Pharmacology/Therapeutics I Block II Handouts – 2016-17

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SYNAPTIC TRANSMISSION: TARGETS OF DRUG ACTION

Date: August 16, 2016, 8:30 – 9:20 am

LEARNING OBJECTIVES

1. Describe the 5 steps involved in neurotransmission including the site where each step takes place within the neuron or synapse.

2. Describe the pre-synaptic mechanisms by which drugs can enhance or decrease neurotransmission.

3. Describe the post-synaptic mechanisms by which drugs can enhance or decrease transmission.

4. Discuss how drugs that act pre-synaptically differ in their ability to selectively influence the effects of a specific neurotransmitter from drugs that act post-synaptically.

5. Describe how selectivity of drug action is maintained by differences in the accessibility of a drug to the cytoplasm of the target cell.

6. Distinguish between noradrenergic and peptidergic neurotransmission with regard to the 5 steps of neurotransmission and discuss how differences between the two processes influence strategies for their pharmacological manipulation.

7. Describe how adrenergic neurotransmission is most commonly manipulated with clinical pharmaceuticals.

8. Describe the effects of the following drugs or drug classes on adrenergic neurotransmission:

- metyrosine
- reserpine
- bretylium
- cocaine
- tricyclic antidepressants
- monoamine oxidase inhibitors
- SSRIs
- amphetamines
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, \( \alpha \)-adrenergic receptors can inhibit, while \( \beta \)-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 rough endoplasmic reticulum. Various cleavage processes mediated by peptidases ensue that lead to the production of active neuropeptide.

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 though this is an active area of pharmaceutical research.
Items that are bolded are important knowledge that should be gained from the lecture material

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Mechanism of Action</th>
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<tbody>
<tr>
<td>Metyrosine</td>
<td>Hypertension</td>
<td>Competitive inhibition of tyrosine hydroxylase</td>
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<tr>
<td>Reserpine</td>
<td>Hypertension</td>
<td>Inhibits VMAT uptake of monoamines</td>
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<tr>
<td>Bretylium</td>
<td>Ventricular Arrhythmia</td>
<td>Inhibit action potential generation and calcium dependent synaptic vesicle fusion</td>
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<tr>
<td>Cocaine</td>
<td>Analgesia in surgery</td>
<td>Blocks monoamine reuptake</td>
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<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>
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Pharmacology and Therapeutics  Synaptic Transmission: Target of Drug Action  K.Scrogin, Ph.D.
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 bolded on slides)

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 (those **bolded** in slides).
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 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 – constriction of sphincter muscles of pupil - constriction (miosis), constriction of ciliary muscle regulates accommodation

Heart – sinoatrial node to reduce heart rate, and AV node to slow conduction

Bronchioles – smooth muscle of bronchi – constriction

GI tract – GI tract to promote secretions and motility

Bladder – contraction of detrusor muscle, causes bladder emptying

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

Eye – activation of dilator muscle causes mydriasis, innervation of ciliary epithelium regulates 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 post-synaptic 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>Alpha₁</td>
<td>Most vascular smooth muscle</td>
<td>Contracts (increases vascular resistance)</td>
</tr>
<tr>
<td></td>
<td>Pupillary dilator muscle</td>
<td>Contracts (mydriasis)</td>
</tr>
<tr>
<td></td>
<td>Pitoral smooth muscle</td>
<td>Contracts (arrest heart)</td>
</tr>
<tr>
<td>Alpha₂</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>Beta₁</td>
<td>Heart</td>
<td>Stimulates rate and force</td>
</tr>
<tr>
<td></td>
<td>Juxtaglomerular cells</td>
<td>Stimulates renin release</td>
</tr>
<tr>
<td>Beta₂</td>
<td>Respiratory, uterine, and vascular smooth muscle</td>
<td>Relaxes</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</td>
<td>Causes tremor</td>
</tr>
<tr>
<td></td>
<td>(voluntary muscle)</td>
<td></td>
</tr>
<tr>
<td>Beta₂ (β₂ may also contribute)</td>
<td>Fat cells</td>
<td>Stimulates lipolysis</td>
</tr>
<tr>
<td>Dopamine₁</td>
<td>Renal and other splanchnic blood vessels</td>
<td>Relaxes (reduces resistance)</td>
</tr>
<tr>
<td>Dopamine₂</td>
<td>Nerve terminals</td>
<td>Inhibits adenylyl cyclase</td>
</tr>
</tbody>
</table>


B. Adrenergic Receptor Signaling

1. **α₁-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 adenyl cyclase via Gs 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 adenyl 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 adenyl cyclase via Gs-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 (SR) increasing calcium storage such that the next trigger initiates larger efflux of calcium into the cytoplasm from the SR.

4. β2-adrenergic receptors positively couple to adenylyl cyclase via Gαs 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, β2 adrenergic receptor activation leads to reduced smooth muscle contraction. β2 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 of β2-adrenergic receptors. In this case, the Goi subunit, to which the α2 adrenergic receptor is coupled, inhibits adenylyl cyclase, which, in turn, inhibits cAMP production and PKA activity. Loss of PKA activity leads to activation of MLCK and vascular smooth muscle constriction.

VI. Adrenergic Agonists

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 $\beta$-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.

MAP = CO x 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 \(\mu g/kg/min\), dashed lines in figure at right), \(\beta_2\) receptor activation causes peripheral vasodilation, thereby decreasing diastolic BP; \(\beta_1\) receptor activation has positive inotropic and chronotropic effects thereby increasing CO and systolic BP; at higher doses (>0.2 \(\mu g/kg/min\), solid lines) effects of \(\alpha_1\) 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: \(\beta_2\) receptor - bronchodilation, \(\alpha_1\) 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 \(\alpha_1\), \(\alpha_2\) and \(\beta_1\) receptors with little affinity for \(\beta_2\) receptors, susceptible to degradation by metabolic enzymes, short half-life give by controlled infusion.

Cardiovascular effects: due primarily to \(\alpha_1\)-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 \(\beta_1\) 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 \(\beta_2\) 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 D_1 receptors at low concentrations, but also has affinity for β1 and α receptors which may be activated at higher infusion rates; readily metabolized.

Cardiovascular Effects: activates D_1-receptors at low infusion rates (0.5-1.0 μg/kg/min) leading to decreased TPR; at medium infusion rates activates β_1-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: β_2 receptor activation promotes peripheral vasodilation, decreased diastolic BP; β_1 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: β_2 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 $\beta_1$-adrenergic receptor agonist - Dobutamine (adrenergic receptor affinity: $\beta_1 > \beta_2 > \alpha$), though considered by most to be a $\beta_1$ 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 $\beta_2$-mediated vasodilation and reflex tachycardia. However, no agonist is purely selective so at higher doses, $\beta_2$ 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 $\beta$-blockade

C. Selective $\beta_2$ adrenergic agonists: terbutaline, albuterol

Cardiovascular Effects: negligible in most patients due to lack of $\beta_1$ activity. However, can cause some $\beta_1$ agonist-like response

Bronchioles: Bronchodilation

Pregnant Uterus: Relaxation

Toxicity (see Fig): Tachycardia, tolerance, skeletal muscle tremor (see figure right), activation of $\beta_2$-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 $\beta$-agonist therapy. Tolerance to drug can develop with chronic use.

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

D. Selective $\alpha_1$-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, …not effective in ventricular tachycardia

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></th>
<th>Non-Selective (β₁ and β₂)</th>
<th>Cardioselective (β₁)</th>
<th>Partial Agonist (β₁ and β₂)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROPRANOLOL, TIMOLOL, NADOLOL</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>Heart Rate and Force of Contraction (β₁)</td>
<td></td>
<td></td>
<td></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 bronchoconstricti on 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 production and thus reduced vasoconstriction, probably reduced sympathetic activation due to central effects of lipid soluble drugs. Some peripheral vasoconstriction due to blockade of β₂ adrenergic 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, 2\textsuperscript{nd} and 3\textsuperscript{rd} degree heart block, cardiogenic shock

C. Cardioselctive $\beta_1$-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, 2\textsuperscript{nd} or 3\textsuperscript{nd} degree heart block, cardiogenic shock

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
<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-ureine</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-ureine</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-ureine</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>Drug</td>
<td>Brand(s)</td>
<td>Duration</td>
<td>Class</td>
<td>Metabolism</td>
<td>Side Effects</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------------</td>
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<td>---------------------------------------------------</td>
</tr>
<tr>
<td>Pseudo-ephedrine</td>
<td>Sudafed</td>
<td>4.3-8 hr</td>
<td>Indirect sympathomimetic</td>
<td>Liver</td>
<td>Nasal decongestion</td>
</tr>
<tr>
<td>Tyramine</td>
<td>tyramine</td>
<td>Normally very short</td>
<td>Displaces NE MAO</td>
<td>Not therapeutic</td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td>Inderal</td>
<td>4 hr</td>
<td>β-blocker</td>
<td>Liver</td>
<td>Hypertension, angina due to atherosclerosis, MI</td>
</tr>
<tr>
<td>Timolol</td>
<td>Blocaden (po)</td>
<td>4 hr</td>
<td>β-blocker</td>
<td>Liver</td>
<td>Glaucoma.</td>
</tr>
<tr>
<td></td>
<td>Timoptic (opth)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nadolol</td>
<td>Corgard</td>
<td>20-24 hr</td>
<td>β-blocker</td>
<td>Urine</td>
<td>Long-term angina, hypertension</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hypertension, angina, MI</td>
</tr>
<tr>
<td>Atenolol</td>
<td>Tenormin</td>
<td>6-7 hr</td>
<td>β1-blocker</td>
<td>Urine</td>
<td></td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Lopressor, Toprol</td>
<td>3-7 hr</td>
<td>β1-antagonist</td>
<td>Liver</td>
<td>Hypertension, long-term angina rx</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(with partial agonist activity)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pindolol</td>
<td>Visken</td>
<td>3-4 hr</td>
<td>β-antagonist (with partial agonist activity)</td>
<td>Urine</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Esmolol</td>
<td>Breviblock</td>
<td>~9 min</td>
<td>β1-blocker</td>
<td>Esterases in RBC</td>
<td>Supraventricular tachycardia</td>
</tr>
<tr>
<td>Phenoxybenzamine</td>
<td>Dibenzyline</td>
<td>24 hr (iv)</td>
<td>α-blocker</td>
<td>Conjugates to receptor</td>
<td>Pheochromocytoma</td>
</tr>
<tr>
<td>Phentolamine</td>
<td>Regitine</td>
<td>19 min</td>
<td>α-blocker-</td>
<td>Urine</td>
<td>Test for pheochromocytoma, rx for pheo. before surg., Catecholamine extravasation</td>
</tr>
<tr>
<td>Prazosin</td>
<td>Minipress</td>
<td>2.3 hr</td>
<td>α-blocker</td>
<td>Liver</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Drug</td>
<td>Brand Name</td>
<td>Duration</td>
<td>Type</td>
<td>Location</td>
<td>Adverse Effect</td>
</tr>
<tr>
<td>--------------</td>
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<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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<td>Norepinephrine</td>
<td>Levophed</td>
<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>
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

![Diagram of 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 system.
The nicotinic receptors are pentomeric (five) transmembrane polypeptides, the subunits of which form a cation-selective channel permeable to sodium and potassium. Two main subtypes exist (Nm, Nn). Nicotinic receptors are located on plasma membranes of parasympathetic and sympathetic postganglionic cells in the autonomic ganglia (Nn) and on the membranes of skeletal muscles (Nm). Neuronal nicotinic receptors (Nn) are also expressed in cortical and subcortical nuclei in the brain.

III. NICOTINIC AGONISTS

Because nicotinic receptors are present on post-ganglionic 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 Nn 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...
neuromuscular junction. Causes depolarization block (see lecture on neuromuscular relaxants). Used clinically as a muscle relaxant during intubation or electroconvulsive 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. ACETYLCHOLINE (prototype compound): \((\text{CH}_3)_3\text{N}-\text{CH}_2-\text{CH}_2-\text{O}-\text{C}-\text{CH}_3\)

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): \((\text{CH}_3)_3\text{N}-\text{CH}_2-\text{CH}-\text{O}-\text{C}-\text{CH}_3\)

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): \((\text{CH}_3)_2\text{N}-\text{CH}_2-\text{CH}_2-\text{O}-\text{C}-\text{NH}_2\)

Carbamatic 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): \((\text{CH}_3)_2\text{N}-\text{CH}_2-\text{CH}_2-\text{O}-\text{C}-\text{NH}_2\)

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 M2 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.

![Diagram of eye structures](image)

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

Acetylcholinesterase catalyzes the hydrolysis of acetylcholine

\[
\text{AChE} \\
\xrightarrow{\text{Acetylcholine}} \text{Choline + Acetic Acid}
\]

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) ≡ muscarinic actions.
2. Autonomic ganglia ≡ nicotinic actions.
3. Motor endplates of striated muscle ≡ nicotinic actions.
4. Central nervous system ≡ 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 acetylcholinesterase 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:**

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 PRALIDOXMINE (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
- inapproiate 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>Butyrl 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 Carbstat</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>Medicine</td>
<td>Brand (if applicable)</td>
<td>Duration</td>
<td>Action</td>
<td>Location</td>
<td>Effect</td>
</tr>
<tr>
<td>---------------</td>
<td>-----------------------</td>
<td>----------</td>
<td>--------</td>
<td>----------</td>
<td>--------</td>
</tr>
<tr>
<td>Edrophonium</td>
<td>Tensilon, Enlon or Reversol</td>
<td>~10 min</td>
<td>AchE inhibitor</td>
<td>Bile</td>
<td>Diag of myasthenia gravis, reversal of neuromuscular block</td>
</tr>
<tr>
<td>Physostigmine</td>
<td>Antilirium</td>
<td>45-60 min</td>
<td>Reversible AchE inhibitor</td>
<td>AchE</td>
<td>Delirium from anticholinergic drugs, glaucoma</td>
</tr>
<tr>
<td>Donepezil</td>
<td>Aricept</td>
<td>~70 hrs</td>
<td>Reversible AchE Inhibitor</td>
<td>Liver</td>
<td>Alzheimer’s Dx.</td>
</tr>
<tr>
<td>Pralidoxime</td>
<td>2-PAM</td>
<td>~75 min</td>
<td>Peripheral AchE reactivator</td>
<td>Urine</td>
<td>Respiratory muscle weakness in organophosphate poisoning</td>
</tr>
<tr>
<td>Echotoxiphtae</td>
<td>Phospholine</td>
<td>Very long</td>
<td>Irreversible AchE Inhibitor</td>
<td>unknown</td>
<td>Open angle glaucoma</td>
</tr>
<tr>
<td>Atropine</td>
<td>Atropine</td>
<td>2 hr</td>
<td>Muscarinic antag</td>
<td>Liver</td>
<td>Excess secretions during surgery, the ↑ freq and urg. assoc with cystitis, hypertonic gut, organophosphate poisoning, bradycardia</td>
</tr>
<tr>
<td>Scopolamine</td>
<td>Isopto</td>
<td>~9.5 hrs for transdermal, 24 for intra</td>
<td>Muscarinic antagonist</td>
<td>unknown</td>
<td>Motion sickness, anti-salilagoue in surgery</td>
</tr>
<tr>
<td>Glycopyrrolate</td>
<td>Robinul</td>
<td>0.5-2 hrs</td>
<td>Muscarinic receptor antagonist</td>
<td>urine</td>
<td>Protects against excessive muscarinic activation during reversal of neuromuscular blockade, anti-salilagoue</td>
</tr>
</tbody>
</table>
NEUROMUSCULAR RELAXANTS

Date: August 22th – 8:30-9:20 AM

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. Describe the mechanisms by which baclofen and benzodiazepines alter somatic motor neuron excitation.

12. List the major side effects of baclofen and benzodiazepines and discuss how the route of delivery can reduce side effects.

13. Describe the basic mechanisms by which Tizanidine and Dantrolene reduce muscle spasticity and list the major side effects of both drugs.
NEUROMUSCULAR RELAXANTS

I. NEUROMUSCULAR RELAXANTS

Neuromuscular relaxants selectively block the nicotinic receptors at the neuromuscular junction. Some degree of muscle relaxation can also be achieved by blockade of interneurons at the level of the spinal cord. The latter therapy is less selective and is primarily limited to the treatment of muscle spasms due to injury, upper motor neuron dysfunction or certain orthopedic manipulations.

II. NEUROMUSCULAR BLOCKADE

A. NEUROMUSCULAR JUNCTION NEUROTRANSMISSION

1. Nicotinic Receptors - Pentameric ligand-gated ion channel. Different nicotinic receptors are made up of different combinations of receptor subunits (expressed in greek letters). There are numerous isoforms of each subunit type, leading to a large number of different nicotinic receptors. However, certain combinations of subtypes characterize nicotinic receptors with specific functions. This difference allows some selectivity for therapeutic drugs that target a subset of nicotinic receptors, such as those of the neuromuscular junction.

   Muscle receptor - 2 $\alpha$, 1 $\beta$, 1 $\gamma$, 1 $\epsilon$

   Ganglionic receptor – 2 $\alpha$, 3 $\beta$

2. Acetylcholine is released from presynaptic vesicles into the synapse.

3. Binding of nicotinic receptor opens cation channels and increases Na$^+$ and K$^+$ conductance. If sufficient membrane depolarization develops, action potentials are generated. The action potentials are propagated down transverse tubules near the sarcoplasmic reticulum causing calcium release into the intracellular space.


4. Muscle Twitch = Action potential-dependent increase in [Ca2+]i followed by fall in [Ca2+]i due to sequestration by sarcoplasmic reticulum

Clonus = reduced ability to lower calcium between stimulations due to increased frequency of stimulation leads to incomplete relaxation

Tetanic contraction = no appreciable reduction in [Ca2+]i between stimuli leads to physiological muscle contraction

5. Propagation of the action potential generated by sufficient acetylcholine receptor (AchR) agonist binding is dependent upon availability of voltage-gated Na⁺ channels in the resting state. There must be sufficient channels in the resting state to maintain the action potential until it reaches the t-tubules allowing for release of calcium sufficient to enable cross-bridge formation.
Normal neurotransmission is depicted in the image above

B. CLASSIFICATION OF NEUROMUSCULAR RELAXANTS ACTING ON NICOTINIC RECEPTORS

1. Non-depolarizing agents (Curare drugs)
2. Depolarizing agents (Succinylcholine)

C. NON-DEPOLARIZING BLOCKING DRUGS - COMPETITIVE ANTAGONISTS (e.g. D-TUBOCURARINE, PANCURONIUM, VECURONIUM)

1. MECHANISM OF ACTION

Competitive antagonists at nicotinic acetylcholine receptors

Overcome by excess Ach through
1) tetanic stimulation
2) Cholinesterase inhibitors

At higher concentrations blockade of channel pore develops
Less sensitive to excess Ach.
2. CLINICAL CHARACTERISTICS

Competitive binding of curare-like drugs to the nicotinic receptor prevents opening of nicotinic receptor ion channel thus preventing membrane depolarization and end-plate potentials. Numerous curare type drugs have been developed. Choice of drug depends on preferred pharmacokinetic characteristics and route of elimination. One should consider the shortest possible duration of action required for the procedure, as well as the best route of elimination when choosing a compound to use for muscle relaxation. Shown below are the volume of distribution (Vd), clearance rate (Cl) and biological half-life (t½) of a subset of commonly used non-depolarizing neuromuscular blockers.

A. Pharmacokinetics

Rapid distribution

T½ dependent on route of elimination

kidney > liver > plasma cholinesterase

Use the following chart to gain an appreciation for the relative half-life of the various compounds available and how half-life relates to the drug's mode of elimination (don't memorize the chart!).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Vd  (ml / kg)</th>
<th>Cl  (ml / kg / min)</th>
<th>t½ (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancuronium</td>
<td>140 - 205</td>
<td>1.2 - 1.6</td>
<td>75 - 107</td>
</tr>
<tr>
<td>Tubocurarine</td>
<td>297 - 522</td>
<td>1.8 - 3.0</td>
<td>107 - 237</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>270</td>
<td>5.2</td>
<td>65 - 75</td>
</tr>
<tr>
<td>Mivacurium</td>
<td>333</td>
<td>4.6</td>
<td>~ 3 - 5</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>217</td>
<td>4.9</td>
<td>~ 60</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Percentage Elimination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>30 - 80</td>
</tr>
<tr>
<td>Tubocurarine</td>
<td>40 - 60</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>&gt; 25</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>10 - 20</td>
</tr>
<tr>
<td>Mivacurium</td>
<td></td>
</tr>
</tbody>
</table>
Typically one should avoid drugs that are primarily metabolized by liver enzymes for patients with liver failure, or alternatively avoid drugs excreted by the kidney in patients with renal failure.

B. Receptor Reserve - The biological half-life of the curare compounds tend to be longer than their therapeutic effect (duration of action). While this is true for most drugs as plasma levels fall below the therapeutic window, this is exaggerated in the curare drugs because quite high receptor occupancy is required before an effect (i.e., reduced muscle twitch) is observed. The percentage of receptors that must be occupied by an antagonist to inhibit contraction is directly related to the receptor reserve. This concept is illustrated in the figure above. Stimulation induced muscle twitches are used to gauge the degree of muscle relaxation during administration of neuromuscular blocker prior to surgery. A small electrical stimulus is applied and the resulting muscle twitch is assessed. The top of the illustration demonstrates leg muscle twitches. The fraction of muscle nicotinic receptors occupied by tubocurarine is shown in the bottom graph. Note that in the illustration, 75% of the receptors must be occupied before any decrement in function (i.e., loss of muscle twitch) develops. Almost 100% occupancy is required before full relaxation is observed. Different muscle beds have different receptor reserve and so will demonstrate the effects of curare type drugs at different plasma concentrations. Respiratory muscles have the highest reserve, followed by larger limb and trunk muscles followed by fine muscles. This results in a characteristic onset of drug effect:

Muscle weakness followed by paralysis
Affects small muscles first then large muscles of limb and trunk
Order: Extraocular, hands and feet, head and neck, abdomen and extremities, diaphragm-respiratory muscle
Recovery is in reverse order

3. CLINICAL USES:

Muscle relaxation for surgical procedures (many different drugs)
Endotracheal intubation (rocuronium, mivacurium)
Reduced resistance during ventilation (many)

4. SIDE EFFECTS:

Non-analgesic (all)
Apnea (all)
Histamine release (hypotension, bronchospasm: mivacurium)
Muscarinic blockade (increased HR and CO, pancuronium, rocuronium)
5. **DRUG INTERACTIONS:**

Inhalation anesthetics (enhances effect)
Antibiotics (enhance effect, particularly aminoglycosides)
Local anesthetics

6. **CHEMICAL ANTIDOTES:**

Cholinesterase inhibitors - neostigmine
Muscarinic blockers - glycopyrrolate (minimizes muscarinic effects of cholinesterase inhibitor)

D. **DEPOLARIZING BLOCKING DRUGS -AGONISTS (e.g. SUCCINYLCHOLINE)**

1. **MECHANISM OF ACTION** - There are two phases. During phase 1 block, occupancy of the receptor by succinylcholine causes opening of the ion channel and thus depolarization of the motor end plate. The drug also appears to enter the channel, which causes a prolonged flickering of ion conductance. **Succinylcholine is metabolized by plasma cholinesterase** (not acetylcholinesterase).

![Diagram of succinylcholine phase I](image)

Plasma cholinesterase is not available at the synapse, therefore depolarization of the membrane is prolonged resulting in inactivation of voltage-gated Na⁺ channels. The Na⁺ channels cannot regain their resting state until the membrane is repolarized. Consequently, no further action potential can be propagated resulting in flaccid paralysis.

**Phase I - Depolarizing block**

- Depolarization of muscle with sustained muscle contraction - 4-8 min (opens cation channel to cause end plate depolarization)
- Flickering of ion conductance due to blockade of channel
- Flaccid paralysis
- Cholinesterase inhibitors augment blockade

When succinylcholine exposure exceeds ~30 min, the membrane becomes repolarized. This is known as Phase II block. Despite repolarization, the receptor remains desensitized. The mechanism is unclear but may relate to blockade of the channel pore by succinylcholine. **Phase II**
blockade has characteristics similar to non-depolarizing block in that blockade is overcome with cholinesterase inhibitors or tetanic stimulation. The duration of action becomes unpredictable at this point. This phase is best avoided by using other agents during longer cases since recovery is not as predictable. Patient should be monitored using muscle stimulation to assess Phase II block. To reverse phase II block, cholinesterase inhibitors can be used, but one must ensure that remnants of Phase I block are gone, i.e., succinylcholine must be gone…wait 20 min after last succinylcholine dose, since cholinesterase inhibitors will actually prolong Phase I block.

Phase II - desensitization block
Repolarization of membrane
Desensitization (exact mechanism unknown)

2. PHARMACOKINETICS OF DEPOLARIZING DRUGS

More rapid onset of action than non-depolarizing agents
Rapidly metabolized in plasma by cholinesterase (not at synapse)
Action terminated by diffusion of drug away from motor end plate.
Genetic variant in cholinesterase can prolong drug action

3. CLINICAL MANIFESTATIONS:

Muscle fasciculation due to initial contractions
Order: arm, neck, leg, diaphragm; followed by neuromuscular blockade

4. CLINICAL USES:

Endotracheal intubation
Control convulsions during ECT

5. SIDE EFFECTS:

- Non-analgesic
- Apnea
- Muscle pain from fasciculations
- Increased intraocular and intragastric pressure
- Stimulation of nicotinic receptors of autonomic ganglia and cardiac muscarinic receptors in sinus node (arrhythmia, hypertension, bradycardia)
- Hyperkalemia due to K+ release from motor end plate (associated with burns or nerve damage).
- Can initiate malignant hyperthermia in children with undiagnosed muscle myopathies.

6. DRUG INTERACTIONS:

local anesthetics (enhance effect)
cholinesterase inhibitors (enhance effects of Phase I block)
7. **CHEMICAL ANTIDOTES:**

Phase I

None—rapidly (5-10 min) hydrolyzed by plasma cholinesterase
Atropine for bradycardia due to muscarinic effects

Phase II
Cholinesterase inhibitors

8. **CONTRAINDICATIONS:**

Family history of malignant hyperthermia,
acute phase of significant trauma (7-10 days) due to hyperkalemia
patients with skeletal myopathies

III. **SPASMOLYTIC DRUGS**

A. **SKELETAL MUSCLE RELAXANTS:**

1. Mechanisms of spasticity
   Heightened skeletal muscle tone
   Release from inhibitory supraspinal control
   Increased activity of facilitory pathways
   Heightened excitability of alpha and gamma motor systems
2. Treatment of spasticity

Reduce activity of Ia fibers that excite the primary motor neuron
Enhance activity of inhibitory internuncial neurons.

B. TYPES OF SPASMOLYTIC DRUGS:

1. **BACLOFEN**
Mechanism of action:

- **GABA\textsubscript{A} agonist**
  - Reduces calcium influx, and therefore reduces the release of excitatory transmitters and substance P in spinal cord

Clinical usages:

- Spinal spasticity
- Spasticity due to multiple sclerosis

Side effects:

- Drowsiness
- Mental disturbance

2. **BENZODIAZEPINES (e.g. DIAZEPAM, CLONAZEPAM)**

Mechanism of action:

- Facilitate GABA mediated presynaptic inhibition

Clinical usages:

- Flexor and extensor spasms
- Spinal spasticity
- Multiple sclerosis

Side effects:

- Sedation and drowsiness
3. **TIZANIDINE.**

Mechanism of action:
- **Alpha2-adrenergic agonist**
- Promotes pre- and post-synaptic inhibition in the spinal cord

Clinical Uses:
- Multiple sclerosis
- Spinal Spasticity

Side Effects:
- Drowsiness
- Hypotension

4. **DANTROLENE**

Mechanism of action:
- Blocks calcium release from sarcoplasmic reticulum in muscle, thus interfering with excitation-contraction in the muscle fiber
- Fast muscle fibers are more sensitive
- Cardiac and smooth muscle insensitive

Clinical usages:
- Spasticity due to stroke, spinal injury, multiple sclerosis, cerebral palsy
- *Malignant hyperthermia* - characterized by sudden and prolonged calcium release

Side effects:
- Muscle weakness
- Sedation
- Hepatitis (occasionally)
IV. **LIST OF DRUGS COVERED IN LECTURE:** for more detail consult on-line reference [www.rxlist.com/cgi/generic/albut2_cp.htm](http://www.rxlist.com/cgi/generic/albut2_cp.htm). Text in bold font are important.

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Duration of action</th>
<th>Mechanism of Action</th>
<th>Elimination</th>
<th>Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Succinylcholine</td>
<td>Anectine</td>
<td>Duration &lt; 8 min</td>
<td>Depolarization Blockade of muscle nicotinic receptors</td>
<td>Metab by plasma cholinesterase</td>
<td>Tracheal intubation or ECT</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>Pavulon</td>
<td>Duration 30-60 min</td>
<td>Non-depolarizing blockade of muscle nicotinic receptors</td>
<td>Primarily renal excretion</td>
<td>Adjuvant in surgical anesthesia, sp. Abdominal wall relaxation &amp; orthopedic procedures</td>
</tr>
<tr>
<td>D-tubocurarine</td>
<td>Generic</td>
<td>Duration &gt;60 min</td>
<td>Non-depolarizing blockade of muscle nicotinic receptors</td>
<td>Liver clearance &amp; renal elimination</td>
<td>Prototype only used in lethal injection</td>
</tr>
<tr>
<td><strong>Rocuronium</strong></td>
<td>Zemuron</td>
<td><strong>Duration</strong></td>
<td>~25 min.</td>
<td><strong>Non-depolarizing blockade of muscle nicotinic receptors</strong></td>
<td><strong>Liver</strong></td>
</tr>
<tr>
<td><strong>Mivacurium</strong></td>
<td>Mivacron</td>
<td><strong>Duration</strong></td>
<td>15-20 min</td>
<td><strong>Non-depolarizing blockade of muscle nicotinic receptors</strong></td>
<td><strong>Plasma cholinesterase</strong></td>
</tr>
<tr>
<td><strong>Vecuronium</strong></td>
<td>Norcuron</td>
<td><strong>Duration</strong></td>
<td>30-45 min</td>
<td><strong>Non-depolarizing blockade of muscle nicotinic receptors</strong></td>
<td><strong>Liver metab. &amp; clearance, renal elimination</strong></td>
</tr>
<tr>
<td><strong>Baclofen</strong></td>
<td>Baclofen</td>
<td><strong>Duration</strong></td>
<td>1.5 hrs.</td>
<td><strong>Inhibits neurotransmitter release from skeletal muscle sensory afferent</strong></td>
<td><strong>Urine</strong></td>
</tr>
<tr>
<td><strong>Diazepam</strong></td>
<td>Valium</td>
<td><strong>Duration</strong></td>
<td>43 hr</td>
<td><strong>Benzodiazepine receptor agonist</strong></td>
<td><strong>Liver</strong></td>
</tr>
<tr>
<td><strong>Tizanidine</strong></td>
<td>Zanaflex</td>
<td><strong>Duration</strong></td>
<td>2.5 hr</td>
<td><strong>Centrally acting α2 agonist</strong></td>
<td><strong>Liver</strong></td>
</tr>
<tr>
<td><strong>Dantrolene</strong></td>
<td>Dantrium</td>
<td><strong>Duration</strong></td>
<td>8 hr</td>
<td><strong>Uncouples excitation-contraction of skeletal muscle (blocks ryanodine receptor)</strong></td>
<td></td>
</tr>
</tbody>
</table>
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 Therapeutics

I. Serotonin Neurotransmission

A. Serotonin Synthesis: L-tryptophan is an essential amino acid (i.e., it must be ingested and is not made by the body) precursor of serotonin. Tryptophan hydroxylase is the rate limiting enzyme in serotonin production. It hydroxylates L-tryptophan to 5-hydroxy-L-tryptophan (5-HTP), the latter of which is an over the counter nutraceutical commonly used to combat melancholy.

Tryptophan hydroxylase is not normally saturated by its substrate. Manipulations of dietary tryptophan is thought to modulate serotonin production. Clinically significant changes in serum tryptophan requires manipulation of several different amino acids which compete with tryptophan for neutral amino acid transporters that carry tryptophan across the blood brain barrier. The ratio of tryptophan to these amino acids in ingested foods is thought to determine brain tryptophan levels. Whole milk and dried prunes, and semi-sweet chocolate rather than turkey have the appropriate ratio to boost brain tryptophan levels. Human studies are being conducted to test the effect of beverages containing tryptophan depleting or loading formulations to affect impulsiveness and depression.

B. Serotonin Receptors

Numerous receptors have been identified which have sensitivity to serotonin. All are G-protein coupled receptors except the 5-HT\textsubscript{3} receptor, which is a ligand gated ion channel. Many of these are
the target of clinically used therapeutics. The receptors are grouped into families based on their signaling mechanisms and homology.

The 5-HT₁ family consists of 5-HT₁A, 5-HT₁B and 5-HT₁D. These receptors are negatively coupled to adenylal cyclase and reduce cAMP formation, or activate K⁺ channels. 5-HT₁A receptors are found both on pre- and post-synaptic membranes (relative to the serotonin releasing cell). Pre-synaptic 5-HT₁A are found at the cell soma and dendrites and act as auto receptors to limit action potential generation by the serotonin-containing neuron. The 5-HT₁B receptor is found both pre- and post-synaptically, but pre-synaptic receptors are found at the serotonin cell axon terminal where they negatively regulate serotonin release by inhibiting phosphorylation of voltage-gated calcium channels by PKA. 5-HT₁D receptor are found exclusively post-synaptically.

5-HT₂A, 2B and 2C receptors couple to Gq proteins to stimulate Phospholipase C, and IP₃ + DAG formation. They are found exclusively on post-synaptic membranes of target neurons

5-HT₃ receptors are found post-synaptically receptors conduct cation influx when activated by serotonin.

5-HT₄ receptors are found post synaptically and are positively coupled to adenylal cyclase through Gαs proteins.

5-HT₅, 6, 7 and less well understood in terms of physiological function and are not currently manipulated for therapeutic benefit.
Table 1.

<table>
<thead>
<tr>
<th>Serotonin System</th>
<th>Receptor</th>
<th>Location</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT₁A</td>
<td>Cortex, hypothalamus</td>
<td>Mood, cognitive function, neuroendocrine function</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Raphe nuclei</td>
<td>Inhibition of 5-HT release</td>
<td></td>
</tr>
<tr>
<td>5-HT₁D</td>
<td>Cerebral VSM nerve terminal</td>
<td>Vasoconstriction</td>
<td></td>
</tr>
<tr>
<td>5-HT₂A/₂C</td>
<td>Striatum Frontal CTX</td>
<td>Hallucination inhibits DA release</td>
<td></td>
</tr>
<tr>
<td>5-HT₅</td>
<td>Enteric chromaffin cells Area Postrema Emetic Center</td>
<td>Gut motility Nausea, Vomiting</td>
<td></td>
</tr>
<tr>
<td>5-HT₄</td>
<td>Myenteric Plexus (enteric nervous system)</td>
<td>Gut motility</td>
<td></td>
</tr>
<tr>
<td>5-HT transporter</td>
<td>5-HT nerve terminals</td>
<td>Removal of 5-HT from synapse</td>
<td></td>
</tr>
</tbody>
</table>

Specific serotonin populations that are targeted by clinically used therapeutics are indicated in Table 1.

Table 2.

<table>
<thead>
<tr>
<th>Serotonergic Drugs: Primary Actions and Clinical Uses</th>
<th>Receptor</th>
<th>Action</th>
<th>Drug Examples</th>
<th>Clinical Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT₁A</td>
<td>Partial agonist</td>
<td>Buspirone</td>
<td>Anxiety, Depression</td>
<td></td>
</tr>
<tr>
<td>5-HT₁D</td>
<td>Agonist</td>
<td>Sumatriptan</td>
<td>Migraine</td>
<td></td>
</tr>
<tr>
<td>5-HT₂A/₂C</td>
<td>Antagonist</td>
<td>trazodone, risperidone,</td>
<td>Depression, schizophrenia</td>
<td></td>
</tr>
<tr>
<td>5-HT₅</td>
<td>Antagonist</td>
<td>Ondansetron</td>
<td>Chemotherapy-induced emesis</td>
<td></td>
</tr>
<tr>
<td>5-HT₄</td>
<td>Agonist</td>
<td>Mosapride</td>
<td>GI Disorders</td>
<td></td>
</tr>
<tr>
<td>5-HT transporter</td>
<td>Inhibitor</td>
<td>Fluoxetine, Sertraline</td>
<td>Depression, panic disorder, obsessive, compulsive disorder, post-traumatic stress disorder, social phobia</td>
<td></td>
</tr>
</tbody>
</table>

Drugs used clinically to target these receptor populations are shown above in Table 2.
C. Drugs Affecting Serotonin Neurotransmission

1. 5-HT\textsubscript{1} receptor agonists

![Diagram of serotonin neurotransmission](image)

**Buspirone.** Buspirone is a partial agonist of the 5-HT\textsubscript{1A} receptor. It is FDA approved for the treatment of Generalized Anxiety Disorder defined as the persistent, excessive, and unrealistic worry about everyday things. It is also used in combination with serotonin reuptake inhibitors (SSRIs) for the treatment of major depression. 5-HT\textsubscript{1A} receptor distribution is widespread so the 5-HT\textsubscript{1A} receptor agonists mechanism of action in anxiety is not entirely clear, but it is thought to be associated with blockade of post-synaptic receptors in the cortex, probably expressed by inhibitory interneurons. Thus they may indirectly activate or disinhibit cortical neurons. The onset of antidepressant effects may be delayed 2-3 weeks. The mechanism for delay is also not clear, but it may be related to suppression of endogenous serotonin release by agonist action on 5-HT\textsubscript{1A} autoreceptors expressed by serotonin neurons. Autoreceptors are thought to be more susceptible to desensitization compared to post-synaptic 5-HT\textsubscript{1A} receptors. As such, after prolonged use of 5-HT\textsubscript{1A} receptor agonists, endogenous serotonin release should recover while post-synaptic effects remain intact with continued use. Side effects of anxiety during initial therapy may be due to suppression of endogenous serotonin neurotransmission prior to autoreceptor desensitization. Additional side effects include drowsiness and nausea.

5-HT\textsubscript{1D} receptor agonists are used for the treatment of migraine. **Sumatriptan** is the prototype drug. There are two proposed mechanisms of action. 5-HT\textsubscript{1D} receptor agonists are thought to inhibit release of nociceptive and inflammatory neutoransmitters from the trigeminal nerve axons. In addition 5-HT\textsubscript{1D} receptors promote cerebrovascular vasoconstriction by decreasing cAMP and PKA mediated inhibition of MLCK. Side effects are related to this mechanism of action and include coronary vasoconstriction. As such, these drugs are contraindicated in patients with coronary artery disease.
Selective Serotonin reuptake inhibitors (SSRI) increase availability of serotonin by preventing reuptake at the axon terminal. This increases serotonin both at post-synaptic and pre-synaptic 5-HT\textsubscript{1A} receptors. Fluoxetine (Prozac\textsuperscript{®}) is the prototype and Sertraline (Zolof\textsuperscript{®}) is commonly used clinically. Anti-depressant effects are thought to be mediated by activation of cortical 5-HT\textsubscript{1A} receptors which disinhibit cortical activity. SSRIs are also now used for severe anxiety from post-traumatic stress, and in obsessive compulsive disorders. Side effects include sexual dysfunction and insomnia due to increased activation of alternative receptor populations (see below). SSRIs are contraindicated in patients taking monoamine oxidase (MAO) inhibitors for depression since serotonin is readily metabolized by MAOs and the combination of SSRIs and MAOs can lead to serotonin-syndrome (hyperthermia, muscle tremor, twitching, agitation, arrhythmia, seizure).

Serotonin antagonist-reuptake inhibitors (SARI) both decrease reuptake and block 5-HT\textsubscript{2A} and 5-HT\textsubscript{2C} receptors which may mediate some side effects of reuptake inhibitors. Prototype is trazadone. Trazadone was approved in the 80’s for depression. It is now rarely used alone for this indication. It is now sometimes used for anxiety and in combination with SSRIs for depression. Trazadone causes drowsiness and is now used more commonly as an off-label therapy for insomnia without depression. Use of the drug has waned since a black box warning for increased suicidality among young adults was included on packaging.

2. 5-HT\textsubscript{2} receptor antagonists: Disorders related to dopamine release are treated with drugs that also affect serotonin receptors. Four important dopamine pathways regulate both cognitive and motor functions. Dopamine neurons arise from the substantia nigra to innervate the globus pallidus and help to initiate and smooth motor movement. Additional pathways from the ventral tegmental area project to the limbic system, forming the mesolimbic projections, and to the prefrontal cortex to form the mesocortical projection. Psychosis (loss of contact with reality) is thought by some to be mediated by an imbalance of dopamine neurotransmission in the mesocortical (too low) and mesolimbic (too high) pathways. Risperidone is a second order anti-psychotic that blocks both 5-HT\textsubscript{2A} receptors as well as dopamine D\textsubscript{2} and D\textsubscript{3} receptors. This combination of effects is thought to reduce dopamine
neurotransmission in the mesolimbic pathway and increase DA neurotransmission in the mesocortical pathway. Risperidone is used for schizophrenia with psychosis and for psychosis associated with manic episodes of bipolar disease. Risperidone has significant side effects including weight gain, anxiety, and akathisia (constant need to move).

3. **5-HT₃ receptor antagonists:**
90% of serotonin in the body is found in the gut in the enterochromaffin cells that are found wedged between the gut epithelial cells. These cells manufacture serotonin through the same pathway as serotonin positive neurons.

The enteric nervous system is an autonomous network of nerves that regulate secretion and contraction of the gut. Enterochromaffin cells respond to chemical, mechanical and other toxic stimuli to provoke secretions and peristalsis. Serotonin released in response to enterochromaffin cell stimulation binds to receptors found on neurons that innervate muscle and secretory plexi that layer the gut lumen. Serotonin also activates vagal afferents that arise from the luminal layer. Vagal afferents project to emetic center and area postrema in the brainstem to stimulate nausea and vomiting. Serotonin 5-HT₃ receptors are expressed on the vagal nerve terminals and are activated by local serotonin release. The same nerve release serotonin which activates 5-HT₃ receptors on emetic and area postrema where they mediate nausea and vomiting in response to gut stimulation by toxins. **Ondansetron** is a 5-HT₃ receptor antagonist used clinically for nausea and vomiting due to chemotherapy. This drug has few if any recognized side effects and is well tolerated by most patients.

4. **5-HT₄ receptor agonists:** Peristalsis of the GI tract is stimulated by serotonin action on submucosal intrinsic primary afferent neurons (IPAN) which release acetylcholine in the myenteric plexus which, in turn, excites projections to neighboring longitudinal and circular muscle layers of the gut. 5-HT₄ receptors activate IPANs and stimulate peristalsis. 5-HT₄ receptor agonists have been used clinically in the past for the treatment of gastroparesis (slow gut motility). The 5-HT₄ receptor agonist cisapride has been discontinued due to evidence of long QT syndrome and potential for
ventricular arrhythmias. Mosapride is marketed elsewhere in the US. **Metoclopramide** (see below) is a dopaminergic antagonist with 5-HT4 agonist properties that is used in the US for short term stimulation of gastric emptying in diabetic and post-surgical patients with slow gastric emptying. Side effects associated with dopamine agonist effects limit duration of use.

II. **Dopamine Pharmacology:** The central dopaminergic system consists of 4 important pathways that include the mesolimbic (ventral tegmentum to limbic) mesocortical (ventral tegmentum to prefrontal cortex), tuberoinfundibular pathways (from the arcuate nucleus of the hypothalamus to the median eminence of the pituitary) and the chemotrigger zone located in the brainstem and accessed by circulating dopamine. Excess dopamine in limbic regions contributes to psychosis. Deficits in dopamine in prefrontal cortex lead to negative affect, lack of motivation and other negative effects of schizophrenia. Deficits in dopamine in striatum lead to Parkinson’s Disease.

**A. Dopamine Synthesis:** Dopamine is the precursor to norepinephrine, and dopamine neurons lack the enzyme necessary to make norepinephrine. As a consequence dopamine is the terminal catecholamine in these neurons. Therapeutic manipulation of the dopamine system include loading of the neurotransmitter precursor L-DOPA in the treatment of Parkinson’s Disease. Dopamine itself cannot cross the blood brain barrier therefore receptor agonists and antagonists are used for manipulation of specific sites of central dopamine neurotransmission in the treatment of schizophrenia and nausea. Inhibitors of dopamine breakdown are also used in Parkinson’s Disease.

**B. Dopamine receptors:** There are 5 dopamine receptor subtypes that belong to two
main families. The D₁ receptor family includes D₁ and D₅ receptors. These receptors are positively coupled to adenylate cyclase and increase cAMP. D₂ receptors are negatively coupled to adenylate cyclase and also increase K⁺ currents and decreased voltage-gated calcium currents to negatively modulate excitability of the neurons.

C. Clinically utilized therapeutics that manipulate dopamine neurotransmission.

<table>
<thead>
<tr>
<th>Dopaminergic Drugs: Primary Actions and Clinical Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
</tr>
<tr>
<td>D₁</td>
</tr>
<tr>
<td>D₂</td>
</tr>
<tr>
<td>AADC</td>
</tr>
<tr>
<td>MAO-B</td>
</tr>
<tr>
<td>COMT</td>
</tr>
<tr>
<td>Dopamine transporter</td>
</tr>
<tr>
<td>D₂</td>
</tr>
<tr>
<td>D₂</td>
</tr>
<tr>
<td>D₁</td>
</tr>
</tbody>
</table>

**L-DOPA** is the precursor of dopamine and is a primary treatment of Parkinson’s Disease. It is used to target D₁ and D₂ targets to regulate motor movement. It is administered orally and can reach significant concentrations in the systemic circulation. As such, it has the potential to be taken up by sympathetic neurons where it can be used to synthesize excess dopamine, norepinephrine or epinephrine and lead to arrhythmia, anxiety and nausea. L-DOPA is also transported across the blood brain barrier where it is taken up into dopaminergic cells. Excess dopamine in the CNS can also stimulate hallucinations (limbic targets). Long term use of L-DOPA can lead to dyskinesia in a subset of patients (most commonly young patients). Dyskinesia is characterized by smooth exaggerations of voluntary movements. Reduced doses can help alleviate side effects. As such cocktails of drugs that effect multiple sights of dopamine neurotransmission are now being used to produce the greatest benefit with the least side effects. To combat side effects associated with L-DOPA-mediated systemic production of dopamine, norepinephrine and epinephrine, the aromatic L-amino acid decarboxylase inhibitor, **carbidopa**, is co-administered with L-DOPA. Unlike L-DOPA, carbidopa cannot cross the blood brain barrier. As such, it reduces the production of peripheral dopamine and reduces nausea. With Carbidopa almost 10% of the dose of L-DOPA crosses into the brain. Whereas without carbidopa most of the drug would be metabolized in the gut, or make its way into the systemic circulation where it might cause toxicity.

**Bromocriptine** is a D₂ receptor agonist thought to activate post-synaptic D₂ receptors in the basal ganglia. Its beneficial effects are also likely related to free radical scavenging which can reduce the oxidative damage that kills dopamine cells. As
such, it produces the best result when used early in the course of the disease. Side effects include valvular fibrosis with long-term use. In a small percentage of patients (5%) D₂ receptor agonists may contribute to decreased impulse control which can be expressed by risky behaviors that are atypical for the patient, e.g., gambling, hypersexuality, excess food intake.

**Selegiline** is a monoamine oxidase-B inhibitor used in the treatment of Parkinson ‘s disease (low dose) and depression (high dose). Because it is selective for the monoamine oxidase B it does not require the same strict dietary restrictions as non selective monoamine oxidase inhibitors when used at lower doses. However, caution should be used since at higher doses or in susceptible individuals diet may have potential to interact with drug due to inhibition of monoamine oxidase A which normally protects against tyramine absorption in the gut. Side effects include dizziness due to hypotension (low dose) due to increased dopamine, or hypertension and serotonin syndrome when used at high concentrations. Dry mouth also results from increased activity of sympathetic system.

**Tolcapone** is used in combination with L-DOPA to help increase efficacy of L-DOPA. Tolcapone is an inhibitor of catecholamine-O-methyl transferase and prolongs the half life of dopamine released into the synapse. When used in combination with L-DOPA it can reduce the dose of L-DOPA required for clinical effect. It helps to prolong L-DOPA’s effect and reduces “off” time which can occur in approximately 40% of patients with long term use of L-DOPA. After long-term use, patients may experience oscillations in motor function due to fluctuations in the efficacy of L-DOPA. “Off time” refers to those periods when the drug is less effective. Side effects include those associated with excess dopamine: dyskinesia, hallucinations, and nausea.

**Haloperidol** is a D₂ receptor antagonist. D₂ receptor antagonists are first generation antipsychotics. Clinical studies showed that the IC₅₀ of various drugs against haloperidol was strongly and directly related to their efficacy in controlling symptoms of schizophrenia. In contrast, the IC 50 of D₁ receptor antagonists was not related to their clinical efficacy. Haloperidol is available as an injection which allows for rapid onset therapy for acute psychosis with onset of action within 30-60 minutes. The drug can also be given in a slow release depot formula that lasts one month for poorly compliant patients. The main side effect is extrapyramidal motor disturbances (e.g., tardive dyskinesia) that can become permanent. These include tics, involuntary movement of the mouth and tongue, akathisia, or chorea movements.

**Metaclopramide** is a D₂ receptor antagonists with some serotonin 5-HT₄ agonist activity. It is given for short term treatment of chemotherapy and post-op nausea and vomiting, as well as gastric paresis. Side effects include akathisia and focal dystonia when given at high dose, or long term, or in susceptible individuals.

**Methylphenidate** (Ritalin®) is a dopamine and norepinephrine reuptake inhibitor used for the treatment of attention deficit disorder. It acts by increasing activity in frontal cortex. Its main side effect is tachycardia. It is contraindicated in patients with arrhythmia, hypertension and in those taking tricyclic antidepressants as it can further exacerbate synaptic concentrations of catecholamine.

fMRI showing serial sections with increased (red) and decreased (blue) brain activity from ventral to dorsal view after 20 mg dose of methylphenidate.
GENERAL ANESTHETICS

Date: Wednesday, August 22, 2016

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-short acting agents because their rapid entry into the CNS is followed by a relatively quick 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 though 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.
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 Narpin®, 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 L$_2$–3 caudad (to avoid hitting the spinal cord which ends at L$_1$–2.) 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 (Procaine =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>
</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.
#23- #24- Non Steroidal Anti-inflammatory Drugs (NSAIDs) I & II

Date: Wednesday August 24th, 2016 1-3 pm

Relevant reading:

LEARNING OBJECTIVES and KEY CONCEPTS:
At the end of the lecture the learner will be able to:

1. List the major indications, clinical uses and contraindications for the three major classes of NSAIDs drugs

2. Describe the mechanism of action and physiological effects of Aspirin, traditional NSAIDs and celecoxib and how any differences between them influence the specific indications of each class of drug

3. Describe the major differences in expression and function between COX-1 and COX-2 and how these differences influence the clinical and adverse effects of the NSAID drugs

4. Describe the mechanism underlying the use of low dose Aspirin as a prophylactic treatment in the prevention of platelet activation and the development of atherosclerosis

5. List the major adverse effects of Aspirin, traditional NSAIDs and celecoxib

6. Describe the pharmacokinetics of aspirin and the mechanisms that lead to salicylate toxicity

7. List the indications, clinical uses and contraindications for acetaminophen

8. Describe the mechanism of action of acetaminophen

9. Describe the mechanism by which acetaminophen overdose can lead to hepatic failure, the enhancing role of chronic alcohol in acetaminophen-induced hepatic toxicity and the therapeutic approach to limit liver damage.

10. Apply your knowledge of the pharmacology of the Salicylates, NSAIDs and acetaminophen classes of drugs to select the most appropriate medication for the pharmacotherapy of a specific patient based upon patient-specific criteria.
Drugs to be covered in this lecture:

Note: This is a list of the most commonly used NSAIDs currently in clinical use. However, rather than learn the specific details of each individual NSAID drug, it is far more important that you appreciate the use of the NSAID class of drugs as a whole, as well as the fundamental differences between the three distinct classes of NSAIDs and the non-NSAID related analgesic, acetaminophen.

1. Aspirin and Salicylic Acids
   Aspirin (Bayer™)
   Diflusinal (Dolobid™)
   Salsalate (Disalcid™)

2. Non-Selective and traditional NSAIDs
   Ibuprofen (Advil™/Motrin™/Nuprin™)
   Naproxen (Aleve™/Anaprox™/Naprosyn™)
   Oxaprozin (Daypro™)
   Ketoprofen (Actron™)
   Indomethacin (Indocin™)
   Diclofenac (Cataflam™)
   Sulindac (Clinoril™)
   Ketorolac (Toradol™)
   Tolmetin (Tolectin™)
   Meloxicam (Mobic™)
   Piroxicam (Feldene™/Fexicam™)
   Meclofenamate (Meclomen™)
   Mefenamic acid (Ponstel™)
   Nabumetone (Relafen™)
   Etodolac (Lodine™)

3. COX-2 specific inhibitors
   Celecoxib (Celebrex™)

4. Non-NSAID Related Analgesic
   Acetaminophen (Tylenol™/Paracetamol™)
(A) Background information.
A1. Principal therapeutic applications of NSAIDs
NSAIDs are used to treat inflammation, pain & fever specifically:
   a) Mild to moderate pain associated with inflammation
   b) Chronic inflammatory diseases: - Rheumatoid Arthritis
      - Osteoarthritis
      - Acute gout (except Aspirin & Salicylates)
   c) Localized musculoskeletal syndrome: sprains, strains and lower back pain
   d) Pain associated with: - headache and migraine
      - Dysmenorrhoea/Menstrual cramps
      - metastatic bone cancer
      - surgical procedures/post-operative pain/dental procedures
   e) Fever associated with the common cold, influenza and other infections
   f) Certain types of cancer e.g. colon cancer
   g) Prophylactic prevention of platelet aggregation, MI and stroke – Aspirin Specific Use

A2. NSAIDS: Mechanism of action
1. All NSAIDs work by inhibiting the activity of cyclooxygenase enzymes.

2. There are two distinct cyclooxygenase (COX) enzymes: COX-1 and COX-2. They catalyze the conversion of membrane-derived Arachidonic Acid into Prostaglandins and Thromboxane.

3. Prostaglandins and Thromboxane are a diverse set of potent lipid mediators that play a role in the regulation of many inflammatory, pain and fever-related processes, as well as numerous homeostatic functions.

4. COX-1 is associated with regulating homeostatic functions, whereas COX-2 is primarily associated regulation of inflammatory responses.

5. NSAIDs inhibit the production of Prostaglandins and Thromboxanes by preventing the binding of the arachidonic acid substrate to the active site of either COX-1 or COX-2.

6. Different NSAIDs exhibit distinct specificity towards either COX-1 or COX-2.

A3. Cyclooxygenase enzymes: Expression and Function

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<thead>
<tr>
<th></th>
<th>COX-1</th>
<th>COX-2</th>
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<tr>
<td>Expression</td>
<td>Constitutive</td>
<td>Inducible in many cell</td>
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<td>Tissue Location</td>
<td>Ubiquitous</td>
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<td>brain, ovaries, uterus &amp; small</td>
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<tr>
<td>Subcellular location</td>
<td>Endoplasmic Reticulum</td>
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<td>Functional Role</td>
<td>General housekeeping: Protection and maintenance of different tissues</td>
<td>Pro-inflammatory respo Signaling &amp; mitogenes</td>
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<td>Induction</td>
<td>Generally no induction</td>
<td>Induced by many pro-inflam</td>
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<td></td>
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<td>and other stimuli e.g. LPS, IL-1, IFN-γ, EGF, PDGF, FG</td>
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A4. Normal physiological functions of prostaglandins

(A) Prostaglandins produced by COX-2 are associated with the regulation of physiological functions that lead to increased inflammation, fever and pain: Inhibition of production of these specific prostaglandins in relevant cell type is therapeutically beneficial and results in amelioration of clinical symptoms.

(B) Prostaglandins produced by COX-1 are primarily associated with the regulation of normal homeostatic physiological functions: Inhibition of the production of these COX-1-derived prostaglandins can lead to adverse drug effects.

A4.1 Disease-related functions of prostaglandins

(i) Inflammation

- COX-2 is specifically upregulated in inflammatory cells
  - PGE2 & PGI2 (prostacyclin) produced by COX-2 expression in inflammatory cells act to dilate blood vessels & increase blood flow which contributes to the heat and redness associated with inflammation
  - PGE2 also enhances migration of phagocytes to site of inflammation
  - PGE2 promotes vascular permeability which contributes to edema
  - PGE2 & PGI2 are found in synovial fluid of rheumatoid arthritis patients

(ii) Pain

- prostaglandin production by COX-2 in inflammatory cells affects primary afferent neurons by lowering their threshold to painful stimuli
  - systemically produced inflammatory cytokines upregulate expression of COX-2 in the dorsal horn neurons causing the production of prostaglandins, which act as pain neuromodulators in the spinal cord by enhancing the depolarization of secondary sensory neurons
  - prostaglandins increase recruitment of leukocytes to the site of inflammation, causing the release of additional inflammatory mediators

(iii) Fever

- systemically produced inflammatory mediators (e.g. IL-1/TNF-) induce the expression of COX-2 in the endothelial cells lining the hypothalamus causing the production of PGE2, which then acts on the Organum Vasculosum Lamina Terminalis (OVLT: the thermoregulatory center of the hypothalamus) to cause fever.
A4.2 Homeostatic functions of prostaglandins- associated with adverse NSAID effects

(i) Stomach and GI tract
- COX-1 is the predominant enzyme isofrom expressed in the stomach and produces prostaglandins constitutively
- PGE2 & PGI2 are cytoprotective for the stomach by limiting damage to the stomach lining caused by gastric acid and digestive enzymes

\[ \text{PGE2 & PGI2: inhibit production of acid} \]
\[ \text{increase the production of gastric bicarbonate} \]
\[ \text{increase production of gastric mucus} \]
\[ \text{cause vasodilation & increase gastric blood flow} \]

- Inhibition of COX-1 in the stomach is the cause of significant adverse effects of both Aspirin and the traditional NSAIDs

(ii) Cardiovascular system
- Prostaglandins are very important in the regulation of the cardiovascular system
- Platelets express only COX-1 and principally produce TXA2 (thromboxane), which is a vasoconstrictor and promotes both platelet aggregation and activation.
- Endothelial cells express both COX-1 and COX-2, but lack TXA2 synthetase and hence are unable to produce TXA2. They produce primarily PGI2 (prostacyclin), which is a vasodilator and inhibits platelet aggregation.
- The balance between the production of TXA2 & PGI2 regulates systemic blood pressure and thrombogenesis.

(iii) Kidney
- Prostaglandin production in the kidney:
  - Promotes vasodilation thereby increasing renal blood flow and preventing renal ischemia
  - Increases the glomerular filtration rate
  - Increases water and salt secretion
  - is especially important in disease states (e.g. renal disease, Heart failure) where the vaso-dilatory effects of prostaglandins are required to counteract the presence of disease-induced vasoconstrictors

- NSAID treatment decreases renal blood flow, decreases GFR and promotes water/salt retention - can therefore compromise kidney function especially in patients with underlying kidney disease or heart failure (e.g. the elderly)
(iv) Female reproduction
- Overproduction of PGE2 & PGF2 during menstruation can lead to dysmenorrhea/menstrual cramps
- PGE2/PGF2α production stimulates uterine contraction and plays a role in birth
- **hence NSAID treatment during pregnancy may delay labor**

(v) Control of the ductus arteriosus
- The ductus arteriosus is a fetal structure that allows blood to shunt from the left pulmonary artery to the aorta bypassing circulation to the lungs (N.B. the fetus receives oxygen from the placenta and not the lungs)
- The ductus is kept open during fetal life via the actions of prostaglandins
- NSAID treatment during pregnancy may therefore lead to premature closing of the ductus
- At birth the ductus normally closes spontaneously
- **In cases of newborns where the ductus fails to close (patent ductus), the ductus can be closed by treatment with NSAIDs e.g. indomethacin**

(B) The NSAIDs drugs

B1. NSAID drug classes.
There are three distinct classes of NSAIDs:
- a) Aspirin and other salicylates
- b) Traditional NSAIDs e.g. ibuprofen and naproxen
- c) Coxibs- selective COX-2 inhibitors e.g. celecoxib

B2. Aspirin and other salicylates
B2.1 Aspirin- the prototypical NSAID
- Aspirin – acetylsalicylic Acid is a weak acid with a pKa= 3.5
- Rapidly absorbed in the stomach
- Short serum half life ~15-20 mins
- Metabolized by serum esterases to Salicylic acid + acetic acid
- Both aspirin and salicylic acid exhibit anti-inflammatory activity

\[
\text{Acetylsalicylic Acid} \rightarrow \text{Salicylic Acid + Ace}
\]

B2.2 Aspirin: Mechanism of action
- Aspirin is a **NON-SELECTIVE** inhibitor of **BOTH** COX-1 and COX-2
- Aspirin has a **unique** mechanism of action compared to all other NSAIDs
- Aspirin **irreversibly** inhibits COX-1 by **acetylating** the enzyme within its active site thereby inhibiting the binding of the arachidonic substrate
- Aspirin **also** acetylates COX-2, although is a **much less potent** inhibitor of this enzyme isoform, because the COX-2 active site is larger and more flexible than the corresponding site in COX-1 and can still accommodate the arachidonic acid substrate.
- Salicylate the metabolized form of aspirin cannot acetylate COX enzymes (because it lacks the acetyl group) – it inhibits COX activity by acting as a simple competitive antagonist of arachidonic acid binding

**B2.3 Aspirin: Indications**

(i) Treatment of mild to moderate pain
(ii) Inflammatory diseases e.g. Rheumatoid Arthritis
(iii) Fever reduction
(iv) Prophylactic prevention of cardiovascular events i.e. MI and stroke
(v) Cancer chemoprevention: frequent use of aspirin is associated with a 50% decrease in the risk of colon cancer

**B2.4 Aspirin Dosage**

- Anti-platelet activity: 81 mg/day
- Analgesic/Anti-pyretic: ~2,400 mg/day
- Anti-inflammatory: 4,000-6,000 mg/day

**B2.5 Use of low dose Aspirin in the treatment of cardiovascular disease**

Low dose aspirin is used:

a) as a prophylactic treatment in the primary prevention of stroke and myocardial infarction in individuals at moderate to high risk of CVD
b) as a treatment in acute occlusive stroke
c) as secondary prevention of CVD after-
   (i) a myocardial infarction
   (ii) an occlusive stroke
   (iii) a transient ischemic attack
   (iv) stable angina
   (v) a coronary heart bypass

Extensive clinical studies have shown that this treatment has a significant effect on reducing future cardiovascular events, as well as decreasing overall mortality

**B2.6 Mechanism of action of low-dose aspirin in the treatment of CVD**

- At low doses aspirin acetylates COX-1 in platelets permanently inhibiting COX-1 activity and thereby preventing platelets from producing pro-thrombogenic TXA2

- Since platelets lack the ability to re-synthesize COX-1 (i.e. because platelets lack a nucleus they are unable to transcribe additional COX-1 mRNA), this inhibition is long lasting and acts for the lifetime of the platelet (7-10 days)

- Since endothelial cells are able to re-synthesize COX-1 via de novo gene expression and constitutively express COX-2, this low level of aspirin does not significantly affect the production of endothelium-derived PGI2 (prostacyclin: an inhibitor of platelet aggregation).

- By inhibiting platelet-derived TXA2 and sparing the synthesis of PGI2, aspirin promotes an anti-thrombogenic environment

- At higher inflammatory concentrations of aspirin, the anti-thrombogenic activity of low dose aspirin is lost, as at high aspirin doses not only platelet COX-1, but also endothelial COX-1 and COX-2 are effectively inhibited, which results in the decreased production of both platelet-derived TAX2 (pro-thrombogenic) and endothelium-derived PGI2 (an inhibitor of platelet aggregation). These two effects therefore offset each other.

- Other NSAIDs also inhibit COX-1 in platelets, but because their inhibition is reversible their actions are not as effective or as long lasting as those of aspirin
B2.7 Other Salicylates

**Salsalate**
- Dimer of salicylic acid
- Converted to salicylic acid after absorption
- Competitive inhibitor of COX enzymes
- Used in treatment of mild to moderate pain, fever and inflammation

**Diflunisal**
- difluorophenyl derivative of salicylic acid
- Not converted to Salicylic acid in vivo
- Competitive inhibitor of COX enzymes
- More potent anti-inflammatory agent than aspirin
- **Cannot cross the blood brain barrier, hence has no anti-pyretic effect due to poor CNS penetration**
- Fewer and less intense GI side effects
- Weaker anti-platelet effect than aspirin

Others include: sodium thiosalicylate, choline salicylate, magnesium salicylate and methyl salicylate (Oil of Wintergreen- constituent of muscle liniments)

**NOTE:** Unlike aspirin, the salicylates are **non-acetylated** and consequently do not irreversibly inhibit COX-1, hence these drugs may be **preferable** for use in patients with asthma, an increased risk of **GI complications** or those with **bleeding tendencies** (e.g. hemophiliacs).

B2.8 Aspirin/Salicylates Pharmacokinetics

- Non-ionized salicylates are rapidly absorbed from the stomach and upper small intestine
- Salicylates enter the serum in 5–30 mins and reach peak serum concentrations in 1-2 hrs
- All salicylates (except diflunisal) cross the blood brain barrier and the placenta, hence diflunisal is **ineffective** as an anti-pyretic agent
- Salicylates are 50-90% protein bound and can therefore affect the blood concentrations of other highly protein-bound drugs e.g. warfarin
- Salicylate is metabolized in the liver to water-soluble conjugates that are rapidly cleared by the kidney
- Salicylates are excreted in the urine as free salicylic acid (10%) or as salicylate-conjugates (90%)
- Excretion of free salicylate is extremely variable and depends on the dose and the pH of the urine
- At normal **low doses**, salicylates are eliminated with **1st order kinetics** and exhibit a serum half-life of ~3.5 hrs
- At anti-inflammatory **high doses** (>4g/day), the hepatic metabolic enzymes become saturated and salicylate is eliminated with **zero-order kinetics** and a serum half-life of >15h.
- Salicylate is secreted in the urine and can affect uric acid secretion.
  - At low doses (<2 g/d) aspirin decreases uric acid excretion by inhibiting anion transporters in the renal tubules, thereby increasing the serum uric acid concentration leading to the potential precipitation of gout in pre-disposed individuals.
  - At high doses (>4g/d) aspirin blocks the reabsorption of uric acid by the proximal
tubules, thereby promoting uric acid secretion in the urine.

- Because of these effects of aspirin on uric acid levels, the drug is not given to individuals with gout

- **Alkalization of the urine increases the rate of salicylate excretion** and is a useful treatment for salicylate overdose

### B2.6 Salicylate toxicity

- Although widely used and relatively safe at normal doses, excessive consumption of aspirin is very toxic and can result in death
- Aspirin intoxication occurs with doses of >10-30 g (adult) or > 3g (child)
- Mortality: Acute exposure ~2%; Chronic Exposure ~25%

**Symptoms**

**Early:** nausea and vomiting, abdominal pain, lethargy, tinnitus and vertigo

**Late:** hyperthermia, hyperventilation, respiratory alkalosis, metabolic acidosis, hypoglycemia, altered mental status (agitation, hallucinations and confusion), tremors, seizure, cerebral edema and coma.

**Mechanism:**

- Salicylates trigger increased respiration resulting in an initial respiratory alkalosis followed by a compensatory metabolic acidosis
- Acidified blood promotes the transport of salicylates into the CNS resulting in direct toxicity, cerebral edema, neural hypoglycemia, coma, respiratory depression and death

**Treatment for salicylate intoxication:**

- Mild cases- symptomatic treatment and increasing urinary pH to enhance the elimination of salicylate
- Severe- gastric lavage & administration of iv fluids and dialysis

### B2.7 Aspirin: Adverse Effects

#### (i) GI tract (Most common side effect of all NSAIDs)

- Symptoms include epigastric distress, nausea and vomiting
- NSAID treatment can lead to **GI bleeding** (5-10% mortality rate)
- NSAID treatment can aggravate and promote development of gastric & duodenal ulcers
- Gastric damage caused by two effects:
  a) Direct damage to gastric epithelial cells caused by intracellular salicylic acid
  b) Inhibition of COX-1-dependent prostaglandin synthesis in the stomach, which normally acts to prevent damage caused by gastric acid and digestive enzymes
- These adverse effects can be ameliorated by co-administration of **Misoprostol** (a PGE1 analog) that promotes gastric mucous production and thereby acts to prevent damage to the stomach wall or by **Omeprazole** (a proton pump blocker).

#### (ii) Kidney

(A) Aspirin can cause hemodynamically-mediated acute renal failure
- Caused primarily in patients with underlying kidney disease or conditions of volume depletion such as heart failure or cirrhosis
- Especially a problem in elderly patients
- Not typically seen in normal patients because prostaglandins do not play a major role in renal hemodynamics under normal non-pathological conditions
- In the disease state the levels of vasodilatory prostaglandins are increased to counteract the effects of disease-induced vasoconstrictors
- Aspirin treatment inhibits prostaglandin synthesis thereby allowing the vasoconstrictors to act unopposed leading to decreased renal blood flow, renal ischemia and ultimately acute renal failure
- Usually reversible following discontinuation of the drug

(B) Acute Interstitial Nephritis and the Nephrotic Syndrome
- Rare but clinically important (~15% of all patients hospitalized for renal failure)
- Drug-induced kidney failure associated with an inflammatory infiltrate
- Typically seen after several months of exposure
- Exact mechanism unknown
- More common in elderly and in women
- Symptoms: Nausea, vomiting, malaise, WBC in the urine and proteinuria
- Typically spontaneously resolves several weeks after drug discontinuation

(C) Analgesic Nephropathy/Chronic Interstitial Nephritis
- Slowly progressive renal failure leading to end stage renal disease
- Associated with chronic daily overuse of drug over many years
- Typically seen in patients taking NSAID drug combinations

(iii) Exacerbation of hypertension and heart failure
- Not seen with low-dose aspirin, only with high-dose aspirin
- High-dose aspirin promotes vasoconstriction, which can lead to increased blood pressure in patients with pre-existing hypertension
- Increased vasoconstriction can also increase cardiac afterload resulting in further decreased cardiac output in patients with pre-existing heart failure

(iv) Increased Bleeding
- By blocking TXA2 production aspirin prolongs the bleeding time
- Aspirin is therefore contraindicated in hemophilia patients and individuals about to undergo surgery
(v) ****Reye’s Syndrome (- unique Aspirin side effect)
- Reye’s syndrome is a rare, often fatal liver degenerative disease with associated encephalitis
- Not seen with other NSAIDS, only with aspirin
- It is associated with the administration of aspirin given during the course of a febrile viral infection in young children (e.g. chickenpox, influenza etc) Because of this aspirin is not generally administered to young children

(vi) Hypersensitivity
- ~1.5% of patients taking aspirin exhibit an airway hypersensitivity reaction leading to a rapid, often severe asthma attach within 30-60 mins
  - Symptoms include: - Wheezing and severe airway obstruction
    - Ocular & nasal congestion,
    - Urticaria (Hives),
    - angioneurotic edema,
- Fatal anaphylactic shock is rare
- Not caused by an immunological hypersensitivity reaction, but is thought to result from increased production of leukotrienes due to a build up of arachidonic acid
- Aspirin-sensitive patients are also reactive to other NSAIDs

(vii) GOUT
- Aspirin can promote the occurrence of an acute attack of gout in susceptible individuals
- Low doses of Aspirin (<2g/day) block URIC acid excretion by blocking anion transporters in the kidney. The resulting increase in serum uric acid levels can precipitate gout in pre-disposed individuals
- Paradoxically, high doses of aspirin blocks the reabsorption of uric acid in the proximal tubules and as a result promotes uric acid excretion in the urine
- As a general rule Aspirin and the salicylates are not given to patients with a prior history of GOUT
**B3. Traditional NSAIDs**

There are many distinct traditional NSAIDs on the market. They all have a common mechanism of action and exhibit very similar efficacy and adverse drug effect profiles. Hence, it is probably best to think about this class of drugs as a whole rather than focus on the specifics of any individual drug in this class. However, in section B3.2 below I will try to point out some of the unique and important aspects of some of the selected individual drugs.

**B3.1 General Properties:**
- All traditional NSAIDs are reversible competitive inhibitors of COX activity
- All traditional NSAIDs work by blocking the production of prostaglandins
- Traditional NSAIDs are mostly **NON-SELECTIVE** COX inhibitors and inhibit both COX-1 and COX-2 to varying degrees
- All traditional NSAIDs exhibit **anti-inflammatory**, **anti-pyretic** and **analgesic** effects.

**B3.2 Pharmacokinetics of traditional NSAIDs**
- most traditional NSAIDs are weak acids and are well absorbed in the stomach and upper intestine
- highly protein bound 90-95%- therefore can interact with other protein-binding drugs e.g. warfarin
- specifically accumulate in the synovial fluid and at other sites of inflammation i.e. ideally suited for the treatment of arthritis
- metabolized by the liver
- Mostly excreted by the kidney- hence drugs can accumulate in patients with impaired renal function resulting in increased risk of adverse effects

**B3.3 Key features of selected traditional NSAIDs**

**Ibuprofen (Advil™/Motrin™/Nuprin™)**
- equipotent with aspirin and better tolerated
- potent analgesic and anti-inflammatory properties
- rapid onset of action 15-30 mins- ideal for treatment of fever and acute pain
- GI bleeding occurs less than with aspirin
- Low doses are effective as an analgesic
- High doses required for anti-inflammation
- commonly prescribed OTC for analgesia

**Naproxen (Aleve™/Anaprox™/Naprosyn™)**
- 20x more potent than aspirin
- rapid onset of action- 60 mins- ideal for anti-pyretic use
- long serum half life of 14 hrs/twice daily dosing
- low incidence of GI bleeding
- considered to be one of the safest NSAIDs

**Indomethacin (Indocin™)**
- 10-40X more potent than aspirin as an anti-inflammatory
- also inhibits neutrophil migration
- most effective NSAID at reducing fever
- not well tolerated (50% of users experience side effects)
- should only be used after less toxic drugs prove ineffective
- can delay labor by suppressing uterine contractions
- drug of choice to promote closure of patent ductus arteriosus

**Sulindac (Clinoril™)**
- equipotent to aspirin
- closely related to indomethacin- less potent/fewer adverse effects
Keterolac (Toradol™) - relatively weak anti-inflammatory activity
- used as i.v. analgesic for moderate/severe post surgical pain
- can be used as replacement for opioid analgesic e.g. morphine

B3.3 Adverse Effects of traditional NSAIDs

(I) GI disturbance
- Significant GI problems although lower than that caused by aspirin
- Symptoms include: Nausea, Dyspepsia, Ulceration, Bleeding & Diarrhoea
- Caused by inhibition of COX-1 in the stomach leading to a reduction in the production of cytoprotective prostaglandins

(II) Renal damage
(A) NSAID-induced vasoconstriction (most common)
- Decreased renal blood flow due to inhibition of vasodilatory prostaglandin production
- Increased salt and fluid retention
- Caused by inhibition of both COX-1 and COX-2, which is constitutively expressed in the kidney
- Particular problem for those with pre-existing renal disease and heart failure
- Risk of renal failure increases in patients also taking ACE inhibitors and diuretics

(B) NSAID-induced acute interstitial nephritis and the nephritic syndrome
- Rare, but clinically important (accounts for ~15% of patients hospitalized for renal failure)
- Drug induced kidney failure associated with inflammatory cell infiltration
- Typically occurs after several months of exposure
- Associated with the nephrotic syndrome from minimal change disease
- Most common in the elderly and in women
- Symptoms include: nausea, vomiting, malaise, WBC in the urine and proteinuria
- Spontaneous recovery typically occurs weeks after drug discontinuation

(C) NSAID-induced chronic interstitial nephritis/Analgesic nephropathy
- Slowly progressive renal failure leading to end stage renal disease
- Associated with chronic daily overuse of NSAIDs over many years
- Often linked to history of chronic lower back pain, migraine, chronic musculoskeletal pain
- Can occur with all NSAIDs, but is particularly associated with drug combinations

(III) Cardiovascular

(A) Increased risk of of heart attack and stroke
- All NSAIDs (except ASPIRIN and Naproxen)
- Overall risk is small ~ 2+ events /1,000 patient years (no prior CVD)
  ~ 8-9 events/1,000 patient years (pre-existing CVD)
- Associated with higher doses and chronic treatment

(B) modest worsening of underlying hypertension
- Not associated with 1st occurrence heart failure, but can worsen pre-existing disease due to increased afterload due to systemic vasoconstriction

(IV) Liver
- Elevated liver enzymes
- Liver failure rare
- Increased risk with sulindac (27/100,000 prescriptions)

(V) Anti-platelet effect/Increased bleeding
- All NSAID drugs except celecoxib can interfere with the beneficial anti-platelet effects of aspirin by binding to platelet COX-1 and preventing the binding of aspirin
- when necessary aspirin should be taken first followed by the NSAID several hours later
- NSAID use should be avoided in patients with pre-existing platelet deficiency
- NSAID use should be avoided prior to surgery for at least 4-5 X drug half-life (1 week in the case of aspirin)

(VI) NSAID hypersensitivity
- Can occur in susceptible patients
- Symptoms include: vasomotor rhinitis, fever, rash, urticaria, angiodema, pulmonary infiltrate and asthma

(VII) CNS
- Tinnitus (common)
- Aseptic meningitis (non-infectious brain inflammation)- increased risk in Lupus patients
- Psychosis & cognitive dysfunction- more common in the elderly and those on indomethacin

(VIII) Skin reactions
- Associated with potentially life threatening skin conditions (RARE)
- Toxic epidermal necrolysis & Stevens-Johnson syndrome (mucosal blistering)
- Piroxicam highest risk- 1/100,000 patients

(IX) Pseudoprophyria/Photosensitivity
- blistering in sun-exposed areas
- Is due to the chemical nature of NSAIDs in the skin absorbing UV e.g. Ibuprofen, ketoprofen, naproxen, ketorolac, piroxicam & diclofenac

(X) Pregnancy
- associated with increased rate of miscarriage
- can promote premature closure of the ductus arteriosus
- can delay labor
- NSAID use late in pregnancy is associated with post-partum hemorrhage

B4. Selective COX-2 inhibitors
Since inflammation is associated with increased COX-2 activity and aspirin and the traditional non-selective NSAIDs are associated with significant adverse effects, drugs that specifically target COX-2 were developed. The underlying hypothesis being that these drugs should exhibit anti-inflammatory activity without the serious adverse effects of aspirin and the traditional NSAIDs that are associated with the inhibition of COX-1.

Three selective COX-2 inhibitors were developed and brought to market:

Celecoxib (Celebrex®)
- Selectively inhibits COX-2 not COX-1
- Anti-inflammatory, anti-pyretic and analgesic properties similar to traditional NSAIDs
- Associated with fewer GI side effects (does not inhibit COX-1 in the stomach)
- No effect on platelet aggregation as does not inhibit COX-1
- Similar renal toxicities to traditional NSAIDs due to constitutive expression of COX-2 in kidney
- Recommended for the treatment of rheumatoid arthritis and osteoarthritis
- However- no evidence that Celecoxib is any more efficacious than traditional NSAIDs
- May be indicated in patients with increased risk of GI complications
- Approved for the treatment of colon cancer

B4.1 Features of Celecoxib (Celebrex®)

Rofecoxib (Vioxx®) – withdrawn Dec 2004 due to increased MI & stroke
Valdecoxib (Bextra®) – withdrawn April 2005 due to increased MI & stroke

B4.2 COX-2 inhibitors and increased cardiovascular risk
a) Several large clinical trials have shown that both Rofecoxib and Valdecoxib are associated with a significantly increased risk of heart attack and stroke
-similar findings have also been reported for Doclofenac and Meloxicam – two traditional NSAIDs that exhibit preference towards COX-2 inhibition

b) This increased cardiovascular risk is believed to be caused by the selective inhibitory effect of these COX-2 inhibitors on the endothelial production of the anti-thrombotic prostaglandin PGI2 (prostacyclin). (N.B. COX-2 is constitutively expressed in endothelial cells).

c) Since these COX-2 inhibitors do not inhibit COX-1, they do not block the production of the platelet-derived pro-thrombotic prostaglandin TXA2. Hence these drugs shift the TXA2/PGI2 balance towards increased platelet aggregation.

B5. NSAID: Contraindications

a) Patients with a history of GI ulcers (not celecoxib)

b) Patients with bleeding disorders or on anti-coagulant therapy, since decreased platelet aggregation may prolong bleeding time in these individuals (not Celecoxib)

c) Aspirin and the salicylates are contraindicated in gout because they inhibit the elimination of uric acid by the kidney leading to an increased risk of precipitating an acute gouty attack

d) Patients with renal disorders
  ※ as NSAIDs decrease renal blood flow and promote water/salt retention leading to hypertension
  ※ also since NSAIDs are cleared by the kidney the drugs may accumulate more rapidly in these patients due to underlying renal disease leading to increased toxicity

e) Patients at increased risk of Cardiovascular disease
  - Evidence that celecoxib in particular and perhaps all NSAIDs are associated with increased risk of developing cardiovascular events (exact mechanism not understood)
  - Should exercise caution in these patients especially with high doses of drug
  - Naproxen is recognized as being the safest NSAID with the lowest risk

f) Patients with hypersensitivity to aspirin

g) Pregnant patients as NSAID treatment may delay the onset of labor or cause the premature closure of the ductus arteriosus (typically not given 6-8 days prior to labor)

h) Elderly patients- because NSAIDs cause toxicities to which the elderly are particularly susceptible i.e. GI bleeds & Renal toxicity
B6. Some clinically important NSAID Drug Interactions

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Type of NSAID</th>
<th>Specific Effect</th>
</tr>
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<tr>
<td>Low-dose aspirin</td>
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<td>Antagonize beneficial effects of low-dose aspirin (Prevents binding of aspirin to COX-1)</td>
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<tr>
<td>Oral anti-coagulants</td>
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<td>Diuretic agents</td>
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<td>Lithium</td>
<td>All NSAIDs</td>
<td>Increased Lithium toxicity (Decreased Renal Clearance)</td>
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<tr>
<td>Methotrexate</td>
<td>All NSAIDs</td>
<td>Increased Methotrexate toxicity (Protein displacement/Decreased Renal Clearance)</td>
</tr>
<tr>
<td>Aminoglycosides</td>
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B7 Choice of NSAID

(i) While the anti-inflammatory, anti-pyretic and analgesic effects of NSAIDs do vary these differences may not be particularly clinically significant

(ii) The choice of NSAID does not usually make a substantial difference in the clinical outcome – especially treatment of rheumatoid arthritis and osteoarthritis

(iii) In general, an NSAID with a rapid onset of action/short duration (e.g. aspirin, 1hr; ibuprofen, 15-30 mins; naproxen, 1hr) is ideal for treating a simple fever, whereas drugs with a longer duration of action (e.g. sulindac, 7hrs, naproxen, 14hrs; oxaproxin 40-60hrs) are more preferable for long-term pain management

(iv) If one NSAID proves ineffective switching to another NSAID drug is advised

(v) Therapy is usually directed at achieving the desired clinical effect, at the lowest possible dose, while minimizing adverse effects.

(vi) The COX-2 inhibitor celecoxib is indicated for patients at highest risk of GI bleeds

(vii) Overall the choice of NSAID requires a balance of:

a) clinical efficacy
b) Safety
c) Cost effectiveness
C. Related non-NSAID analgesic: Acetaminophen (e.g. Tylenol™)

C1. Acetaminophen: Overview
- An important **ANALGESIC** drug in the treatment of mild to moderate pain & Fever
  - Anti-pyretic and analgesic activity (equivalent to Aspirin)
  - **No** anti-inflammatory activity because acetaminophen *does not* inhibit peripheral COX-2
  - **No** anti-platelet activity because acetaminophen *does not* inhibit Platelet COX-1
  - Only a very weak inhibitor of COX-1 and COX-2 in peripheral tissues- thought to be due to the inhibitory effects of high concentrations of hydroperoxides in the periphery
  - Reduced Adverse effects compared to NSAIDs due to lack of effect on peripheral COX-1
  - Most potent effect are on the pain and thermoregulatory centers of the CNS
  - Acetaminophen is selectively metabolized in the brain to an active metabolite AM404
  - AM404 inhibits COX-1 and COX-2 activity in the CNS
  - AM404 also acts on the cannabinoid system to decrease pain and Fever
  - The effects of acetaminophen are blocked by antagonists of the cannabinoid system
  - Well absorbed orally and is metabolized in the liver
  - Peak blood levels are achieved in 30-60 mins with a serum half-life of 2-3 hrs.

**Acetaminophen: Mechanism of Action**

**PERIPHERY**
- Very weak inhibitor of COX-1/COX-2 in periphery
- Acetaminophen
- Due to high concentration of hydroperoxides in periphery
- COX-1/COX-2
  - No anti-inflammatory
  - No anti-platelet effect
  - Reduced Adverse effects
  - No GI Toxicity/Renal effects

**CNS**
- Potent inhibitor of COX-2 in CNS
- Acetaminophen
- Metabolized
- AM404 (N-arachidonyl phenolamine)
  - Cannabinoid Receptors
  - COX-2
  - Pain ➔ Fever

**Acetaminophen: Indications**

a) Mild to moderate pain not associated with inflammation (Dosage 325-500 mg x 4 daily)
b) Used for the relief of pain associated with headaches, muscle aches and mild forms of arthritis
c) Alone is not an effective therapy for arthritis. However, may be used as an adjunct therapy together with NSAIDs.
d) Preferred analgesic in patients that are **allergic** to Aspirin, or where salicylates are poorly tolerated
e) Preferred Analgesic/Anti-pyretic in children with viral infections (to avoid Reye’s syndrome)
f) Preferred Analgesic/Anti-pyretic in patients with hemophilia or a history of peptic ulcer- does not affect the bleeding time or promote GI bleeding
g) Does not affect uric acid levels, therefore can be used together with Probenecid in the treatment of gout
h) Should not be taken with alcohol as together they can cause serious liver damage

Acetaminophen: Adverse effects and toxicity

a) At normal doses (4g/day) Acetaminophen is essentially free of adverse effects
b) Larger doses might result in dizziness, excitement and disorientation
c) Ingestion of very large doses (>15 g) acetaminophen can be fatal due to severe hepatotoxicity
d) Hepatotoxicity is due to the build up of the toxic metabolite N-acetyl-p-benzoquinoneimine that is caused by the acetaminophen-dependent depletion of hepatic glutathione
e) Treatment is with N-acetyl cysteine (given within 8-10 hrs of overdose), which works by replenishing cellular glutathione levels
NSAIDs: Key Facts/Quick Review Points

1. NSAIDs are indicated for the treatment of: inflammation, pain, fever

2. Three types of NSAIDs
   a) Aspirin and salicylates
   b) Traditional NSAIDs
   c) COX-2 specific inhibitors

3. Mechanism of action: Inhibition of COX activity preventing the production of prostaglandins

4. All NSAIDs inhibit COX enzymes by preventing the binding of the arachidonic acid substrate
   - Aspirin and the traditional NSAIDs are non-selective and inhibit BOTH COX-1 and COX-2
   - COX-2 specific inhibitors only inhibit COX-2

5. Aspirin has a unique mechanism of action- it covalently attaches an acetyl group to the active site of COX enzymes irreversibly inhibiting COX-1 activity. Note aspirin also acetylates COX-2, but because the active site of COX-2 is larger and more flexible arachidonic acid can still gain access to the active site, albeit less efficiently- hence aspirin is a less potent inhibitor of COX-2 than COX-1. Other than Aspirin, all other NSAIDs competitively inhibit COX enzyme activity blocking access of arachidonic acid to the active site.

6. COX-1 is constitutively expressed and is primarily involved in housekeeping functions

7. COX-2 is primarily induced in macrophages, synovioocytes and fibroblasts in response to inflammatory stimuli and is involved in pro-inflammatory responses- also constitutively expressed in kidney, brain and endothelium

8. Low dose aspirin is an effective anti-thrombotic agent as it permanently inhibits COX-1 in platelets blocking the production of pro-thrombotic thromboxane. Because COX-1 is resynthesized in the endothelium, low-dose aspirin does not effectively inhibit the production of anti-thrombotic prostacyclins

9. Key Features of Selected NSAIDs
   - Ibuprofen- rapid onset of action, ideal for fever and acute pain
   - Naproxen – rapid onset of action, long serum half-life 14hrs- twice daily dosing
   - Oxpiprofen- long serum half life 50-60 hrs, one daily dosing
   - Indomethacin- potent anti-inflammatory, >toxicity; used to close patent ductus arteriosus
   - Diclofenac- relatively selective for COX-2; associated with increased risk of MI/stroke
   - Ketorolac- mainly used as IV analgesic as a replacement for opioid analgesics

10. Primary adverse effects of NSAIDs include:
    a) GI and stomach
    b) Renal
    c) Cardiovascular system
    d) Anti-platelet effects/increased bleeding
    e) Hypersensitivity
    f) CNS
    g) Skin
    h) Liver
    i) Photosensitivity
    j) Pregnancy- ductus arteriosus

11. The stomach and GI disturbances caused by Aspirin and traditional NSAIDs are due to the inhibition of COX-1 in these tissues, which is responsible for the production of prostaglandins that act to prevent damage to gastric and intestinal epithelial cells caused by gastric acid and digestive enzymes.

12. COX-2 inhibitors are no more efficacious than other NSAIDs, but might be preferable in patients with a prior history of GI bleeds and/or ulcers
13. NSAIDs are contraindicated in: a) patients with GI ulcers b) patients with bleeding disorders c) patients with renal disorders (e.g. Elderly) d) patients with a previous hypersensitivity to aspirin e) pregnant women f) patients at increased risk of cardiovascular disease g) children with febrile viral infections (Aspirin only-Reye’s syndrome) h) aspirin is contraindicated in gout due to its effects on uric acid secretion (i.e. inhibition at low doses).

14. NSAID drug interactions include:

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15. Acetaminophen is an important drug used in the treatment of mild to moderate pain and Fever. It does not effectively inhibit either COX-1 or COX-2 expressed in the periphery

16. Acetaminophen is metabolized selectively in the brain to an active metabolite (AM404) that both inhibits COX-2 in the CNS, as well as acts on the endogenous cannabinoid system in the pain and thermoregulatory centers of the CNS to reduce pain and fever

17. Acetaminophen has both anti-pyretic and analgesic properties, but no anti-inflammatory activity and no anti-platelet activity due to its failure to inhibit COX-1 & COX-2 in peripheral tissues.

18. Due to its lack of activity against peripheral COX-1 activity, acetaminophen is NOT associated with the adverse effects commonly observed with the NSAIDs

19. Acetaminophen is the preferred analgesic in: a) patients that are allergic to Aspirin or other Salicylates b) Children with viral infections- to avoid Reye’s syndrome associated with Aspirin c) Patients with hemophilia or increased risk of bleeding d) Patients with a prior history of gastric/peptic ulcers

20. Acetaminophen overdose results in the build up of the toxic metabolite N-acetylbenzoquinoneimine, which depletes hepatic glutathione, N-acetylcysteine is used as an antidote because it replenishes endogenous glutathione levels.