligand mediating the vascular response.

GI tract - decreased motility, can override normal enteric nervous system during fight or flight.

Bladder - inhibits emptying by contracting urethral sphincters and relaxing body of bladder (detrusor muscle) during urine storage.

Metabolic functions - increases blood sugar (gluconeogenesis, glycogenolysis, lipolysis).
IV. Adrenergic Function

A. Adrenergic Neurotransmission

1. synthesis- Tyrosine hydroxylase (the rate limiting step in DOPA formation. DOPA is metabolized to dopamine (DA). Half the DA produced is transported into storage vesicles via the vesicle monoamine transporter (VMAT), the other half is metabolized.

2. Storage in vesicles – Synaptic vesicles contain ATP and dopamine β-hydroxylase the latter of which converts dopamine to norepinephrine. Adrenal medullary cells produce norepinephrine (NE), or epinephrine (EPI). EPI-containing cells also synthesize an additional enzyme, phenylethanolamine-N-methyltransferase, that converts NE to EPI.

3. Release of catecholamines - Voltage dependent opening of calcium channels elevates intracellular calcium and stimulates the interaction of SNARE proteins to enable vesicle fusion with postsynaptic membrane and exocytosis of the vesicle contents.

4. Binding of neurotransmitter to post-synaptic or pre-synaptic sites- Neurotransmitters bind to receptors localized on pre-synaptic or post-synaptic cell membranes. The action of neurotransmitter binding depends upon the receptor type, the second messenger system as well as the machinery of the cell type.

5. Termination of action -three mechanisms account for termination of action in sympathetic neurons: 1) re-uptake into nerve terminals or post-synaptic cell, 2) diffusion out of synaptic cleft and 3) metabolic transformation. Inhibition of reuptake produces potent sympathomimetic effects indicating the importance of this process for normal termination of the neurotransmitter’s effects. Inhibitors of metabolism, i.e., inhibitors of monoamine oxidase (MAO) and catechol-o-methyltransferase (COMT) are very important in the metabolism of catecholamines within the nerve terminal and circulation respectively.

V. Adrenergic Receptors

Adrenergic receptors are coupled to G proteins that mediate receptor signaling by altering ion channel conductance, adenylyl cyclase activity and phospholipase C activation, as well as gene expression. Several adrenergic receptor subtypes are targeted in clinical pharmacology including α₁-, α₂-, β₁- and β₂-receptor subtypes. β₃ receptors are involved in fat metabolism and will become an important therapeutic target in the future.

A. Distribution of Adrenergic receptor subtypes

<table>
<thead>
<tr>
<th>Type</th>
<th>Tissue</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha_1</td>
<td>Most vascular smooth muscle</td>
<td>Contracts (↑ vascular resistance)</td>
</tr>
<tr>
<td></td>
<td>Pupillary dilator muscle</td>
<td>Contracts (mydriasis)</td>
</tr>
<tr>
<td></td>
<td>Pilomotor smooth muscle</td>
<td>Contracts (erects hair)</td>
</tr>
<tr>
<td>Alpha_2</td>
<td>Adrenergic and cholinergic nerve terminals</td>
<td>Inhibits transmitter release</td>
</tr>
<tr>
<td></td>
<td>Platelets</td>
<td>Stimulates aggregation</td>
</tr>
<tr>
<td></td>
<td>Some vascular smooth muscle</td>
<td>Contracts</td>
</tr>
<tr>
<td>Beta_1</td>
<td>Heart</td>
<td>Stimulates rate and force</td>
</tr>
<tr>
<td></td>
<td>Juxtaglomerular cells</td>
<td>Stimulates renal release</td>
</tr>
<tr>
<td>Beta_2</td>
<td>Respiratory, uterine, and vascular smooth</td>
<td>Relaxes</td>
</tr>
<tr>
<td></td>
<td>muscle</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Liver</td>
<td>Stimulates glycogenolysis</td>
</tr>
<tr>
<td></td>
<td>Pancreatic B cells</td>
<td>Stimulates insulin release</td>
</tr>
<tr>
<td></td>
<td>Somatic motor nerve terminals (voluntary</td>
<td>Causees tremor</td>
</tr>
<tr>
<td></td>
<td>muscle)</td>
<td></td>
</tr>
<tr>
<td>Beta_3 (β_1, β_2 may also contribute)</td>
<td>Fat cells</td>
<td>Stimulates lipolysis</td>
</tr>
<tr>
<td>Dopamine_1</td>
<td>Renal and other splanchnic blood vessels</td>
<td>Relaxes (reduces resistance)</td>
</tr>
<tr>
<td>Dopamine_2</td>
<td>Nerve terminals</td>
<td>Inhibits adenylyl cyclase</td>
</tr>
</tbody>
</table>


B. Adrenergic Receptor Signaling

1. α-adrenergic receptors are positively coupled to Phospholipase C (PLC) via Gq/11 α protein of the heterotrimeric G protein family to increase IP3/DAG.

Ex: Vascular smooth muscle contraction. NE, EPI or other α1 -adrenergic receptor agonists bind to α1-adrenergic receptor of vascular smooth muscle, the Gaq subunit activates PLC, which liberates inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG). IP3 activates IP3 receptor that also acts as a calcium release channel in the sarcoplasmic reticulum. When activated the IP3 receptor releases stored calcium into the intracellular space, thereby increasing calcium concentrations and stimulating smooth muscle contraction.

2. **α₂-adrenergic receptors** negatively couple to adenylyl cyclase via Gαi subunit which inhibits cAMP formation.

Ex: Pre-synaptic α₂ receptor activation decreases neurotransmitter release (reduced calcium influx). Agonist ligand binds to pre-synaptic α₂ adrenergic receptor and inhibits adenylyl cyclase in the pre-synaptic cell which reduces cAMP and, in turn, reduces activation of phosphokinase A (PKA). Consequently, phosphorylation of N-type calcium channels on nerve terminals is reduced, thereby reducing calcium influx during membrane depolarization and reducing vesicular release of neurotransmitter.

3. **β₁-adrenergic receptors** positively couple to adenylyl cyclase via Gαs-proteins – increases cAMP
EX: Positive chronotropy. Activation of adenylyl cyclase and increase of cAMP can activate PKA to promote phosphorylation of calcium channels in the membrane of sinoatrial node cells leading to increased inward calcium current and thus faster nodal cell depolarization to the firing threshold.

EX: Positive Inotropy: Increased cAMP leads to increased PKA-dependent phosphorylation of L-type calcium channels in myocyte membrane which leads to enhanced calcium influx and larger trigger signal for release of calcium from the sarcoplasmic reticulum into the intracellular space. Trigger calcium also enters the sarcoplasmic reticulum increasing calcium storage such that next trigger initiates larger efflux of calcium through ryanodine receptors.

4. \( \beta_2 \)-adrenergic receptors positively couple to adenylyl cyclase via \( G_\alpha \)s protein - increases cAMP

EX: Vascular smooth muscle relaxation: cAMP activates PKA which phosphorylates and inactivates myosin light chain kinase (MLCK). Normally MLCK phosphorylates the light chain of myosin enabling actin and myosin cross-bridge formation and smooth muscle contraction. Phosphorylation of the MLCK enzyme by PKA reduces the affinity of MLCK for Ca-calmodulin resulting in reduced activity of the enzyme so its ability to phosphorylate myosin light chain is inhibited. In this case PKA inactivates MLCK. Therefore, \( \beta_2 \) adrenergic receptor activation leads to reduced smooth muscle contraction. \( \beta_2 \) adrenergic receptors are highly expressed on smooth muscle of the bronchi and some vascular beds and therefore regulates the degree of airway constriction as well as peripheral vascular resistance.
α2-adrenergic receptors produce peripheral vasoconstriction through the opposite mechanism. In this case, the Gαi subunit, to which the α2 adrenergic receptor is coupled, inhibits adenylyl cyclase, which, in turn, inhibits cAMP and PKA. PKA normally phosphorylates and inhibits the activity of myosin light chain kinase. Therefore, inhibition of PKA leads to activation of MLCK and vascular smooth muscle constriction.


VI. Adrenergic Agonists

<table>
<thead>
<tr>
<th>Adrenomimetic agonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct-acting</td>
</tr>
<tr>
<td>Alpha agonists</td>
</tr>
<tr>
<td>Beta agonists</td>
</tr>
<tr>
<td>Beta2-selective</td>
</tr>
<tr>
<td>Beta1-selective</td>
</tr>
<tr>
<td>Alpha2-selective</td>
</tr>
<tr>
<td>Alpha1-selective</td>
</tr>
<tr>
<td>Indirect-acting</td>
</tr>
<tr>
<td>Releasers</td>
</tr>
<tr>
<td>Reuptake inhibitors</td>
</tr>
</tbody>
</table>


A. Direct Acting Sympathomimetics: Direct acting sympathomimetics (i.e., drugs that stimulate the sympathetic system) interact directly with adrenergic receptors to mediate their effects. Sympathomimetic agents have different affinities for adrenergic receptor subtypes. Thus, a specific compound may be more or less potent in producing a specific effect depending upon the affinity of the compound for a specific receptor subtype. The endogenous ligands for adrenergic receptors are NE, EPI and dopamine (DA).
Catecholamines contain two hydroxyl groups on a phenyl ring. This structure makes catecholamines susceptible to degradation by metabolic enzymes. Catecholamines differ in the substitutions present on the terminal amine and the two methyl groups. Adrenergic agonists can be made more or less selective for various adrenergic receptors by altering the substitutions on the methyl and amine groups. For instance, isoproterenol (ISO), a synthetic catecholamine, has a particularly large substitution on the amine group. This gives the compound selectivity for the $\beta_2$-adrenergic receptors. Compounds may also be more or less susceptible to degradation or be more or less lipophilic by altering the hydroxyl groups on the phenyl ring.

It is important to recognize the difference in efficacy of the various catecholamines at different receptors in order to correctly anticipate their physiological effects.

- $\alpha_1$-adrenergic: epinephrine > norepinephrine >> isoproterenol
- $\alpha_2$-adrenergic: epinephrine > norepinephrine >> isoproterenol
- $\beta_2$-adrenergic: Isoproterenol > epinephrine >> norepinephrine
- $\beta_1$-adrenergic: Isoproterenol > epinephrine = norepinephrine

It is important to be able to predict the different hemodynamic effects produced by sympathomimetic agents given their receptor activity in order to effectively predict whether they will be beneficial or potentially hazardous in a particular clinical situation.

$$\text{MAP} = \text{CO} \times \text{TPR}$$

where MAP is mean arterial pressure, CO is cardiac output and TPR is total peripheral resistance.

TPR has a predominant effect on diastolic pressure (prevailing arterial pressure after the systolic wave has passed is mediated by arterial vasoconstriction)

CO has a predominant effect on systolic pressure (acute increase during systole due to contractile force of the heart and blood volume passing through the arterial tree)

Therefore TPR and diastolic pressure are affected more by adrenergic receptors expressed in vasculature while CO and systolic pressure are affected more by adrenergic receptors in cardiac tissue.

1. **Epinephrine:** Stimulates $\alpha_1$, $\alpha_2$, $\beta_1$ and $\beta_2$ receptors ($\beta$–receptor effects predominate at low concentrations), short acting, due to susceptibility to degradation.
Cardiovascular effects: at low infusion rates (<0.01 µg/kg/min, dashed lines in figure at right), β2 receptor activation causes peripheral vasodilation, thereby decreasing diastolic BP; β1 receptor activation has positive inotropic and chronotropic effects thereby increasing CO and systolic BP; at higher doses (>0.2 µg/kg/min, solid lines) effects of α1 receptor activation predominate (more receptors) producing peripheral vasoconstriction, elevated systolic pressure and elevated diastolic pressure. Overall, the cardiovascular effect is a slight increase in mean BP at lower doses, with quite robust increases at higher concentrations.

Bronchiole effect: β2 receptor - bronchodilation, α1 receptor - decrease in bronchial secretions

Toxicity: Arrhythmias, cerebral hemorrhage, anxiety, cold extremities, pulmonary edema

Therapeutic Uses: Anaphylaxis, cardiac arrest, bronchospasm

Contraindications: late term pregnancy due to unpredictable effects on fetal blood flow

2. Norepinephrine: has high affinity and efficacy at α1, α2 and β1 receptors with little affinity for β2 receptors, susceptible to degradation by metabolic enzymes, short half-life given by controlled infusion.

Cardiovascular effects: due primarily to α1-receptor activation which leads to vasoconstriction - increase in TPR, and diastolic BP; also produces significant positive inotropic and chronotropic effects on heart and increased systolic BP due to β1 receptor binding; large rise in pressure leads to reflex baroreceptor response and decrease in HR which predominates over the direct chronotropic effects; Overall increase in MAP; NE has limited affinity for β2 receptors and so has limited effects on bronchiole smooth muscle.

Toxicity: Arrhythmias, ischemia, hypertension

Therapeutic Use: Limited to vasodilatory shock
Contraindications: pre-existing excessive vasoconstriction and ischemia and late term pregnancy.

3. Dopamine: stimulates D1 receptors at low concentrations, but also has affinity for β1 and α receptors which may be activated at higher infusion rates, metabolized readily.

Cardiovascular Effects: activates D1-receptors at low infusion rates (0.5-1.0 μg/kg/min) leading to decreased TPR, at medium infusion rates activates β1-receptors leading to increased cardiac contractility and increased HR; at still higher infusion rates (>10 μg/kg/min) it stimulates α-receptors leading to increased BP and TPR.

Toxicity: low infusion rates – hypotension, high infusion rates – ischemia

Therapeutic Use: Hypotension due to low cardiac output during cardiogenic shock- may be advantageous due to vasodilatory effect in renal and mesenteric vascular beds

Contraindications: uncorrected tachyarrhythmias or ventricular fibrillation

VI. Direct acting sympathomimetics (synthetic compounds)

A. Non-selective β-adrenergic agonists: isoproterenol: potent β-receptor agonist with no appreciable affinity for α receptors. Catecholamine structure means it is susceptible to degradation.

Cardiovascular effects: β2 receptor activation promotes peripheral vasodilation, decreased diastolic BP; β1 receptor - positive inotropy and chronotropy, leads to transient increased systolic BP. Overcome by vasodilatory effect; Overall small decrease in MAP which may contribute to further reflex HR increase.

Bronchioles: β2 receptor – bronchodilation

Toxicity: Tachyarrhythmias

Therapeutic uses: Cardiac stimulation during bradycardia or heart block when peripheral resistance is high.

Contraindications: Angina, particularly with arrhythmias

B. Selective β₁-adrenergic receptor agonist - Dobutamine (adrenergic receptor affinity: β₁>β₂>α), though considered by most to be a β₁ selective agonist, dobutamine is a catecholamine that is rapidly degraded by COMT.

Cardiovascular effects: increased CO, usually little effect on peripheral vasculature or lung; unique in that positive inotropic effect > positive chronotropic effect due to lack of β₂-mediated vasodilation and reflex tachycardia. However, no agonist is purely selective so at higher doses, β₂ agonist activity may cause hypotension with reflex tachycardia.

Toxicity: Arrhythmias, hypotension (vasodilation), hypertension (inotropic and chronotropic effects).

Therapeutic Use: Short-term treatment of cardiac insufficiency in CHF, cardiogenic shock or excess β-blockade

C. Selective β₂-adrenergic agonists: terbutaline, albuterol

Cardiovascular Effects: negligible in most patients due to lack of β₁ activity. However, can cause some β₁ agonist-like response

Bronchioles: Bronchodilation

Pregnant Uterus: Relaxation

Toxicity: Tachycardia, tolerance, skeletal muscle tremor (see figure right), activation of β₂-receptors expressed on pre-synaptic nerve terminals of cholinergic somatomotor neurons increases release of neurotransmitter. This can lead to muscle tremor, a side effect of β-agonist therapy.

Therapeutic Use: Bronchospasm, chronic treatment of obstructive airway disease.

D. Selective α₁-adrenergic agonist: phenylephrine

Cardiovascular Effects: Peripheral vasoconstriction and increased BP, activates baroreceptor reflex and thereby decreases HR.

Ophthalmic Effects: Dilates pupil

Bronchioles: Decrease bronchial (and upper airway) secretions
Toxicity: Hypertension

Therapeutic Use: Hypotension during anesthesia or shock, paroxysmal supraventricular tachycardia, mydriatic agent, nasal decongestant

NOTE: Phenylephrine is not a catecholamine and therefore is not subject to rapid degradation by COMT. It is metabolized more slowly; therefore it has a much longer duration of action than endogenous catecholamines.

Contraindications: Hypertension

E. Selective $\alpha_2$-adrenergic agonists: clonidine

Cardiovascular Effects: Peripherally, clonidine causes mild vasoconstriction and slight increase in BP, also crosses BBB to cause reduced sympathetic outflow thereby reducing vasoconstriction and BP (see figure at right). The loss of sympathetic activity predominates over the direct vasoconstrictor effects of the drug leading to overall reduction in blood pressure.

Activation of $\alpha_2$-receptors on pre-motor neurons that normally provide tonic activation of sympathetic pre-ganglionic cells reduces pre-motor neural activity by unknown mechanism. Reduction of tonic excitatory input to the sympathetic cells reduces sympathetic output to vascular smooth muscle.

Toxicity: Dry mouth, sedation, bradycardia, withdrawal after chronic use can result in life-threatening hypertensive crisis (increases sympathetic activity).

Therapeutic Use: Hypertension when cause is due to excess sympathetic drive.

VII. Indirectly acting sympathomimetics: Indirect acting sympathomimetic agents increase the concentration of endogenous catecholamines in the synapse and circulation leading to activation of adrenergic receptors. This occurs via either: 1) release of cytoplasmic catecholamines or 2) blockade of re-uptake transporters

A. Releasing agents: amphetamine, methamphetamine, methylphenidate, ephedrine, pseudoephedrine, tyramine. Most are resistant to degradation by COMT and MAO
and therefore have relatively long half-lives (exception is tyramine which is highly susceptible to degradation by MAO and thus has little effect unless patient is taking MAO inhibitor). Amphetamine-like drugs are taken up by re-uptake proteins and subsequently cause reversal of the re-uptake mechanism resulting in release of neurotransmitter in a calcium-independent manner. The resulting increase in synaptic NE mediates the drugs’ effects. Amphetamine-like drugs readily cross the blood brain barrier leading to high abuse potential due to reinforcing effects of central dopamine release.

Cardiovascular Effects: due to NE release, α adrenergic receptor activation causes peripheral vasoconstriction and increased diastolic BP; β receptor activation of heart leads to positive inotropy and increased conduction velocity and increased systolic BP; increased BP can cause decreased HR due to baroreceptor activation, but this can be masked by direct chronotropic effect.

Central Nervous System: Stimulant, anorexic agent

Toxicity: Anxiety, tachycardia

Therapeutic use: Attention Deficit Disorder, narcolepsy, nasal congestion

Contraindications: Hypertension, severe atherosclerosis, history of drug abuse, Rx with MAO inhibitors within previous 2 weeks.
VIII. **β-adrenergic receptor antagonists**

A. **Mechanism of action** of the 3 main categories of β-blockers, i.e., non-selective, cardioselective and partial agonists. FYI: the term "blocker" is equivalent to "antagonist".

<table>
<thead>
<tr>
<th>Category</th>
<th>Non-Selective (β₁ and β₂)</th>
<th>Cardioselective (β₁)</th>
<th>Partial Agonist (β₁ and β₂)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PROPRANOLOL, TIMOLOL, NADOLOL</strong></td>
<td>Decrease both rate and force of contraction</td>
<td>Decrease both rate and force of contraction</td>
<td>Decreases both rate and force of contraction. However, bradycardic response is limited due to partial agonist activity.</td>
</tr>
<tr>
<td>Peripheral Resistance (β₂)</td>
<td>Increase, due to unopposed vasoconstriction by α₁-receptors</td>
<td>Little effect because β₂-receptors are not blocked</td>
<td>May be slight decrease because of partial β₂ agonist properties</td>
</tr>
<tr>
<td>Renin Release (β₁)</td>
<td>Decreased release</td>
<td>Decreased release</td>
<td>Decreased release</td>
</tr>
<tr>
<td>Bronchioles (β₂)</td>
<td>Bronchoconstriction, particularly in asthmatics</td>
<td>Less bronchoconstriction in asthmatics, but still not recommended in these patients</td>
<td>Asthmatics have a reduced capacity to dilate bronchioles.</td>
</tr>
<tr>
<td>Glucose Metabolism (β₂)</td>
<td>Inhibits effects of epinephrine, e.g., hyperglycemia, anxiety, sweating. Use caution in diabetics using insulin, since masks symptoms of hypoglycemia (normally due to epinephrine release)</td>
<td>Little effect</td>
<td>Reduced response to epinephrine because partial agonist activity is not as potent as endogenously-released epinephrine</td>
</tr>
</tbody>
</table>

B. **Non-selective β-blockers:** *propranolol, nadolol, timolol*, first generation β-blockers with potentially harmful side effects for patients with respiratory disease.

Cardiovascular effects: Reduced heart rate and contractility, reduced renin release leads to reduced angiotensin II release and thus reduced vasoconstriction, probably reduced sympathetic activation due to central effects in lipid soluble drugs. Possible peripheral vasoconstriction due to blockade of β₂ receptors.

Bronchioles: can cause bronchiole constriction in those with asthma or chronic obstructive pulmonary disease.

Therapeutic Use: Hypertension, angina, glaucoma, heart failure, arrhythmia, thyrotoxicosis, anxiety
Toxicity: Bronchospasm, masks symptoms of hypoglycemia, CNS effects including insomnia and depression (most significant with lipid soluble drugs), some can raise triglycerides, bradycardia.

Contraindications: Bronchial Asthma, sinus bradycardia, 2nd and 3rd degree heart block, cardiogenic shock

C. Cardioselective $\beta_1$-blockers: metoprolol, atenolol, esmolol, second generation $\beta$-blockers developed for their ability to reduce respiratory side effects.

Cardiovascular Effects: Same as for non-selective $\beta$-blockers with limited effects on peripheral resistance.

Therapeutic Use: Hypertension (metoprolol, atenolol), angina (metoprolol, atenolol), arrhythmia (esmolol-emergent control). Esmolol has very short half-life (~9 min) so is given i.v. in hypertensive crisis, unstable angina or arrhythmias when longer acting beta blockers may be problematic.

Toxicity: (typically mild and transient), Dizziness, depression, insomnia, hypotension, bradycardia.

Contraindications: Sinus bradycardia, 2nd or 3rd degree heart block, cardiogenic shock severe heart failure

D. Partial Agonist: pindolol, partial agonist activity at both $\beta_1$ and $\beta_2$ adrenergic receptors: Therapeutic benefit is good when hypertension is due to high sympathetic output (see figure A below) since blockade of endogenous agonist (i.e., NE and EPI) will predominate over partial agonist effect (see B below) of drug. Partial agonists have less bradycardic effect since some $\beta$ signal remains, while $\beta$ signal is blocked by agonists without agonist activity (see C below). Used when patients are less tolerant of bradycardic effects.
Cardiovascular Effects: Same as above for non-selective β-blockers, particularly when sympathetic activity is high.

Therapeutic Use: Hypertension in those who are less tolerant of bradycardia and reduced exercise capacity caused by other beta blockers without partial agonist activity.

Toxicity: same as for non-selective

Contraindications: Same as above

IX. α-adrenergic receptor antagonists

A. Non-selective α-receptor antagonists: phenoxybenzamine (irreversible) and phentolamine (reversible).

Cardiovascular Effects: Inhibit vasoconstriction therefore, decreases BP, increased inotropy and chronotropy due to blockade of pre-synaptic α2-receptor and increased release of NE from nerve terminals, reflex increase in NE release also occurs in response to hypotension, unmasks vasodilatory effect of EPI (which has both α and β2 effects.)

Therapeutic Use: Hypertension associated with perioperative treatment of pheochromocytoma, test for pheochromocytoma, dermal necrosis and sloughing with vasoconstrictor extravasation.

Toxicity: Prolonged hypotension, reflex tachycardia, nasal congestion

Contraindications: Coronary artery disease

B. Selective α1-receptor blockers: prazosin, doxazosin, and terazosin:

Cardiovascular Effects: Inhibit vasoconstriction, resulting in vasodilation and decreased BP, produces less cardiac stimulation than non-selective α-blockers due to preservation of α2-adrenergic function (see figure below).
Therapeutic Use: Hypertension, benign prostatic hyperplasia

Toxicity: Syncope, orthostatic hypotension

X. Drugs Covered in Lecture (Bold text is information you should know) Do not memorize bold half-lives but have a general idea of the drug's half-life relative to other drugs in its class, e.g. nadolol vs propranolol.
<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Half-life</th>
<th>Mechanism of action</th>
<th>Elimination</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>Adrenaline Chloride</td>
<td>short</td>
<td>α and β agonist</td>
<td>COMT-urine</td>
<td>Anaphylaxis, shock, cardiac arrest and heart block</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>Levophed</td>
<td>short</td>
<td>α-agonist, β1-agonist</td>
<td>MOA and COMT -urine</td>
<td>Acute hypotension due to shock</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Dopamine</td>
<td>~2min</td>
<td>β-agonist, some α-agonist activity</td>
<td>MOA and COMT</td>
<td>Cardiogenic shock</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>Isuprel</td>
<td>short</td>
<td>β-agonist</td>
<td>COMT-urine</td>
<td>Transient heart block, broncho-spasm during anesthesia</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>Dobutrex</td>
<td>2-3 min</td>
<td>β1-agonist</td>
<td>COMT-urine</td>
<td>Short term Rx for low cardiac contractility</td>
</tr>
<tr>
<td>Terbutaline</td>
<td>Brethine</td>
<td>2.9</td>
<td>β2-agonist</td>
<td>Urine</td>
<td>Prevent and reverse bronchospasm in asthma, bronchitis and emphysema</td>
</tr>
<tr>
<td>Albuterol</td>
<td>Ventolin</td>
<td>5 hr</td>
<td>β2-agonist</td>
<td>Urine</td>
<td>Bronchial SM relaxation</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>Neo-synephrine</td>
<td>&lt; 1 hr</td>
<td>α1-agonist</td>
<td>MAO</td>
<td>Pressor agent for anesthesia, nasal congestion, dilate pupil for eye exam, supraventricular tachycardia</td>
</tr>
<tr>
<td>Clonidine</td>
<td>Catapres</td>
<td>12-16 hrs</td>
<td>α2-agonist</td>
<td>Urine</td>
<td>Hypertension, analgesia</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>Adderall</td>
<td>10-13 hr</td>
<td>Indirect sympathomimetic</td>
<td>Urine</td>
<td>ADHD</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>Ritalin</td>
<td>2-3 hr</td>
<td>Indirect sympathomimetic</td>
<td>Urine</td>
<td>ADHD</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>Ephedrine</td>
<td>3-6 hr</td>
<td>Indirect sympathomimetic</td>
<td>Urine</td>
<td>Pressor agent with anesth.</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>Ritalin</td>
<td>2-3 hr</td>
<td>Indirect sympathomimetic</td>
<td>Urine</td>
<td>ADHD</td>
</tr>
<tr>
<td><strong>Pseudo-ephedrine</strong></td>
<td><strong>Sudafed</strong></td>
<td><strong>4.3-8 hr</strong></td>
<td><strong>Indirect sympathomimetic</strong></td>
<td><strong>Liver</strong></td>
<td><strong>Nasal decongestion</strong></td>
</tr>
<tr>
<td><strong>Tyramine</strong></td>
<td><strong>Tyramine</strong></td>
<td><strong>Normally very short</strong></td>
<td><strong>Displaces NE</strong></td>
<td><strong>MAO</strong></td>
<td><strong>Not therapeutic</strong></td>
</tr>
<tr>
<td><strong>Propranolol</strong></td>
<td><strong>Inderal</strong></td>
<td><strong>4 hr</strong></td>
<td><strong>β-blocker</strong></td>
<td><strong>Liver</strong></td>
<td><strong>Hypertension, angina due to atherosclerosis, MI</strong></td>
</tr>
<tr>
<td><strong>Timolol</strong></td>
<td><strong>Blocaden (po)</strong></td>
<td><strong>4 hr</strong></td>
<td><strong>β-blocker</strong></td>
<td><strong>Liver</strong></td>
<td><strong>Glaucoma.</strong></td>
</tr>
<tr>
<td><strong>T</strong></td>
<td><strong>Timoptic (opth)</strong></td>
<td><strong>4 hr</strong></td>
<td><strong>β-blocker</strong></td>
<td><strong>Liver</strong></td>
<td><strong>Long-term angina, hypertension</strong></td>
</tr>
<tr>
<td><strong>Nadolol</strong></td>
<td><strong>Corgard</strong></td>
<td><strong>20-24 hr</strong></td>
<td><strong>β-blocker</strong></td>
<td><strong>Urine</strong></td>
<td><strong>Hypertension, angina, MI</strong></td>
</tr>
<tr>
<td><strong>Atenolol</strong></td>
<td><strong>Tenormin</strong></td>
<td><strong>6-7 hr</strong></td>
<td><strong>β1-blocker</strong></td>
<td><strong>Urine</strong></td>
<td><strong>Hypertension, long-term angina rx</strong></td>
</tr>
<tr>
<td><strong>Metoprolol</strong></td>
<td><strong>Lopressor, Toprol</strong></td>
<td><strong>3-7 hr</strong></td>
<td><strong>β1-antagonist</strong></td>
<td><strong>Liver</strong></td>
<td><strong>Hypertension, long-term angina rx</strong></td>
</tr>
<tr>
<td><strong>Pindolol</strong></td>
<td><strong>Visken</strong></td>
<td><strong>3-4 hr</strong></td>
<td><strong>β-antagonist (with partial agonist activity)</strong></td>
<td><strong>Urine</strong></td>
<td><strong>Hypertension</strong></td>
</tr>
<tr>
<td><strong>Esmolol</strong></td>
<td><strong>Breviblock</strong></td>
<td><strong>~9 min</strong></td>
<td><strong>β1-blocker</strong></td>
<td><strong>Esterases in RBC</strong></td>
<td><strong>Supraventricular tachycardia</strong></td>
</tr>
<tr>
<td><strong>Phenoxy-benzamine</strong></td>
<td><strong>Dibenzyline</strong></td>
<td><strong>24 hr (iv)</strong></td>
<td><strong>α-blocker</strong></td>
<td><strong>Conjugates to receptor</strong></td>
<td><strong>Pheochromocytoma test for pheochromocytoma, rx for pheo. before surg., Catecholamine extravasation</strong></td>
</tr>
<tr>
<td><strong>Phentolamine</strong></td>
<td><strong>Regitine</strong></td>
<td><strong>19 min</strong></td>
<td><strong>α-blocker</strong></td>
<td><strong>Urine</strong></td>
<td><strong>Hypertension</strong></td>
</tr>
<tr>
<td><strong>Prazosin</strong></td>
<td><strong>Minipress</strong></td>
<td><strong>2.3 hr</strong></td>
<td><strong>α-blocker</strong></td>
<td><strong>Liver</strong></td>
<td><strong>Hypertension</strong></td>
</tr>
<tr>
<td>Drug</td>
<td>Brand</td>
<td>Duration</td>
<td>Action</td>
<td>Metabolism</td>
<td>Side Effects</td>
</tr>
<tr>
<td>------------------</td>
<td>--------</td>
<td>----------</td>
<td>----------</td>
<td>------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>Doxazosin</td>
<td>Cardura</td>
<td>22 hr</td>
<td>$\alpha_1$-antagonist</td>
<td>Liver</td>
<td>Prostatic hyperplasia, hypertension</td>
</tr>
<tr>
<td>Terazosin</td>
<td>Hytrin</td>
<td>12 hr</td>
<td>$\alpha_1$-blocker</td>
<td>Urine and fecal</td>
<td>Prostatic hyperplasia, hypertension</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Adrenaline Chloride</td>
<td>short</td>
<td>$\alpha$ and $\beta$ agonist</td>
<td>COMT-urine</td>
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<tr>
<td>Norepinephrine</td>
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<td>short</td>
<td>$\alpha$-agonist, $\beta_1$-agonist</td>
<td>MOA and COMT-urine</td>
<td>Acute hypotension due to shock</td>
</tr>
</tbody>
</table>
ADRENERGIC ANTAGONISTS

Date: August 21, 2015

LEARNING OBJECTIVES

1. List the conditions that are most commonly treated with β-blockers and the mechanism by which β-blockers produce their beneficial effects in that condition.

2. Identify the 6 β-adrenergic antagonists discussed in class and assign them to one of the 3 commonly recognized categories of β-blockers they belong.

3. Describe how the 6 β-adrenergic antagonists discussed in class differ from one another in their receptor subtype selectivity, relative duration of action and ability to cross the blood brain barrier; and describe what advantage these attributes may provide in treating particular patient populations.

4. Describe how toxic side effects of the drugs differ with their receptor subtype selectivity.

5. List the 5 prominent α-adrenergic antagonists discussed in lecture, their receptor subtype selectivity and the conditions for which they are used.

6. List the most serious side effects produced by selective and non-selective α-adrenergic receptor antagonists.

7. Explain why selective α1-adrenergic receptor antagonists are more preferable for use in hypertension than non-selective α-adrenergic receptor antagonists.
CHOLINERGIC AGONISTS AND ANTAGONISTS


LEARNING OBJECTIVES

1. Distinguish the main structural and functional differences between nicotinic and muscarinic receptors, including their most well recognized function, signaling mechanisms, and location in the autonomic nervous system.

2. Describe the difference between parasympathetic and nicotinic effects in the body.

3. Describe the difference in mechanism of action of directly and indirectly acting cholinergic agonists.

4. List the differences in the pharmacological activity of key quaternary nitrogen analogs of choline (e.g., nicotinic vs. muscarinic activity).

5. List the 3 key quaternary analogs of acetylcholine discussed in lecture and their pharmacological actions in the body.

6. List the prototype tertiary amine muscarinic agonist discussed in lecture and describe the major chemical feature that distinguishes it from the quaternary analogs and how this feature affects the drug’s clinical effects.

7. Describe the relative susceptibility of the quaternary analog agonists to enzymatic degradation.

8. List common clinical uses for the 4 muscarinic agonists discussed in class.

9. List 3 key representative reversible cholinesterase inhibitors discussed in lecture and describe their relative duration of action (vs. one another), and their primary clinical applications.

10. Describe the mechanism of action of the irreversible cholinesterase inhibitors, and describe the mechanism by which 2-PAM can act as an antidote to irreversible cholinesterase inhibition.

11. Describe the pharmacologic effects and the treatment for organophosphate toxicity.

12. Describe the dose-dependent pharmacological effects of atropine.


14. Describe various clinical applications for atropinic agents.
15. Describe how, when and why glycopyrrolate is used during recovery from anesthesia
CHOLINERGIC AGONISTS AND ANTAGONISTS

Under normal conditions, adrenergic and cholinergic function in the autonomic nervous system remains balanced and carefully regulated. A chronic or acute imbalance of adrenergic or cholinergic activation, whether through disease or exogenous agents, can result in significant clinical symptoms. This lecture will focus on agents that activate (agonists) and inhibit (antagonists) cholinergic function which is normally mediated by the endogenous agonist of cholinergic receptors, acetylcholine.

I. CHOLINERGIC STIMULANTS

II. CHOLINERGIC RECEPTORS

Two classes of cholinergic receptors (i.e., receptors sensitive to acetylcholine): G protein linked (muscarinic receptors) and ligand-gated ion channels (nicotinic receptors).

Of the 5 identified muscarinic receptors, 3 are known to have physiological functions (M₁, M₂, M₃). They are expressed in various organs and couple to different signaling mechanisms resulting in diverse receptor functions. Muscarinic receptors are located on smooth muscle, cardiac muscles, most exocrine glands, sweat glands, in blood vessels of the major vascular
beds, and at cortical and subcortical sites in the central nervous system.

The nicotinic receptors are pentomeric (five) transmembrane polypeptides, the subunits of

**Muscarinic Receptors**

| M₁  | Increased IP₃, DAG and [Ca²⁺] | Activates myenteric plexus |
| M₂  | Opens K channels              | Decreases heart rate and contraction (decreases cardiac output) |
|     | Decreased cAMP, decreased Ca²⁺| Inhibits norepinephrine release from sympathetic nerve terminals |
| M₃  | Increased IP₃, DAG and [Ca²⁺] | Contacts circular ciliary muscle (pupillary constriction), ciliary muscle (near-vision accommodation), bronchiolar muscle, GI smooth muscle, urogenital muscle, and bladder detrusor muscle (micturition) |
|     |                             | Relaxes vascular muscle (via nitric oxide from endothelium) |
|     |                             | Stimulates secretions of GI tract, eccrine sweat glands, tear glands, salivary glands, pancreas digestive fluids, and liver bile |

From Castro, Merchut, Neafsey and Wurster, In: Neuroscience, an outline approach Mosby Inc., St. Louis, 2002

which form a cation-selective channel permeable to sodium and potassium. Two main subtypes exist (M₃, M₅). Nicotinic receptors are located on plasma membranes of parasympathetic and sympathetic postganglionic cells in the autonomic ganglia (M₃) and on the membranes of skeletal muscles (M₅). Neuronal nicotinic receptors (M₅) are also expressed in cortical and subcortical nuclei in the brain.

III. **NICOTINIC AGONISTS**

Because nicotinic receptors are present on postganglionic cells of both the sympathetic and parasympathetic nervous systems, nicotinic agonists can activate both the sympathetic and parasympathetic systems simultaneously.

A. **PROTOTYPICAL COMPOUNDS:**

1. **NICOTINE** (Nicotrol): Stimulates N₅ receptors in autonomic ganglia and CNS. Patch or inhaler used to control withdrawal symptoms during smoking cessation. Side Effects include irritation at site of administration and dyspepsia.

2. **SUCCINYLCHOLINE** (Anectine): Blocks nicotinic receptors at the

From B.G. Katzung, In: Basic and Clinical Pharmacology 10th Ed
neuromuscular junction. Causes depolarization block (see lecture on neuromuscular relaxants). Used clinically as a muscle relaxant during intubation or electro convulsive shock therapy (more detail in Neuromuscular Relaxants lecture). Contraindicated in pts with family history of familial hyperthermia, or pts with skeletal muscle myopathies, or several days after multiple and wide spread skeletal muscle injury.

IV. MUSCARINIC AGONISTS (PARASYMPATHOMIMETIC AGENTS)

Muscarinic agonists are available both as quaternary nitrogen analogs and as naturally occurring tertiary amine alkaloids and synthetic analogs. The quaternary compounds are structurally derived analogs of acetylcholine. Acetylcholine interacts with the muscarinic receptor with a tight fit. Therefore, changes in the molecular structure of muscarinic, direct-acting agonists will affect the drug-receptor complex, and thus the efficacy of action of the compound. Factors affected by structural modifications include relative muscarinic vs. nicotinic activity of the compound, and relative resistance of the compound to breakdown by cholinesterases, i.e., enzymes present in synaptic cleft, neuromuscular junction (acetylcholinesterase) or plasma (plasma cholinesterase) that very rapidly metabolize acetylcholine and other esterase-sensitive muscarinic agonists.

A. QUATERNARY NITROGEN ANALOGS:

1. ACETYLCOLCHOLINE (prototype compound): (CH₃)₃N-CH₂-CH₂-O-C-CH₃

   +

   Binds to both nicotinic and muscarinic receptors of the autonomic nervous system, the CNS and the neuromuscular junction. It is rapidly hydrolyzed by acetyl- and plasma cholinesterases. Therefore, it has no therapeutic use.

2. METHACHOLINE (Acetyl-β-Methylcholine): (CH₃)₃N-CH₂-CH-O-C-CH₃

   +

   CH₃

   O

   Differs from acetylcholine by methyl group on the β carbon. Hydrolyzed by acetylcholinesterase, but hydrolysis is slowed, has a longer duration of action than acetylcholine, has limited nicotinic effects, primarily muscarinic effects on smooth muscle, glands and the heart. The drug is used to diagnose bronchial hyperactivity in patients suspected of having asthma. Toxicity includes bronchiolar constriction. Contraindicated in pts given β-blockers since antidote to overdose is β-agonist.
3. **CARBACHOL (Carbamylcholine):** \((\text{CH}_3)_3\text{N-CH}_2\text{-CH}_2\text{-O-C-NH}_2\) 

Carbamic group replaces the esteratic group of acetylcholine. The drug is more resistant to hydrolysis by acetylcholinesterase. It stimulates both muscarinic and nicotinic receptors. Its principal use is in ophthalmology as a miotic agent. It is applied topically to the conjunctiva, producing prolonged miosis to reduce intraocular pressure in glaucoma. It is used when the eye has become intolerant or resistant to other miotic agents. It is also used as an intraocular injection to reduce pressure after cataract surgery. Side effects are related to excessive muscarinic and nicotinic receptor activation.

4. **BETHANECHOL (Urecholine):** \((\text{CH}_3)_3\text{N-CH}_2\text{-CH-O-C-NH}_2\) 

Combines structural features of both methacholine and carbachol, i.e., resistance to hydrolysis by acetyl- and plasma cholinesterases and lack of nicotinic effects. It has selective action on muscarinic receptors of GI tract and urinary bladder. Used clinically to treat postoperative non-obstructive urinary retention, post partum urinary retention and neurogenic atony of the bladder. Fewer side effects than carbachol because less activity at \(M_2\) receptors (expressed in heart), but can still cause bradycardia. Contraindicated in peptic ulcer, asthma and bradycardia.

C. **NATURALLY OCCURRING TERTIARY AMINES:**

Several tertiary amine compounds with muscarinic agonist properties are available. Some of these are natural alkaloids, others have been prepared synthetically. The charge of the tertiary amine determines if the compound can cross the blood brain barrier.

1. **MUSCARINE:**

   Alkaloid in wild mushrooms of the Clitocybe inocybe species. Prototype compound, though not used clinically. Historically one of the first cholinomimetic drugs to be studied. Pure muscarinic activity. Resistant to hydrolysis by acetylcholinesterase (no ester moiety). It is clinically important as a source of muscarinic poisoning with ingestion of certain mushrooms. It has no clinical utility but muscarinic poisoning causes profound parasympathetic activation, and is treated with atropine, a muscarinic receptor antagonist. Note that though tertiary amine compounds have structural similarities with muscarine, muscarine itself has a quaternary ammonium structure.
2. **PILOCARPINE:**

   Alkaloid from leaf of tropical American shrub, *Pilocarpus jaborandi*. Pure muscarinic activity. Crosses blood brain barrier. Has appreciable CNS effects. Therapeutic use is dry mouth due to head and neck radiotherapy or Sjogren’s syndrome, an autoimmune disorder in which immune cells attack and destroy the exocrine glands that produce tears and saliva. Also used in the treatment of open and angle-closure glaucoma. Administer with care to pts taking β-blockers due to exacerbation of conduction slowing.

---

V. **INDIRECTLY ACTING CHOLINERGIC AGONISTS (CHOLINESTERASE INHIBITORS)**

   Acetylcholinesterase catalyzes the hydrolysis of acetylcholine

   \[
   \text{AChE} \\
   \rightarrow \text{ACETYLCHOLINE} \rightarrow \text{CHOLINE} + \text{ACETIC ACID}
   \]

   Inhibition of cholinesterase protects acetylcholine from hydrolysis, and leads to the accumulation of endogenous acetylcholine and increased cholinergic activity. Thus, cholinesterase inhibitors act indirectly as cholinergic agonists.

   Two distinct types of endogenous cholinesterases exist:

   A. **Acetylcholinesterase** (AChE, true, specific, red blood cell cholinesterase).
      
      **Distribution:** Neurons, motor endplate, red blood cells.
      
      **Function:** Hydrolysis of acetylcholine liberated in synaptic cleft or in neuroeffector transmission.
B. **Butyrylcholinesterase** (BuChE, pseudo, nonspecific, plasma cholinesterase).

**Distribution:** Plasma, glial cells, liver.

**Function:** Uncertain, however does hydrolyze certain exogenous drugs, e.g., succinylcholine.

The accumulation of acetylcholine resulting from cholinesterase inhibition occurs at all cholinceptive sites, resulting in the following effects:

1. Autonomic effectors (smooth muscle and gland cells) \(\equiv\) muscarinic actions.
2. Autonomic ganglia \(\equiv\) nicotinic actions.
3. Motor endplates of striated muscle \(\equiv\) nicotinic actions.
4. Central nervous system \(\equiv\) stimulation, depression. (both receptor types)

Acetylcholinesterase inhibitors bind competitively to the active sites on the acetylcholinesterase molecule with which acetylcholine normally interacts, prevent acetylcholine from interacting with the enzyme, and protect acetylcholine from being degraded.

Two different general classes of acetylcholinesterase inhibitors have been identified, and distinguished by the extent to which they bind to the acetylcholinesterase molecule, and prevent its regeneration. They are identified in general terms as "reversible" and "irreversible" acetylcholinesterase inhibitors.
A. **REVERSIBLE CHOLINESTERASE INHIBITORS:** molecular mechanism

**CLINICALLY USED ACETYLCHOLINESTERASE INHIBITORS**

1. **NEOSTIGMINE:**

Contains a quaternary nitrogen, and thus poorly penetrates blood brain barrier. Inhibits acetylcholinesterase and has direct stimulatory effect on nicotinic receptors at the skeletal muscle endplate. Therefore used to reverse neuromuscular blockade (see neuromuscular relaxant lecture). Also used in the treatment of **myasthenia gravis** (loss of neuromuscular nicotinic receptor). Side effects due to excessive Ach action at peripheral muscarinic and nicotinic receptors. Contraindicated in intestinal obstruction. Neostigmine’s interaction with acetycholinesterase is longer than acetylcholine's, as the bond it forms is more stable. As such, it can effectively block cholinesterase from binding acetylcholine for over an hour.
2. **EDROPHONIUM:**

Similar in structure to neostigmine, but lacks an ester functional group. Inhibits cholinesterases and stimulates nicotinic receptors at the neuromuscular junction at lower doses than those which stimulate other cholinergic receptors. Has a very rapid onset of action, and a very short duration of action (10-15 min). Clinically used to establish diagnosis of myasthenia gravis or to make a differential diagnosis between progression of myasthenic weakness and a cholinergic crisis (i.e., excessive Ach) due to cholinesterase toxicity. Excessive cholinesterase inhibition can cause neuromuscular block (see neuromuscular relaxant lecture), resulting in muscle weakness which can mimic and be mistaken for myasthenia gravis progression. Treatment with short acting cholinesterase inhibitor reduces symptoms if muscle weakness is due to disease progression. It will worsen symptoms if due to cholinesterase toxicity. Side effects include bradycardia and cardiac standstill. Contraindicated in mechanical block of intestine and urinary tract.

3. **PHYSOSTIGMINE:**

Alkaloid from the calabar bean, Physostigma venosum. Readily crosses the blood brain barrier. Inactivated by plasma cholinesterases but takes a long time. Duration of action up to 2 hours. Used to counteract delirium with excess anticholinergic activation. Side effects related to increased Ach at muscarinic or nicotinic receptors. Toxicities include convulsions as well as respiratory and cardiovascular depression. Contraindicated in asthma, cardiac insufficiency and gut obstruction

4. **DONEPEZIL:**

Indicated in the treatment of Alzheimer's disease. Reversible inhibitor of acetylcholinesterase in the CNS, high bioavailability, long-half life allows once a day oral dosing. Data suggest some improvement of cognition in patients with
C. **IRREVERSIBLE CHOLINESTERASE INHIBITORS:**

Organophosphates used as insecticides and toxic nerve gases are irreversible inhibitors of cholinesterases. They phosphorylate the esteratic site on the acetylcholinesterase molecule. The phosphorylated enzyme becomes a stable complex with time. Recovery from the effects of an irreversible inhibitor usually depends on the synthesis of new acetylcholinesterase molecules. Because of their irreversible action, irreversible cholinesterase inhibitors exhibit severe toxicity. Anticholinesterase poisoning produces what is often called a "cholinergic crisis." Common agent in nerve gases.

**TOXICITY OF ORGANOPHOSPHATES (SLUDGE or DUMBBELLS)**

<table>
<thead>
<tr>
<th>Tissue or system</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td><strong>S</strong>weating (diaphoresis)</td>
</tr>
<tr>
<td>Visual</td>
<td><strong>L</strong>acrimation, <strong>M</strong>iosis, blurred vision, accommodative spasm</td>
</tr>
<tr>
<td>Urinary</td>
<td><strong>U</strong>rinary frequency and incontinence</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Increased bronchial secretions (<strong>B</strong>ronchorrea), bronchoconstriction, weakness or paralysis of respiratory muscles</td>
</tr>
<tr>
<td>Digestive</td>
<td><strong>S</strong>alivation (<strong>S</strong>); increased gastric, pancreatic, and intestinal secretion; increased tone and motility in gut (<strong>G</strong>astric distress), abdominal cramps, vomiting, <strong>D</strong>iarrhea</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>Fasciculations, weakness, paralysis (depolarizing block)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td><strong>B</strong>radycardia (due to muscarinic predominance), decreased cardiac output, hypotension; effects due to ganglionic actions and activation of adrenal medulla also possible</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>Tremor, anxiety, restlessness, disrupted concentration and memory, confusion, sleep disturbances, desynchronization of EEG, convulsions, coma, circulatory and respiratory depression</td>
</tr>
</tbody>
</table>
Treatment of severe organophosphate poisoning consists of:

1. Mechanical ventilation, to counteract effects on neuromuscular junction
2. Suction of oral secretions
3. Atropine, to protect from systemic muscarinic effects
4. Reactivation of the alkylphosphorylated acetylcholinesterase with Pralidoxime Chloride (2-PAM) (see diagram that follows).

**MECHANISM OF ACTION OF PRALIDOXIMINE (2-PAM)**

ECHOTHIOPHATE is an organophosphate that is used clinically to produce long term miosis in the treatment of open angle glaucoma. It is administered topically to the eye to reduce systemic effects. The mechanism of action is as described for other organophosphates. As such its duration of action is longer than other muscarinic acting drugs and thus requires less frequent administration. Can use daily or every other day dosing. Can cause blurred vision and brow ache which typically resolve.
VI. MUSCARINIC ANTAGONISTS (PARASYMPATHOLYTIC AGENTS)

These compounds competitively block muscarinic receptors, inhibiting all parasympathetic functions and sympathetic cholinergic activity. These agents compete with acetylcholine for muscarinic receptors. The effect is reversible, but may persist for hours or days. At doses in excess of those employed clinically, these agents can also block nicotinic cholinergic receptors at autonomic ganglia if given at high enough doses.

A. MUSCARINIC ANTAGONISTS:

1. ATROPINE: used 1) to allay the urgency and frequency of micturition that accompanies urinary tract infections; 2) to relieve hypermotility of colon and hypertonicity of the small intestine; 3) for the treatment of cholinesterase inhibitor induced poisoning; and 4) in ophthalmology to induce mydriasis and cycloplegia, i.e., paralysis of the ciliary muscle and 5) reverse bradycardia of vagal origin.

2. SCOPOLAMINE:
   Prototypic agents. Natural alkaloids. Scopolamine has more of a sedative effect than atropine. Used in preparation for surgical anesthesia to minimize secretions. Scopolamine is also used to treat nausea and vomiting associated with motion sickness and chemotherapy induced nausea. These drugs are contraindicated in narrow angle glaucoma.

3. GLYCOPYRROLATE used following surgery in combination with cholinesterase inhibitors. Its antimuscarinic activity is used to prevent overstimulation of the gut during reversal of neuromuscular blockade (see neuromuscular blockade).

C. ATROPINE POISONING:

"blind as a bat, mad as a hatter, red as a beet, hot as a hare, dry as a bone, the bowel and bladder lose their tone, and the heart runs alone."
In cases of overdosage with atropinic agents, one observes characteristic symptoms of atropine poisoning:

**Peripheral nervous system**
- dry mouth
- difficulty in swallowing
- marked thirst
- hot, dry, and flushed skin
- dilated pupils
- blurred vision and photophobia
- tachycardia
- increased blood pressure
- micturition difficulty
- respiratory collapse

**Central nervous system**
- nervousness
- confusion
- hallucinations
- muscular incoordination and weakness
- inappropiate laughter
- psychosis

**Treatment (symptomatic)**
1. Gastric lavage, if drug is taken orally
2. Supportive measures for maintenance of circulation and respiration
3. Lowering of body temperature with cold sponge
4. Catherization- because bladder tone is low
5. Eyes to be treated with mitotics and patient may be kept in a dark room
6. Barbiturates for sedation
7. Physostigmine (1 to 4 mg) intravenously; repeated as required

### VII. DRUGS COVERED IN LECTURE (Bold text is information you should know)

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Half-Life</th>
<th>Mechanism of action</th>
<th>Elimination</th>
<th>Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine</td>
<td>Nicotrol</td>
<td>1-2 hrs</td>
<td>Activation of neuronal Nicotinic receptors</td>
<td>Urine</td>
<td>Withdrawal symptoms of smoking cessation</td>
</tr>
<tr>
<td>Succinylcholine</td>
<td>Anectine</td>
<td>5-8 min</td>
<td>Depolarizing block of muscle nicotinic receptors</td>
<td>Butyryl cholinesterase</td>
<td>Neuromuscular block for electroconvulsive shock therapy or emergency intubation</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>Not-used clinically</td>
<td>~150 msec</td>
<td>Nicotinic and muscarinic agonist</td>
<td>AchE</td>
<td>None</td>
</tr>
<tr>
<td>Methacholine</td>
<td>Provocholine</td>
<td>relatively short</td>
<td>Muscarinic agonist</td>
<td>AchE</td>
<td>Diag. of subclinical asthma, or test for severity of asthma</td>
</tr>
<tr>
<td>Carbachol</td>
<td>Miostat or Carbastat</td>
<td>Duration 4-8 hrs topically or 24 hrs intraocular</td>
<td>Muscarinic and nicotinic receptor agonist</td>
<td>AchE</td>
<td>Miotic agent in ocular surgery, to reduce pressure following ocular surgery</td>
</tr>
<tr>
<td>Bethanechol</td>
<td>Urecholine</td>
<td>~1 hr</td>
<td>Muscarinic agonist</td>
<td>unknown</td>
<td>Urinary retention, bladder atony</td>
</tr>
<tr>
<td>Pilocarpine</td>
<td>Salagen</td>
<td>~1 hr</td>
<td>Muscarinic agonist</td>
<td>AchE</td>
<td>Dry mouth from head and neck radiation or Sjögren’s syndrome, Narrow angle glaucoma</td>
</tr>
<tr>
<td>Neostigmine</td>
<td>Prostigmin</td>
<td>50-90 min</td>
<td>AchE inhibitor</td>
<td>AchE and plasma esterases</td>
<td>Myasthenia gravis, reverse neuromusc. block</td>
</tr>
<tr>
<td><strong>Edrophonium</strong></td>
<td><strong>Tensilon, Enlon or Reversol</strong></td>
<td><strong>~10 min</strong></td>
<td><strong>AchE inhibitor</strong></td>
<td><strong>Bile</strong></td>
<td><strong>Diag of myasthenia gravis, reversal of neuromusc. block</strong></td>
</tr>
<tr>
<td>----------------</td>
<td>-------------------------------</td>
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<td>-------------------</td>
<td>---------</td>
<td>-----------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Physostigmine</strong></td>
<td><strong>Antilirium</strong></td>
<td><strong>45-60 min</strong></td>
<td><strong>Reversible AchE inhibitor</strong></td>
<td><strong>AchE</strong></td>
<td><strong>Delirium from anticholinergic drugs, glaucoma</strong></td>
</tr>
<tr>
<td><strong>Donepezil</strong></td>
<td><strong>Aricept</strong></td>
<td><strong>~70hrs</strong></td>
<td><strong>Reversible AchE Inhibitor</strong></td>
<td><strong>Liver</strong></td>
<td><strong>Alzheimer’s Dx.</strong></td>
</tr>
<tr>
<td><strong>Pralidoxime</strong></td>
<td><strong>2-PAM</strong></td>
<td><strong>~75 min</strong></td>
<td><strong>Peripheral AchE reactivator</strong></td>
<td><strong>Urine</strong></td>
<td><strong>Respiratory muscle weakness in organophosphate poisoning</strong></td>
</tr>
<tr>
<td><strong>Echotoxiphate</strong></td>
<td><strong>Phospholine</strong></td>
<td><strong>Very long</strong></td>
<td><strong>Irreversible AchE Inhibitor</strong></td>
<td><strong>unknown</strong></td>
<td><strong>Open angle glaucoma</strong></td>
</tr>
<tr>
<td><strong>Atropine</strong></td>
<td><strong>Atropine</strong></td>
<td><strong>2 hr</strong></td>
<td><strong>Muscarinic antag</strong></td>
<td><strong>Liver</strong></td>
<td><strong>Excess secretions during surgery, the ↑ freq and urg. assoc with cystitis, hypertonic gut, organophosphate poisoning, bradycardia</strong></td>
</tr>
<tr>
<td><strong>Scopolamine</strong></td>
<td><strong>Isopto</strong></td>
<td><strong>~9.5 hrs for transdermal, 24 for intra</strong></td>
<td><strong>Muscarinic antagonist</strong></td>
<td><strong>unknown</strong></td>
<td><strong>Motion sickness, anti-saliagogue in surgery</strong></td>
</tr>
<tr>
<td><strong>Glycopyrrolate</strong></td>
<td><strong>Robinul</strong></td>
<td><strong>0.5-2 hrs</strong></td>
<td><strong>Muscarinic receptor antagonist</strong></td>
<td><strong>urine</strong></td>
<td><strong>Protects against excessive muscarinic activation during reversal of neuromuscular blockade, anti-saliagogue</strong></td>
</tr>
</tbody>
</table>
NEUROMUSCULAR RELAXANTS

Date: August 24th – 8:30-9:20 AM
Recommended Reading: Basic and Clinical Pharmacology, 13th Edition, Katzung, et. al.,

LEARNING OBJECTIVES

1. Describe the mechanisms by which skeletal muscle nicotinic receptor activation stimulates skeletal muscle contraction including the agonists, receptors, and postsynaptic mechanisms that initiate contraction.

2. Compare the two distinct mechanisms by which depolarizing and non-depolarizing neuromuscular blockers mediate their effects on the motor end plate.

3. Compare the pharmacokinetics of the two classes of neuromuscular blockers.

4. Describe how cholinesterase inhibition affects the paralysis produced by each type of neuromuscular blocker.

5. List the mechanisms by which the action of both classes of neuromuscular blockers are terminated.

6. List the characteristics of non-depolarizing or depolarizing neuromuscular blockers that make them better suited for specific uses.

7. Describe the prominent side effects of each class of skeletal muscle relaxant.

8. List the antidote for either class of neuromuscular blockers.

9. Describe the characteristics of phase I and phase II block with depolarizing neuromuscular blockers and describe why phase II should be avoided.

10. Describe the characteristics of pancuronium, rocuronium, mivacurium and vecuronium and why certain characteristics make one agent preferable over another for use in long term ventilation, intubation of a healthy patient or patient with renal failure for a relatively short procedure, or a moderate lengthy orthopedic surgery.

11. Diagram the stretch reflex arc including the excitatory and inhibitory synapses.

12. Describe the physiological basis of muscle spasticity.

13. Describe the mechanisms by which baclofen and benzodiazepines alter somatic motor neuron excitation, list their major side effects and discuss how the route of delivery can reduce side effects.

14. Describe the basic mechanisms by which Tizanidine and Dantrolene reduce muscle spasticity and list the major side effects of both drugs.
15. Describe the important alternative use of dantrolene in clinical practice.
Serotonin and Dopamine Drugs


LEARNING OBJECTIVES

1. Describe the major features of serotonin and dopamine neurotransmission.

2. Describe how the 5-HT$_1$ family of receptors is manipulated to treat migraine*.

3. Describe how 5-HT$_{1A}$ receptors are manipulated pharmacologically for treatment of anxiety and depression*

4. Describe how 5-HT$_3$ receptors are manipulated pharmacologically for the treatment of chemotherapy-induced nausea and emesis*

5. Describe how the 5-HT$_4$ receptor is manipulated for treatment of GI disorders*

6. Describe how serotonin transporter function is manipulated therapeutically, and list the indications that are successfully treated with this therapy*

7. Describe how dopamine neurotransmission is manipulated therapeutically for the treatment of Parkinson’s Disease*

8. Describe how D$_2$ neurotransmission is manipulated for the positive symptoms of Schizophrenia*.

9. Describe how DA dopamine neurotransmission is manipulated for the treatment of Attention deficit hyperactivity disorder*

10. *List a prototype drug used for this indication
**Serotonin and Dopamine Drugs**

**Date:** August 24, 2015 (9:30-10:20 AM) **Recommended Reading:** Basic and Clinical Pharmacology, 13th Edition, Katzung, et. al., pp. 271-294, and 474.

**LEARNING OBJECTIVES**

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<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Mechanism of action</th>
<th>Rx</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HTP</td>
<td>5-hydroxytryptophan</td>
<td>5-HT precursor</td>
<td>depression</td>
<td></td>
</tr>
<tr>
<td>Buspirone</td>
<td>buspar</td>
<td>5-HT1A partial agonist</td>
<td>Anxiety/depression</td>
<td>Early increase in anxiety</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>Imitrex</td>
<td>5-HT1D agonist</td>
<td>Migraine</td>
<td>Coronary vasoconstriction</td>
</tr>
<tr>
<td>risperidone</td>
<td>Resperidone</td>
<td>5-HT2A/2C antagonist</td>
<td>Depression/psychosis</td>
<td>Weight gain/akinesia</td>
</tr>
<tr>
<td>Odansetron</td>
<td>Zofran</td>
<td>5-HT3</td>
<td>Chemotherapy-induced emesis</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Prozac</td>
<td>SSRI</td>
<td>Depression/OCD/anxiety/panid disorder/PTSD/social phobia</td>
<td>Sexual dysfunction/insomnia</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Zoloft</td>
<td>SSRI</td>
<td>Depression/OCD/anxiety/panid disorder/PTSD/social phobia</td>
<td>Sexual dysfunction/insomnia</td>
</tr>
<tr>
<td>L-DOPA</td>
<td>Levodopa</td>
<td>Dopamine precursor</td>
<td>Parkinson’s Disease</td>
<td>Arrhythmia/dyskinesia</td>
</tr>
<tr>
<td><strong>Bromocriptine</strong></td>
<td><strong>Parlodel</strong></td>
<td><strong>D2 agonist</strong></td>
<td><strong>Parkinson’s Disease</strong></td>
<td><strong>Cardiac valvular fibrosis</strong></td>
</tr>
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</tr>
<tr>
<td><strong>Carbidopa</strong></td>
<td><strong>Lodosyn</strong></td>
<td><strong>Aromatic acid decarboxylase inhibitor</strong></td>
<td><strong>Parkinson’s Disease</strong></td>
<td><strong>Same as L-DOPA since increases DA</strong></td>
</tr>
<tr>
<td><strong>Selegiline</strong></td>
<td><strong>Anipryl</strong></td>
<td><strong>MAO-B inhibitor</strong></td>
<td><strong>Parkinson’s Disease</strong></td>
<td><strong>Potential for hypertensive crisis</strong></td>
</tr>
<tr>
<td><strong>Talcapone</strong></td>
<td><strong>Tasmar</strong></td>
<td><strong>COMT inhibitor</strong></td>
<td><strong>Parkinson’s Disease</strong></td>
<td><strong>Dyskinesia</strong></td>
</tr>
<tr>
<td><strong>Methylphenidate</strong></td>
<td><strong>Ritalin</strong></td>
<td><strong>Dopamine reuptake inhibitor</strong></td>
<td><strong>ADHD</strong></td>
<td><strong>Tachycardia</strong></td>
</tr>
<tr>
<td><strong>Metaclopramide</strong></td>
<td><strong>Reglan</strong></td>
<td><strong>D2 antagonist</strong></td>
<td><strong>Nausea</strong></td>
<td><strong>Akathisia</strong></td>
</tr>
<tr>
<td><strong>Haloperidol</strong></td>
<td><strong>Haldol</strong></td>
<td><strong>D2 antagonist</strong></td>
<td><strong>Psychosis</strong></td>
<td><strong>Extrapyramidal motor disturbances</strong></td>
</tr>
<tr>
<td><strong>Dopamine</strong></td>
<td><strong>Dopamine</strong></td>
<td><strong>Dopamine and adrenergic receptor agonist</strong></td>
<td><strong>Shock, cardiac decompensation</strong></td>
<td><strong>Hypotension (low dose), tachycardia</strong></td>
</tr>
<tr>
<td><strong>Trazadone</strong></td>
<td><strong>Desyrel</strong></td>
<td><strong>5-HT2A/2C antagonist + SSRI</strong></td>
<td><strong>Anxiety/depression</strong></td>
<td><strong>Suicidality early after initiation</strong></td>
</tr>
</tbody>
</table>
Opioids

OBJECTIVES:

Describe the major opioid receptors with regard to their structure, tissue expression, signaling mechanisms and ligand selectivity.

Discuss the underlying neurophysiology for the response to pain.

Describe the effects of opioid receptor agonists on the response to pain and the mechanisms by which activation of the opioid receptor signaling pathways promotes analgesia.

List the indications for the major opioid receptor agonists, partial agonists and antagonists.

Describe the mechanism of action and pharmacodynamic properties of the major drugs affecting the opioid system, including morphine, meperidine, methadone, oxycodone, codeine, pentazocine, buprenorphine and naloxone.

Describe the major adverse effects of the major drugs acting on the opioid receptor system.

Describe any clinically relevant drug interactions with the major drugs acting on the opioid receptor system.

Describe the concepts of opioid tolerance, dependence and addiction.
Pharmacology and Therapeutics Lecture Objectives

LOCAL ANESTHETICS

1. Describe the mechanism of action for all local anesthetic drugs.

2. Identify the various nerve fiber types and compare how they respond to local anesthetic DRUGS.

3. Discuss the primary determinates related to the pharmacokinetics and pharmacodynamics of local anesthetics for the following:
   a. Onset time
   b. Duration
   c. Potency

4. Explain local anesthetic systemic toxicity (LAST) and demonstrate how to treat it.

5. Describe the structure of a prototypical local anesthetic molecule; name the two classes of local anesthetics.

6. Illustrate the structure of the voltage-gated sodium channel and diagram where local anesthetic drugs bind to the channel.

7. Name some common additives to local anesthetics and describe why the drugs are given together.

8. Recall some clinical uses for local anesthetics.
LOCAL ANESTHETICS

1. GENERAL PROPERTIES:

   Definition: Local anesthetics produce loss of sensation and attenuate muscle activity in circumscribed areas of the body by reversibly blocking nerve conduction. This phenomenon is called regional anesthesia.

   A. Physicochemical Characteristics.
      These are similar for local anesthetics, varying in whether they have an ester or amide “linkage”. This linkage dictates the pharmacokinetics and toxicity of the various drugs. The larger portion of the administered local anesthetic exists in the body fluids in a charged, cationic form. The cationic state is the most active form at the receptor site, but the uncharged drug is very important for penetration of biologic membranes.

   B. Pharmacodynamics.
      Local anesthetics block open sodium channels from the cytosolic side. They are most effective on small nerves, on myelinated nerves and those that fire at higher frequencies. Thus, they are most effective at blocking the fast firing pain-conducting neurons.

   C. Pharmacokinetics.
      The balance between the rate of absorption from the locally injected site and the metabolism rate of the drug is a large determinant in the toxicity potential. Within seconds of being absorbed into the circulation, ester-type local anesthetics are metabolized to PABA by circulating plasma cholinesterases. Amide-type anesthetics are more slowly metabolized by liver microsomal enzymes. Local anesthetics produce vasodilation (with the exception of cocaine) and are formulated with epinephrine to produce local vasoconstriction. This decreases local perfusion and the drug’s absorption to effectively enhance the duration of the local anesthesia and reduce the likelihood of toxicity.

   D. Pharmacology and Toxicity.
      Act on all organs in which conduction of impulses occurs. With sufficient absorption into the circulation, amide anesthetics can produce CNS activation and seizures, and cardiovascular toxicity. Hypotension occurs with spinal and epidural anesthesia, the degree of which depends on the level of the block. PABA-induced allergy can occur with ester anesthetics. Amide local anesthetics are not associated with allergy, although, methylparaben, a preservative in which they are sometimes stored, can lead to hypersensitivity.
2. EVALUATION OF SPECIFIC DRUGS.

A. Esters.

Cocaine was the first known local anesthetic and it remains useful primarily because of the vasoconstriction it provides with topical use. Cocaine is easily absorbed from mucous membranes and, therefore, the potential for systemic toxicity is great. CNS stimulation and euphoria are the characteristics responsible for the abuse potential of this drug. Cocaine also blocks reuptake of norepinephrine and can cause hypertension and tachycardia.

Procaine was first synthesized in 1905 and continues to be useful today. It is readily hydrolyzed by plasma cholinesterase, which accounts for its relatively short duration of action. It often is combined with epinephrine for infiltration, nerve block and spinal anesthesia.

Tetracaine is commonly used for spinal anesthesia. Tetracaine is more lipophilic, and thus considerably more potent, long lasting and more toxic, than procaine and cocaine. Since it is only used for spinal anesthesia for which small doses are used, toxicity never occurs.

Benzocaine is an ester of para-aminobenzoic acid (PABA) that lacks the terminal secondary or tertiary amino group. It is so poorly water soluble that it can be applied as a dusting powder or ointment directly to wounds and ulcerated surfaces without major concern for systemic toxicity.

B. Amides.

Lidocaine, introduced in 1948, is well tolerated and is one of the most commonly used local anesthetics. Lidocaine produces more prompt, more intense, longer lasting and more extensive anesthesia than does an equal concentration of procaine. Lidocaine is the prototypical modern local anesthetic.

Mepivacaine has a slightly more prolonged action than that of lidocaine and a more rapid onset of action. The drug has been widely used in obstetrics, but its use has declined recently because of the early transient neurobehavioral effects it produces in the neonate (e.g., lassitude).

Bupivacaine has a particularly prolonged duration of action, and some nerve blocks last more than 24 hrs. This is often an advantage for postoperative analgesia. Its use for epidural anesthesia in obstetrics has attracted interest because it can relieve the pain of labor at concentrations low enough to
permit motor activity of abdominal muscles to aid in expelling the fetus. Fetal drug concentrations remain low due to the high level of binding to plasma proteins and drug-induced neurobehavioral changes are not observed in the neonate. Bupivacaine is more lipophilic, and thus more potent and more toxic, than mepivacaine and lidocaine. In particular, bupivacaine is more cardiotoxic, affecting conduction at lower relative concentrations than lidocaine.

**Ropivacaine** Recently introduced as Naropin®, ropivacaine is the only currently available local anesthetic to be supplied as a pure S-enantiomer. Similar in structure to bupivacaine, ropivacaine seems to offer advantages over bupivacaine: 1) a greater margin of safety, i.e., it is less cardiotoxic. 2) produces less of a motor block (in lower concentrations). Ropivacaine is being promoted as an epidural anesthetic, especially for obstetrics where it is well tolerated by both mother and baby. It also has been used successfully for infiltration anesthesia and peripheral nerve block.

### 3. CLINICAL USES.

A. Topical Anesthesia
B. Infiltration Anesthesia
C. Intravenous Regional Anesthesia
D. Peripheral Nerve Block: a block of a peripheral nerve or plexus occurs when local anesthetic is deposited within the nerve sheath. The block onset will proceed from proximal to distal because the proximal nerve fibers are organized on the exterior of the nerve (mantle fibers), and the distal nerve fibers are located on the interior of the nerve (core fibers). The first sign of a successful nerve block is often loss of coordination in proximal muscle groups due to blockade of A gamma fibers.

E. Spinal Anesthesia: a block of spinal nerves (autonomic, sensory and motor) in the subarachnoid space occurs when local anesthetic is injected into the CSF from L₂₃ caudad (to avoid hitting the spinal cord which ends at L₁₂.) Drugs can be prepared so that they are hyperbaric (more dense than CSF) so they can rise and produce blockade at levels higher than the site of injection. Since a band of drug is placed in the CSF when injected, all nerves caudad to the site are automatically blocked.

F. Epidural Anesthesia: a block of spinal nerves (autonomic, sensory and motor) in the epidural space occurs when drug is deposited there. The block can be done at any level of the cord from the cervical region to the sacrum and drug moves equally caudad and cephalad from the injection level. The resultant block is segmental, so, it is possible to produce a band of anesthesia with retained ability to move the legs.

G. Anti-arrhythmics
Table 1. Properties of some ester and amide local anesthetics.

<table>
<thead>
<tr>
<th></th>
<th>Potency (Procaïne =1)</th>
<th>Onset of Analgesia</th>
<th>Duration of Action</th>
<th>Anesthetic Use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ESTERS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cocaine HCl</td>
<td>2</td>
<td>Rapid (1 min.)</td>
<td>Medium (1 hr)</td>
<td>Topical</td>
</tr>
<tr>
<td>Procaine HCl (Novocain)</td>
<td>1</td>
<td>Slower</td>
<td>Short (30-45 min.)</td>
<td>Infiltration Nerve Block Subarachnoid</td>
</tr>
<tr>
<td>Tetracaine HCl (Pontocaine)</td>
<td>16</td>
<td>Slow for spinal (15-20 min.)</td>
<td>Long (2-5 hr)</td>
<td>Subarachnoid</td>
</tr>
<tr>
<td>Benzocaine (Americaine, etc.)</td>
<td>(For topical use only)</td>
<td>(dependent upon pharmaceutical formulation)</td>
<td></td>
<td>Topical</td>
</tr>
<tr>
<td><strong>AMIDES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lidocaine HCl (Xylocaine)</td>
<td>4</td>
<td>Rapid</td>
<td>Medium (1 ¼ hr)</td>
<td>Infiltration Nerve Block Intravenous - Regional Epidural Subarachnoid</td>
</tr>
<tr>
<td>Mepivacaine HCl (Carbocaine)</td>
<td>2</td>
<td>Rapid (3-5 min)</td>
<td>Medium</td>
<td>Infiltration Nerve Block Epidural</td>
</tr>
<tr>
<td>Bupivacaine HCl (Marcaine)</td>
<td>16</td>
<td>Slower</td>
<td>Long (several hrs)</td>
<td>Infiltration Nerve Block Epidural Subarachnoid</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>16</td>
<td>Slower</td>
<td>Long</td>
<td>Epidural</td>
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</tbody>
</table>
GENERAL ANESTHETICS

Date: Wednesday, August 26, 2015

Reading Assignment: Basic and Clinical Pharmacology,
B.G. Katzung, Chapter 25
Pharmacology, Examination & Board Review,
Katzung & Trevor, Chapter 25

KEY CONCEPTS AND LEARNING OBJECTIVES

1. Describe what a general anesthetic is expected to do and how it can be achieved.

2. Develop a working understanding of the pharmacokinetics of inhalational anesthetics.

3. Discuss how the blood:gas coefficient influences the onset of action (and termination of anesthesia) for inhaled anesthetics

4. Discuss how the ventilation rate and pulmonary blood flow influences the onset of action for inhaled anesthetics

5. In terms of uptake and elimination, describe how blood flow to a tissue influences the tension of an anesthetics gas in that tissue.

6. Explain the minimum alveolar concentration (MAC) and what information it provides about a volatile anesthetic.

7. Discuss the pharmacokinetic properties of the ultrashort-acting hypnotics and explain how these properties make this class of drugs popular general anesthetic agents.

8. Discuss the advantages, disadvantages, clinical indications and contraindications for clinically used inhaled and intravenously administered general anesthetics such as:
   a. Halogenated Hydrocarbons: Isoflurane, Sevoflurane, Desflurane
   b. Inert Gas: Nitrous Oxide
   c. Ultrashort-Acting Barbiturates: Thiopental
   d. Sedative-Hypnotics: Ketamine, Etomidate, Propofol
GENERAL ANESTHETICS

I. PRINCIPLES OF ANESTHESIA:

Characteristics of general anesthesia include: 1) amnesia, 2) analgesia, and 3) unconsciousness, with 4) an inhibition of sensory and autonomic reflexes, and 5) skeletal muscle relaxation.

Balanced anesthesia includes the administration of medications preoperatively for sedation and analgesia, and the intraoperative use of neuromuscular blocking drugs and/or regional anesthetics, along with the administration of general anesthetic drugs.

Signs and stages of anesthesia: A historical taxonomy that was apparent with the very long onset and emergence from ether anesthesia. With modern anesthetics, these stages are blurred or obscured.

Stage I: Analgesia and Amnesia. Begins with induction of analgesia and lasts until consciousness is lost. Amnesia develops before loss of consciousness. Pain sensation is lost, but motor activity and reflexes remain normal.

Stage II: Excitement. Begins with the loss of consciousness and lasts to onset of surgical anesthesia. Stage II is characterized by delirium. With modern drugs, the duration and intensity of this stage during induction are greatly reduced; it is more important on emergence.

Stage III: Surgical Anesthesia Begins with the appearance of rhythmical respirations.

Stage IV: Cardiorespiratory Collapse. Only appears as the consequence of gross negligence with failure to provide assisted or controlled ventilation and support of the circulation. Such depth is never used or required.

II. INHALATIONAL ANESTHETICS:

A. Pharmacology of Inhalational Anesthetics.

1. Mechanism of Action.

Almost all general anesthetics act at the GABA<sub>A</sub> receptor-chloride channel and facilitate the GABA mediated neuronal inhibition at these receptor sites. Nevertheless, the exact mechanism of inhaled anesthetics remains unclear.
2. Safety, Dosage and Potency.
Anesthetics have an unusually narrow margin of safety with therapeutic indices of only 2 to 4.

A measure of potency of inhalational agents is MAC; the minimum alveolar concentration of an anesthetic, at 1 atmosphere, that prevents movement to a standard noxious stimulus (skin incision in humans) in 50% of humans or animals tested (refer to Table 25-1, Katzung). MAC is frequently multiplied by a factor of 1.3 to achieve “nearly” 100 percent clinical efficacy (i.e., ED95). Inhalational anesthetics used in combination appear to have an additive effect. Several factors change MAC. These include body temperature, age and other drugs (e.g., opioids and benzodiazepines). Factors that do not influence MAC include sex, species, state of oxygenation, acid-base changes, and arterial blood pressure. MAC is also used as an equipotent dose model for comparing non-anesthetic effects of these agents.

B. Pharmacokinetics of Inhalational Anesthetics.

1. Uptake and Distribution.
Understanding general anesthesia requires an appreciation of the pharmacokinetics of inhaled drugs. The active form of the drug is the gaseous form. Depth of anesthesia is a function of the partial pressure in the brain and brain tension is in equilibrium with the alveolar or exhaled partial pressure. Therefore, the factors that determine the tension of anesthetic gas in the brain include the (1) inspired concentration, (2) transfer of the gas to the arterial blood and (3) transfer of the agent to the brain. During induction loss of agent to other tissues has little impact, but can be measured.

a. Concentration of the Anesthetic Agent in Inspired Gas and Alveolar Uptake of Anesthetic Gases.
Gases diffuse from areas of high partial pressure (or tension) to areas of low partial pressure. Thus, the tension of anesthetic in the alveolus provides the driving force to establish a therapeutically effective brain tension.

The rate of rise of the alveolar tension of an anesthetic gas is a function of the uptake of the gas by body tissue compartments. The anesthetic is first removed by the vessel rich group (brain, heart, kidneys, liver), then the muscle group, followed by the fat tissue in which it is very soluble, but to which perfusion is slight and, lastly, to the tissues that are very poorly perfused, like tendons, ligaments, cartilage, etc. The more soluble the agent is in blood the slower the rise to equilibrium between the inspired and alveolar concentration.

b. Transfer of Anesthetic Gases from Alveoli to Brain.
In the absence of ventilation-perfusion disturbances, four major factors determine how rapidly anesthetics pass from the inspired gases to brain. These are (i) the solubility of the anesthetic in blood, (ii) rate and depth of ventilation, (iii) the rate of blood flow through the lungs, and (iv) the partial pressure of the anesthetic in arterial and mixed venous blood.
Solubility of the Anesthetic in Blood. This is usually expressed as the blood/gas partition coefficient, or \( \lambda \), which represents the ratio of anesthetic concentration in blood to anesthetic concentration in a gas phase when the two are in partial pressure equilibrium (refer to Table 25-1, Katzung). The more soluble an anesthetic is in blood, the more of it must be dissolved in blood to raise its partial pressure there appreciably. Thus, the blood tension of soluble agents rises slowly. Because the potential reservoir for relatively insoluble gases is small and can be filled more quickly, their tension in blood also rises quickly (Figure 25-3, Katzung).

Pulmonary Ventilation. The rate of rise of anesthetic gas tension in arterial blood is directly dependent on the minute ventilation. The magnitude of the effect at a given time point varies according to the blood/gas partition coefficient. An increase in pulmonary ventilation is accompanied by only a slight increase in arterial tension of an anesthetic with low blood solubility but can significantly increase tension of agents with moderate or high blood solubility. Thus, the partial pressure of a highly soluble anesthetic gas can be increased by over-ventilation during the induction period. Conversely, decreased ventilation (e.g., resulting from respiratory depression produced by premedication) can lead to a slower rate of change of alveolar and arterial gas tension.

Cardiac Output. The pulmonary blood flow (i.e., the cardiac output) affects the rate at which anesthetics pass from the alveolar gases into the arterial blood. An increase in pulmonary blood flow slows the initial portion of the arterial tension curve; but the latter part of the curve tends to catch up, with the overall result that there is little change in the total time required for complete equilibration. Low left-sided cardiac output preferentially feeds the brain and thus causes a more rapid rise in brain (alveolar) tension. Thus, contrary to the effect of altered ventilation, low cardiac output speeds anesthetic induction.

Partial Pressure in Arterial and Mixed Venous Blood. After taking up anesthetic gas from the lung, the blood circulates to the tissue, and anesthetic gas is transferred from the blood to all tissues of the body. Blood cannot approach equilibrium with inhaled gas tension until this process, which tends to decrease the blood tension, is nearly complete.

Venous blood returning to the lungs contains more anesthetic gas with each passage through the body. After a few minutes of anesthesia, the difference between arterial and mixed venous (alveolar) gas tension lessens, and the amount of gas transferred to arterial blood during each minute decreases as time passes.

Solubility of Gas in Tissues. This is expressed as a tissue/blood partition coefficient, a concept analogous to the blood/gas partition coefficient previously discussed. With most anesthetic agents, the tissue/blood partition is near unity for many of the body's lean tissues; that is, these agents are equally soluble in lean tissue and blood. The tissue/blood coefficient for all anesthetics is large for fatty tissues. Their concentration in the fat tissue is much greater than that in blood at the time of equilibrium (when tension in tissue equals blood).

Tissue Blood Flow. Tissues with high rates of blood flow (e.g., the brain) will exhibit rapid rises in concentration of anesthetic and, therefore, are able to take up significant amounts of the agent during the early stages of anesthesia. Because blood flow to adipose tissue is very limited, anesthetic gases will be delivered to, and taken up by, fatty tissues very slowly. Consequently, these tissues contain a significant amount of anesthetic agent only after some time has elapsed.
Partial Pressure of Gas in Arterial Blood and Tissues. As the tissues take up an anesthetic agent, the partial pressure of the gas in tissues increases towards that of the arterial blood. The rate at which gas diffuses from arterial blood to tissues varies with the partial-pressure difference between them and tissue concentration changes rapidly in the early minutes of anesthesia; however, as the tissue tension comes closer to the arterial tension, the tissue uptake of gas slows.

2. Elimination of Inhalational Anesthetics.

The major factors that affect rate of elimination of the anesthetics are the same as those that are important in the uptake phase. Those with low blood/gas solubility wash out more quickly than those with higher coefficients. If administration of anesthesia lasts longer than approximately 45 minutes, enough anesthetic agent has been delivered to the fat tissue compartment to delay emergence for agents with higher fat solubility, regardless of their blood/gas coefficients. As ventilation with anesthetic-free gas washes out the lungs, the arterial blood tension declines first, followed by that in the tissues.

Because of the high blood flow to brain, its tension of anesthetic gas decreases rapidly, accounting for the rapid awakening from anesthesia noted with relatively insoluble agents such as nitrous oxide. (The agent persists for a longer time in tissues with lower blood flow, e.g., fat and muscle.) Thus, termination of anesthesia often is by redistribution of the anesthetic from the brain to blood and other tissues.

C. Clinical Pharmacology of Individual Agents.

1. Volatile anesthetics

a. Halothane

Pharmacokinetics. Halothane, the first of the modern era anesthetics, is a potent agent with a moderately rapid induction and emergence time. It is rarely used today. In practice, thiopental (an ultrashort-acting barbiturate, see Section III.A.) usually was administered for induction of anesthesia; halothane then was introduced for anesthesia maintenance.

CNS. Halothane has a mild analgesic effect, but often requires the addition of another analgesic agent such as N₂O or a narcotic in a balanced technique to achieve the anesthetic state at more modest concentrations.

Cardiovascular. Halothane produces a dose-dependent depression of the myocardium and reduces venous tone; both contribute to the reduction in cardiac output and resultant fall in blood pressure. The decrease in cerebral vascular resistance increases intracranial pressure. Halothane inhibits baroreceptor activity and is thus associated with bradycardia; however, it does sensitize the myocardium to the arrhythmogenic effect of catecholamines.

Respiration. Halothane depresses respiratory minute volume at all levels of anesthesia, leading to a dose-dependent decreased tidal volume. This results in the characteristic pattern of short, rapid breaths. Halothane is far less irritating to the respiratory tract than isoflurane. It does not increase secretions from the tracheobronchial tree, does not induce bronchospasm in light planes of anesthesia and is an effective bronchodilator. It is, therefore, a desirable agent for asthmatic patients.
Muscle. At clinical levels of anesthesia, halothane alone does not produce significant neuromuscular blockade. Relaxation is produced by CNS-mediated depression of muscle activity. Halothane-induced muscle relaxation will potentiate the effects of a skeletal muscle relaxant such as vecuronium.

Evaluation. Halothane is pleasant-smelling and nonirritating to the respiratory tract. It is almost never used today because of its sensitization to catecholamines and its potential to cause liver necrosis.

b. Isoflurane

Pharmacological Properties. Isoflurane is a fairly potent agent with a pharmacokinetic profile similar to halothane. The pungent odor limits its use as a singular induction agent. It is less soluble in tissues than either halothane, thus emergence is more rapid for surgical cases lasting more than 8 hours. This agent has the advantage that only 0.2 - 0.3% of the inhaled dose is biotransformed.

Respiration. Isoflurane is a potent ventilatory depressant.

Cardiovascular. Isoflurane maintains cardiac output by dilating peripheral arterial beds that reduces afterload. It does not sensitize the heart to catecholamines as does halothane. In neurosurgery it has the advantage of not raising the intracranial pressure when patients are hyperventilated.

Muscle. Isoflurane potentates the action of neuromuscular blockers.

Evaluation. The aforementioned advantages have made isoflurane a commonly used volatile anesthetic in North America and Western Europe.

c. Sevoflurane

Pharmacological Properties. Sevoflurane is a potent (MAC =1.7-2.1) general anesthetic that has a number of desirable properties. It has lower solubility in blood (blood/gas partition coefficient of 0.69) than isoflurane and therefore exhibits more rapid induction of anesthesia. Because of a similar fat solubility to isoflurane, brief anesthetics result in rapid emergence, while those in excess of 45 minutes may be associated with more prolonged emergence.

Cardiovascular. Cardiovascular effects similar to isoflurane (produces a direct, calcium-mediated depression of the myocardium; does not sensitize myocardium to catecholamines).

Respiration & Airways. Does not produce airway irritation. Respiratory depression similar to isoflurane. It is pleasant smelling, and so it has been adopted extensively for use in pediatric anesthesia for gas induction.

Muscle. Sevoflurane potentates the action of neuromuscular blockers, decreasing the doses needed of these drugs.
Evaluation. Sevoflurane is a pleasant smelling anesthetic that is non-irritating to the airway. It is readily acceptable to children. It provides a rapid induction and recovery making it especially suitable for brief outpatient procedures. It has minimal cardiac effects, making it suitable for elderly patients. A drawback is its degradation by carbon dioxide absorbents (used to cleanse exhaled gases of carbon dioxide so they can be re-breathed) into a potentially nephrotoxic haloalkene, called Compound A. With proper administration (total diluent gas flows in excess of 2 l/min.), this phenomenon has not resulted in any human cases of nephrotoxicity.

d. Desflurane

Pharmacological Properties. Desflurane is a relatively new general anesthetic agent. It has the lowest solubility in blood of the fluranes, (blood/gas partition coefficient = 0.42) and therefore exhibits the most rapid induction and emergence from anesthesia. Desflurane is a potent anesthetic (MAC = 4.6-7.2).

Cardiovascular. Desflurane causes sympathetic activation leading to increased heart rate and blood pressure. This may be problematic for cranial injuries in which one wants to minimize cerebral edema.

Respiration & Airways. Unlike sevoflurane, desflurane is pungent and is a respiratory irritant and it readily provokes laryngospasm and coughing on induction. Respiratory depression is similar to isoflurane.

Muscle. Desflurane potentiates neuromuscular blockers, decreasing the doses needed of these drugs.

Evaluation. The rapid onset and emergence from anesthesia make it favorable; however, it is extremely irritating to the airway it is not suitable for inhalational induction. Its primary advantage over sevoflurane is speed of emergence after more prolonged surgery.


Pharmacological Properties. MAC for nitrous oxide is 110 percent of one atmosphere and thus it is incapable of independently producing surgical anesthesia outside of a hyperbaric chamber. It is used clinically as a supplement to other agents. Because nitrous oxide is relatively insoluble in blood and tissues (blood/gas partition coefficient=0.47), induction and emergence are rapid.

CNS. Nitrous oxide is a good analgesic: a 50% concentration in the inspired air is equivalent to 10 mg morphine i.m. Relatively high concentrations induce excitement (hence the term laughing gas).

Respiration. Nitrous oxide is not a respiratory irritant and induction is pleasant.

Cardiovascular. Nitrous oxide does not sensitize the heart to arrhythmogenic effects of catecholamines. It does not increase intracranial pressure.

Evaluation. Nitrous oxide is an incomplete anesthetic and cannot be used alone to produce surgical levels of anesthesia and still allow adequate tissue oxygenation. When used with other agents, a summation of MAC's occurs which allows more rapid awakening as well as a reduction
in cardiovascular side effects typical of other anesthetics. The rapid action, analgesic effect, lack of irritation of the tracheobronchial tree and lack of flammability have made nitrous oxide a valuable component of balanced anesthesia.

III. INTRAVENOUS ANESTHETICS AGENTS:

A. Ultrashort-Acting Barbiturates.

Among the barbiturates, two compounds are useful as induction agents for surgical procedures. These barbiturates are thiopental sodium, and methohexital sodium. These drugs are considered ultrashort-acting agents because their rapid entry into the CNS is followed by a relatively quick redistribution of the drug to indifferent tissues, such as skeletal muscle. Thiopental is the prototype for this class.

1. Pharmacokinetic Properties.

Ultrashort-acting barbiturates are uniquely suited to accomplish a rapid induction of unconsciousness. These agents induce anesthesia within one or two circulation times after their administration because they quickly achieve high concentrations in the CNS. The rapid appearance in brain tissue is due to two factors: (i) these anesthetics are very lipid-soluble and they diffuse rapidly through biological membranes, including the blood-brain barrier. (ii) The tissue accumulation of i.v.-administered lipid-soluble drugs is initially proportional to the distribution of cardiac output. The brain has a high blood flow per unit of mass and a large share of the total dose is distributed to this tissue.

As the drug is removed from the blood by the less-richly perfused tissues, or eliminated by metabolism and excretion, or both, plasma levels will fall, and the concentration of anesthetic in the brain will decline precipitously. Tissues having an intermediate blood flow per unit of mass, such as skeletal muscle and skin, are among the first to participate in the drug redistribution process.

2. Pharmacologic Properties.

CNS. Thiopental and other barbiturates are poor analgesics and may even increase the sensitivity to pain when administered in inadequate amounts.

Respiration. Thiopental is not irritating to the respiratory tract, and yet coughing, laryngospasm, and even bronchospasm occur with some frequency. The basis of these reactions is unknown. Thiopental produces a dose-related depression of respiration that can be profound.

Cardiovascular. In the normovolemic patient, thiopental produces myocardial depression and venodilation. It is a weak arterial constrictor. Modest hypotension is primarily the result of the effect of venodilation on cardiac output. In the presence of hemorrhage/hypovolemia, the administration of a normal dose may result in profound hypotension or circulatory collapse. Concentration of catecholamines in plasma is not increased, and the heart is not sensitized to epinephrine. Arrhythmias are uncommon. Cerebral blood flow and cerebral metabolic rate are reduced with thiopental and there is a marked reduction of intracranial pressure. This effect has proven beneficial in anesthesia for neurosurgical procedures.

Muscle. Relaxation of skeletal muscle is transient with little effect on uterine contractions, but thiopental crosses the placenta can depress the fetus.
Evaluation. Most of the complications associated with the use of thiopental are minor and can be avoided or minimized by judicious use of the drug. The advantages of thiopental are rapid, pleasant induction of anesthesia and fast recovery, with little postanesthetic excitement. Methohexital, opposite to thiopental, reduces seizure threshold and is useful only in electroconvulsive therapy for depression or epileptic cerebral mapping.

B. Other Hypnotics.

1. Ketamine

Ketamine has a unique anesthesia profile: profound analgesia, amnesia, and a superficial level of sleep. The state of unconsciousness it produces is trance-like (eyes may remain open until deep anesthesia is obtained), and cataleptic in nature. It is frequently described as dissociative, that is, the patient may experience a strong feeling of dissociation from the environment.

Ketamine causes cardiovascular stimulation, with the increases in heart rate and blood pressure being mediated through a stimulation of the autonomic nervous system. Therefore, this agent may prove useful in anesthetic induction for patients with a poor cardiac reserve or volume contraction. Ketamine is not indicated for patients with hypertension. An important advantage of ketamine is its potential for administration by the intramuscular route. This is useful in anesthetizing children, since anesthesia can be induced relatively quickly in a child who resists an inhalation induction or the insertion of an IV catheter.

The most serious disadvantage to the use of ketamine as an anesthetic agent is the drug's propensity to evoke excitatory and hallucinatory phenomena as the patient emerges from anesthesia. This agent is contraindicated for patients with psychiatric disorders.

2. Etomidate

Etomidate is a potent hypnotic agent used only for induction. A primary advantage of etomidate is its ability to preserve cardiovascular and respiratory stability better than does thiopental. Major disadvantages include pain on injection, myoclonus and the propensity to suppress adrenocortical function in some patients.

3. Propofol

Propofol is an important new intravenously administered anesthetic. It induces anesthesia at a rate that is similar to induction with thiopental, but emergence from propofol-induced anesthesia is more rapid. Emergence is characterized by minimal postoperative confusion. These properties have made propofol a commonly used anesthetic for patients who are undergoing brief surgical procedures (i.e., "day-surgery"). Some pain may occur at the site of injection. Propofol induces peripheral vasodilatation that results in a marked decrease in systemic blood pressure. Propofol can produce apnea during induction and its effects on respiration are similar to those observed during thiopental-induced anesthesia.

C. Opioid Analgesics.

Morphine and fentanyl are frequently employed as supplements during general anesthesia with inhalational or intravenous agents. Respiratory depression, mild decreases in blood pressure, some delay in awakening, and an appreciable incidence of postoperative nausea or vomiting
accompany the use of these drugs. Fentanyl is superior to morphine in that it does not cause histamine release. Therefore, large doses may be tolerated without important cardiovascular effects.
“Using Acupuncture to Explore the Neuropharmacology of the Pain Pathway”

By the end of this presentation, you should be able...

– To list the National Institutes of Health guidelines on the use of acupuncture (JAMA 1998; 280:1518-24).
– To identify the endogenous opioid peptides and major neurotransmitters implicated in acupuncture analgesia.
– To illustrate the neurochemical effects of low frequency/high intensity and high frequency/low intensity electroacupuncture.
– To contrast the inherent thermoelectrical properties of acupuncture needles