Pharmacology/Therapeutics I Block II Handouts – 2017-18

12. Drug Actions in synaptic Transmission – Scrogin
13. Adrenergic Agonists and Antagonists – Scrogin
14. Adrenergic Agonists and Antagonists II - Scrogin
15. Adrenergic agonists and Antagonists III – Scrogin
16. Cholinergic Agonists & Antagonists – Scrogin
17. Neuromuscular Relaxants – Scrogin
18. NSAIDS I – Clipstone
19. NSAIDS II - Clipstone

SYNAPTIC TRANSMISSION: TARGETS OF DRUG ACTION

Date: August 16, 2017, 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

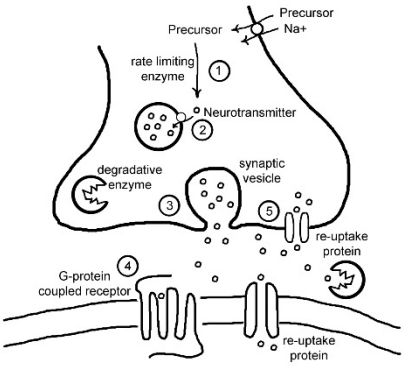
7. Describe how adrenergic neurotransmission is most commonly manipulated with clinical pharmaceuticals

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

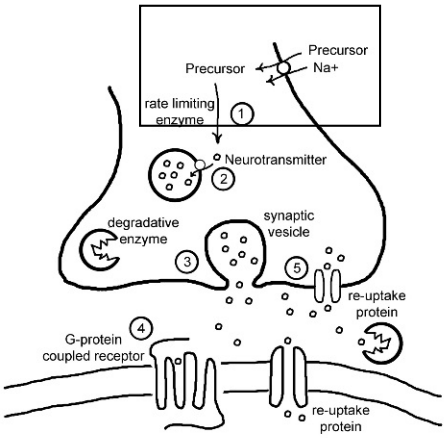
   metyrosine
   reserpine
   bretylium
   cocaine
   tricyclic antidepressants
   monoamine oxidase inhibitors
   SSRIs
   amphetamines

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.



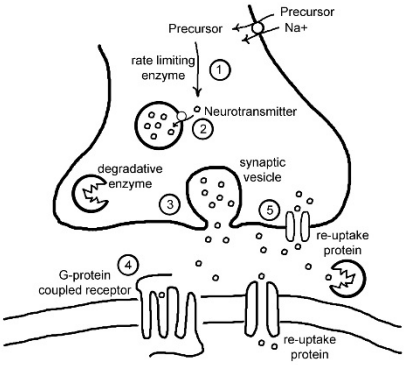
1. Therapeutic drugs can inhibit enzymes involved in neurotransmitter production.

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

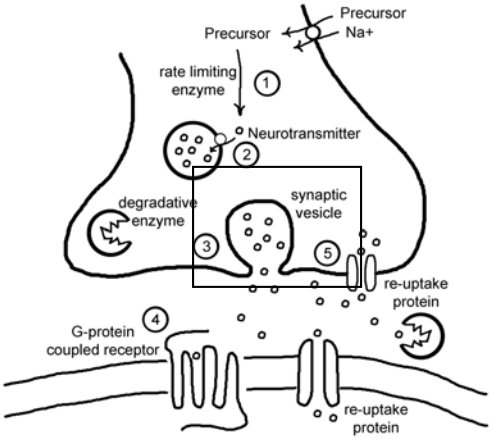
.



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.

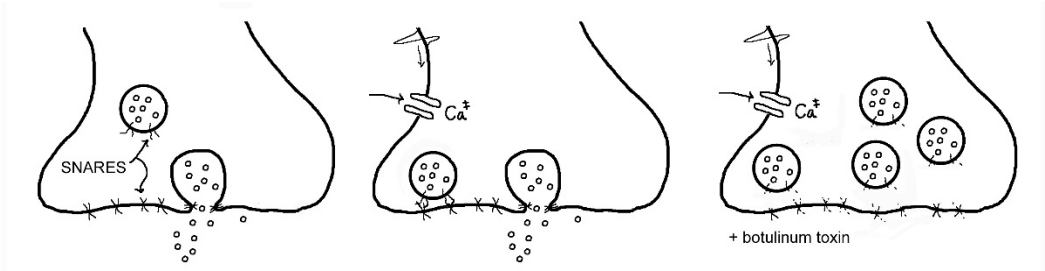
2. Neurotransmitters in the cytoplasm can be degraded when vesicular transport is inhibited resulting in neurotransmitter depletion.

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.



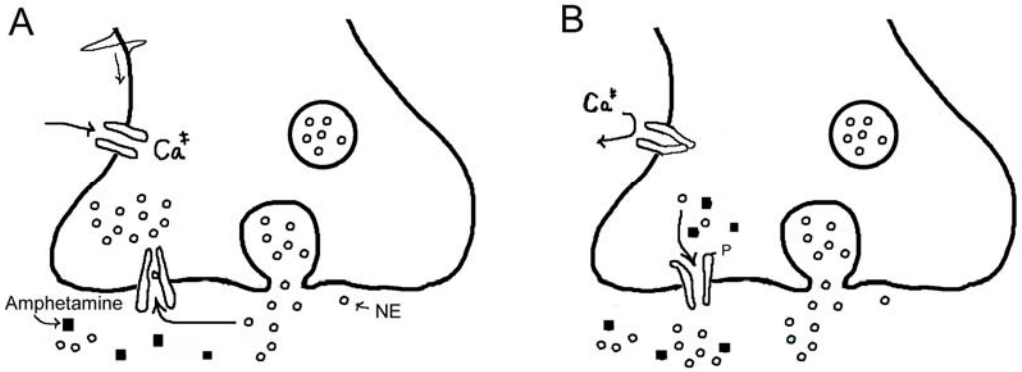
1. Toxins can degrade SNAREs and disrupt fusion of synaptic vesicles with the cell membrane. The pharmacological effect of such disruption depends upon the cell type that takes up the toxin

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".

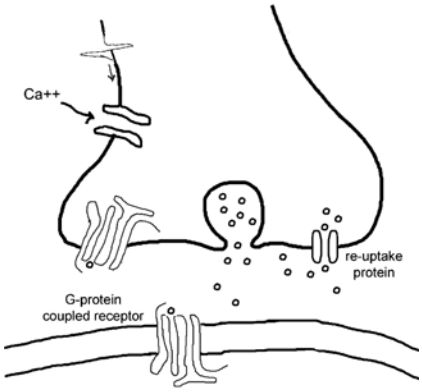
4. Some indirectly acting drugs (i.e., those that do not interact directly with a receptor) stimulate the release of neurotransmitters in a *calcium-independent* manner. Ex: **amphetamine** taken up by re-uptake transporters at the axon terminal (see description of reuptake transporters below under termination 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.

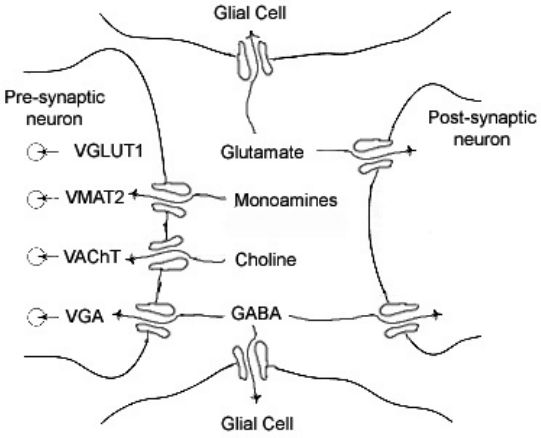
1. Drugs that bind directly to receptors provide the most selective manipulation of synaptic transmission.

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



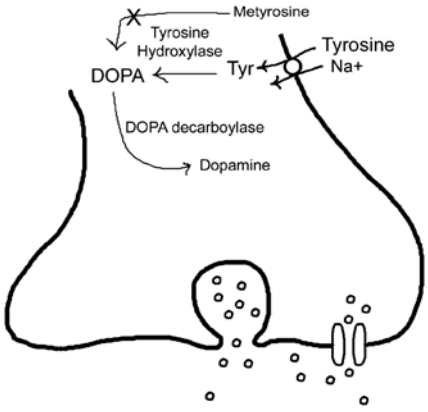
is dependent on the location of reuptake protein expression.

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. .



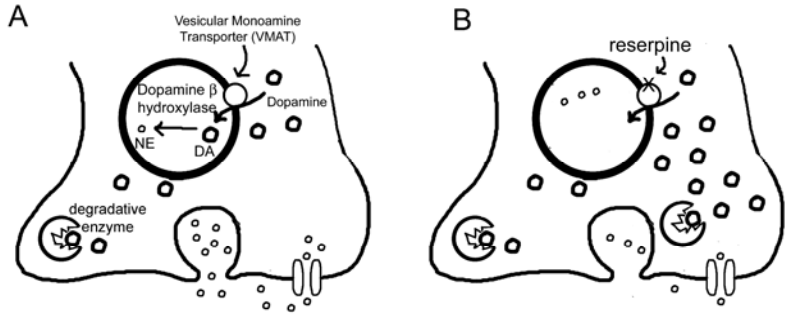
A. Synthesis **–** dopaminergic and noradrenergic neurons transport tyrosine into the cell via an amino acid transporter. Several enzymatic steps eventually lead to tyrosine's conversion to dopamine. Dopamine is the precursor to norepinephrine and epinephrine

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.

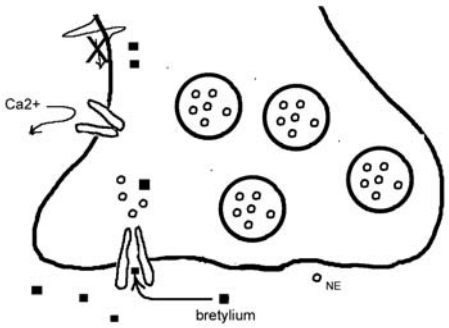
B. Storage- Dopamine is transported into synaptic vesicles by a vesicular transporter specific to monoamines, (i.e., serotonin, norepinephrine, histamine, and dopamine). Dopamine is transformed to norepinephrine by dopamine β-hydroxylase. The dopamine β- hydroxylase enzyme is expressed within the vesicle. 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.

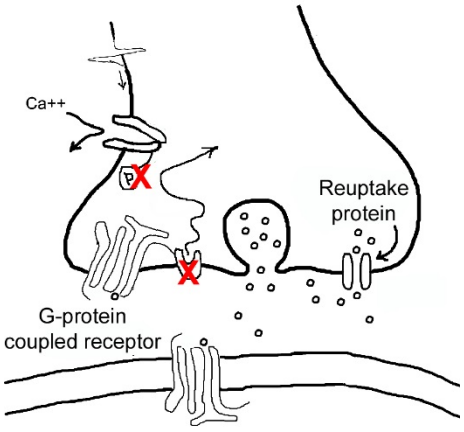


D. Binding – Norepinephrine binds to 2 major types of receptors called α and β adrenergic receptors. Each type of "adrenergic" receptor has several subtypes that mediate different physiological functions depending upon the second messenger systems to which the receptor is coupled and the function of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

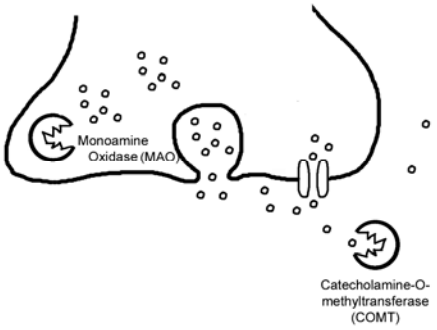
1. Post-synaptic receptor binding influences numerous cell functions that will be addressed in later lectures. Both agonists and antagonists of adrenergic

receptors are used in the treatment of cardiovascular and respiratory diseases as well as mood disorders.

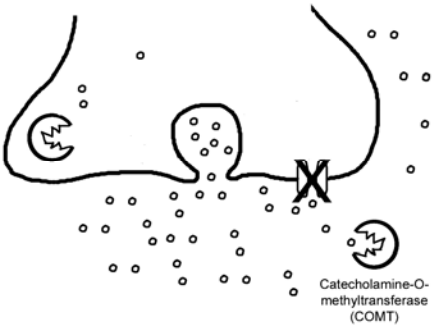
2. Activation of pre-synaptic adrenergic receptors on nerve terminals influences neurotransmitter release. Pre-synaptic α–adrenergic receptors can inhibit, while pre-synaptic β–adrenergic receptors can facilitate neurotransmitter release.



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

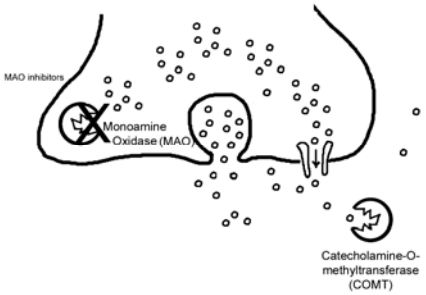


1. Re-uptake is the primary mode of terminating monoamine actions. Inhibitors of monoamine re-uptake have highly significant pharmacological effects. **Cocaine** inhibits re-uptake of monoamines including norepinephrine, dopamine and serotonin. Inhibitors of monoamine re-uptake are now widely used to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

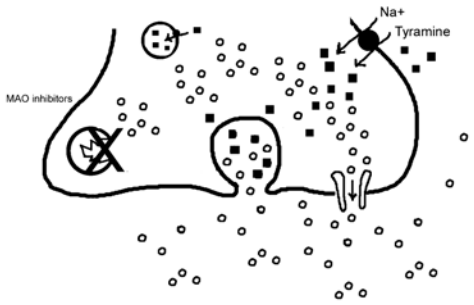


therapeutic effects. They can also have significant systemic side effects, particularly in the cardiovascular system, which is richly innervated by noradrenergic neurons.

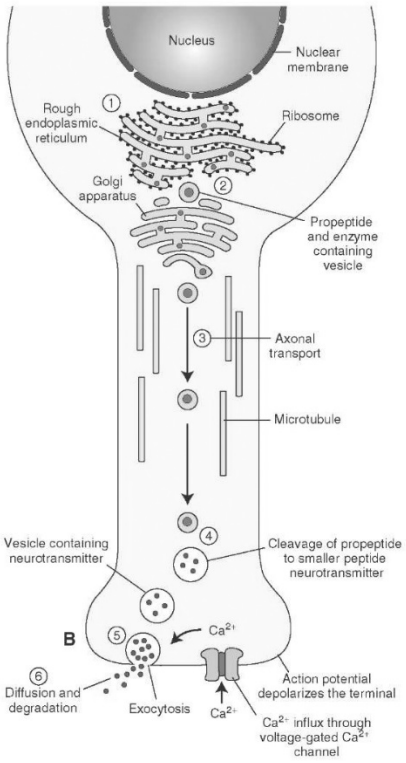
2. Metabolism is less important for termination of endogenously released catecholamine since re-uptake from the synapse is so efficient. Circulating catecholamines such as those released by the adrenal gland or those administered exogenously are subject to metabolism by COMT. This highly efficient enzyme dramatically keeps the half-life of exogenously administered catecholamines short. 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 concentration gradient reverses and transporter protein can reverse 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. **<u>Neuropeptide transmission</u>**. 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. <u>Neuropeptides are often produced within other neuronal types and are co-released when the nerve terminal is activated</u>. 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, <u>many non-peptidergic receptor agonists and antagonists have been developed to allow for penetration into the CNS.</u> 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

Drug	Indication	Mechanism of Action
Metyrosine	Hypertension	**Competitive inhibition of tyrosine hydroxylase**
Reserpine	Hypertension	**Inhibits VMAT uptake of monoamines**
Bretylium	Ventricular Arrhythmia	**Inhibit action potential generation and calcium dependent synaptic vesicle fusion**
Cocaine	Analgesia in surgery	**Blocks monoamine reuptake**
Amphetamine or Ephedrine	Narcolepsy, ADHD	**Reverse monoamine reuptake transporters**
Naloxone, Naltrexone	Opioid overdose or dependence	**Non-peptide blockers of opioid receptors in CNS**
SSRIs	Depression/anxiety	**Selective inhibition of serotonin reuptake transporter**
ACE inhibitors e.g., lisinopril	Hypertension	**Inhibits peptide cleavage of Angiotensin I to Angiotensin II**
Phenylephrine	Hypotension during surgery	**Direct agonist of adrenergic receptor**
MAO inhibitors	Depression	**Blockade of cytoplasmic metabolism of monoamines**
L-DOPA	Parkinson's Disease	**Precursor of dopamine, stimulates dopamine production**
Carbidopa	Parkinson's Disease	**Blocks L-DOPA conversion to dopamine,** does not cross BBB, so protects peripheral adrenergic neurons from producing too much dopamine and norepinephrine
Tyramine	Ingested in diet, not therapeutic	**Competes with NE for transport into synaptic vesicle**

ADRENERGIC AGONISTS I AND II

Date: August 17-18, 2017
Recommended Reading: **Basic and Clinical Pharmacology**, 13th Edition, Katzung, *et. al.*, pp. 133-151.

LEARNING OBJECTIVES

1. Distinguish the anatomical and neurochemical characteristics of the sympathetic, parasympathetic and somatic motor systems (e.g., origin, pathway, neurotransmitters).

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 physiological response of that target organ (as 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 relative efficacy in activating the 4 main adrenergic receptors discussed in lecture.

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

8. Categorize the adrenergic receptor agonists discussed in class 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 (clinical indications) for the endogenous and synthetic adrenergic agonists discussed in class. (**all those bolded** on slides)

FINAL COPY RECEIVED: 8/14/17

11. List 4 commonly used “indirect acting sympathomimetics”

12. Describe the most important toxic side effects and most important clinical indications for indirect acting sympathomimetic drugs (those **bolded** in slides).

FINAL COPY RECEIVED: 8/14/17

ADRENERGIC ANTAGONISTS

Date: August 18, 2017
Recommended Reading: **Basic and Clinical Pharmacology**, 13th Edition, Katzung, *et. al.*, pp. 152-168.

LEARNING OBJECTIVES

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

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

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

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

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

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

7. Explain why selective α_1-adrenergic receptor antagonists are more preferable for use in hypertension than non-selective α-adrenergic receptor antagonists.

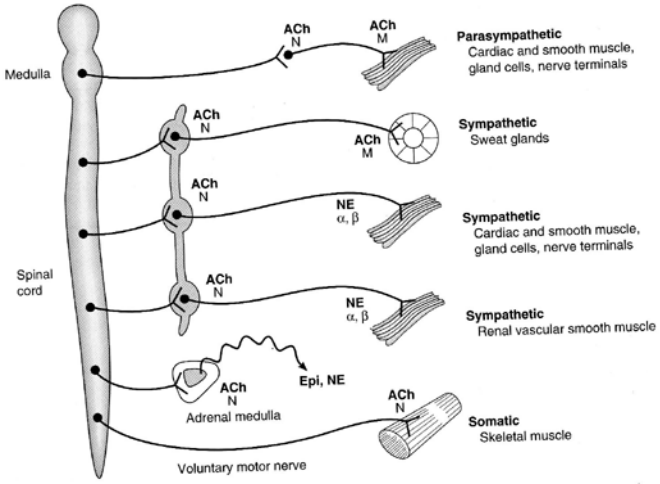
ADRENERGIC AGONISTS & ANTAGONISTS

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. The present lecture material will briefly review some basic concepts in general autonomic function that includes the parasympathetic system, but the focus will be on the sympathetic system. Underlined points should be the main focus of learning.

I. Anatomy

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



Overview of autonomic motor innervation to the organ systems *Modified From: Katzung, Basic and ClinicalPharmacology, 9th Ed.McGraw-Hill, New York, 2004.*

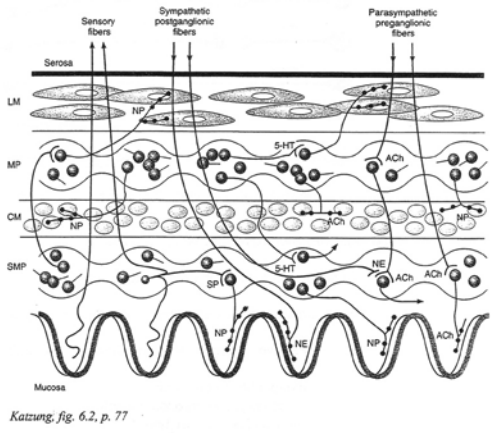
1. Sympathetic - thoracolumbar division (short pre-ganglionic cells and long-post ganglionic cells)

2. Parasympathetic - craniosacral division (long pre-ganglionic cells and short post-ganglionic cells)

3. Enteric nervous system – classified by some as part of the ANS

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).



From: Katzung, Basic and Clinical Pharmacology, 9th Ed.McGraw-Hill, New York, 2004.

II. <u>Neurochemistry</u> of the Autonomic Nervous system

A .<u>Pre-ganglionic fibers release acetylcholine</u>

B. <u>Post-ganglionic parasympathetic fibers release acetylcholine</u>

C. <u>Post-ganglionic sympathetic fibers release norepinephrine (NE)</u>
(NE = noradrenaline; hence "adrenergic")

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

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

III. <u>Functional Organization</u> 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

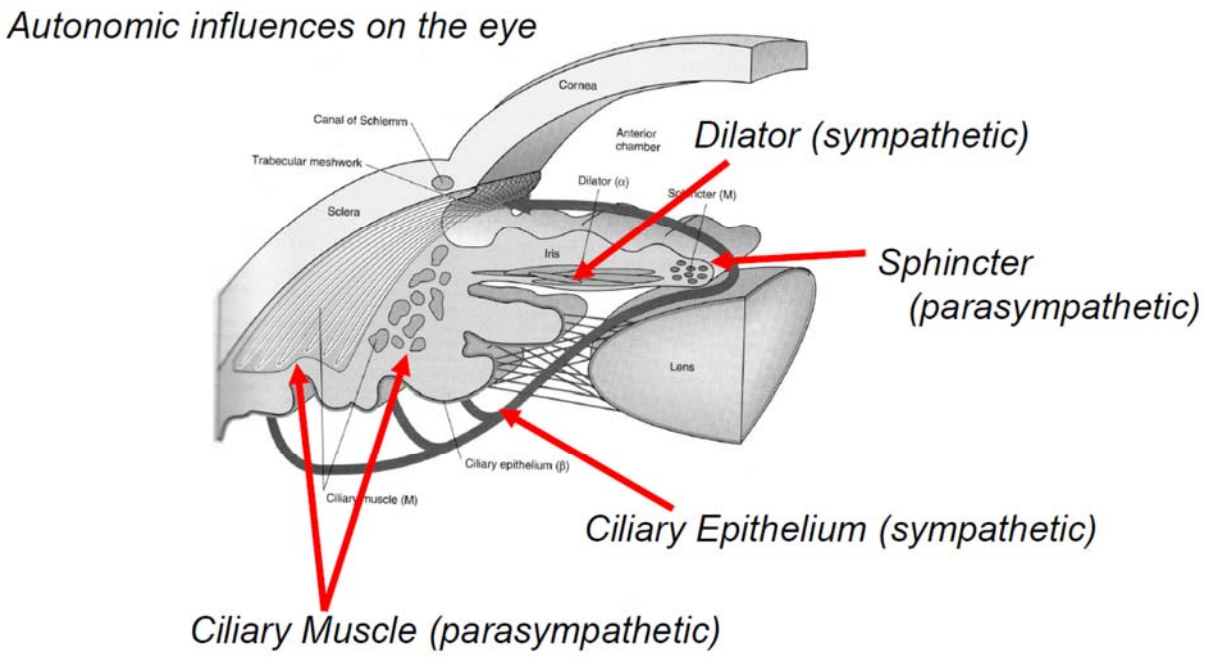
Bronchioles – bronchiole smooth muscle – constriction

GI tract – promotes secretions and motility

Bladder – contraction of detrusor muscle, causes bladder emptying

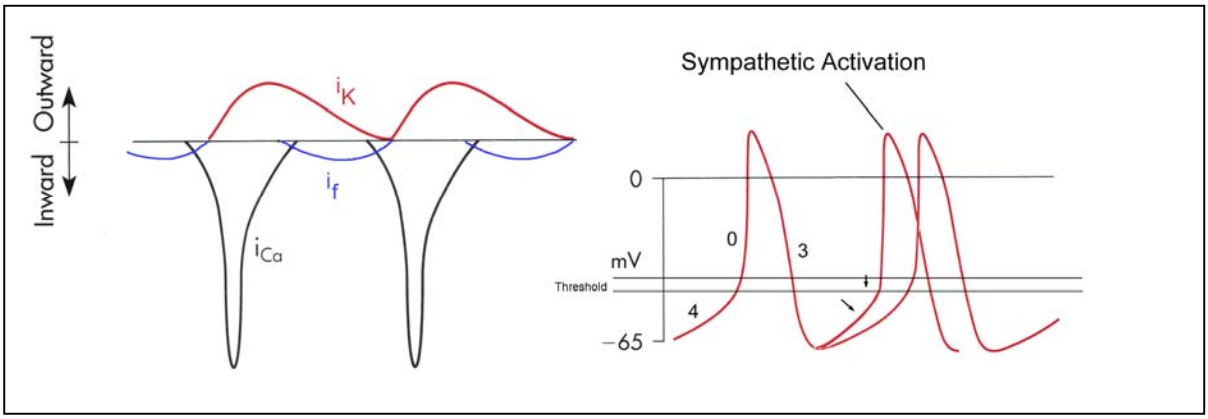
B. Sympathetic - "Fight or Flight", major effects:

Eye – activation of dilator muscle causes mydriasis, innervation of ciliary epithelium regulates production of aqueous humor



Katzung, Basic and ClinicalPharmacology, 9th Ed.McGraw-Hill, New York, 2004.

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



Three main 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, but at negative membrane potentials primarily conducts Na+)
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 – which one depends on the relative density of the receptor population (e.g., alpha$_1$ vs. beta$_2$) expressed in the targeted vascular bed, and the ligand available to mediate the vascular response, (e.g., norepinephrine vs. epinephrine).

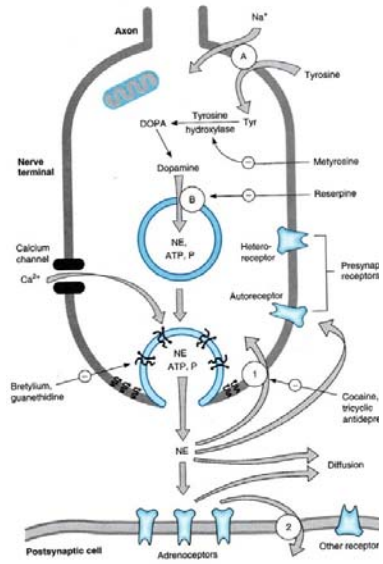
GI tract - decreased motility, can override normal enteric nervous system during fight or flight.

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



from: B.G. Katzung, In: Basic and Clinical Pharmacology, Examination and Board Review, 6th Ed. McGraw-Hill, New York, 2002

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 α_1-, α_2-, β_1- and β_2-receptor subtypes. β_3 receptors are involved in fat metabolism and will become an important therapeutic target in the future.

A. **Distribution** of Adrenergic receptor subtypes

Types of adrenoceptors, some of the peripheral tissues in which they are found, and the major effects of their activation.

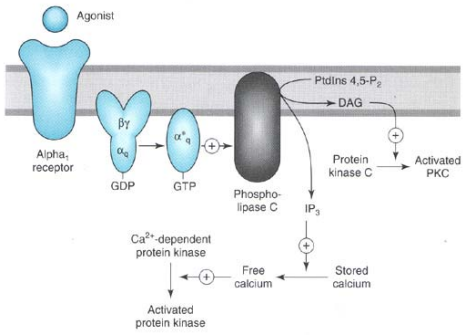
Type	Tissue	Actions
$Alpha_1$	Most vascular smooth muscle	Contracts (↑ vascular resistance)
	Pupillary dilator muscle	Contracts (mydriasis)
	Pilomotor smooth muscle	Contracts (erects hair)
$Alpha_2$	Adrenergic and cholinergic nerve terminals	Inhibits transmitter release
	Platelets	Stimulates aggregation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

Modified from: B.G. Katzung, In: Basic and Clinical Pharmacology, Examination and Board Review, 6th Ed. McGraw-Hill, New York, 2002

B. Adrenergic Receptor Signaling

1. α_1-adrenergic receptors are positively coupled to Phospholipase C (PLC) via $G_{q/11}$ α protein of the heterotrimeric G protein family to increase IP3/DAG.

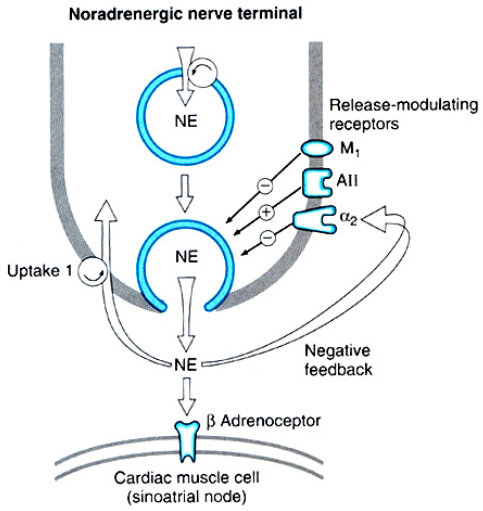
Ex: Vascular smooth muscle contraction. NE, EPI or other α_1 -adrenergic receptor agonists bind to α_1-adrenergic receptor of vascular smooth muscle, the Gαq subunit activates PLC, which liberates inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG). IP3 activates IP3 receptor that also acts as 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.



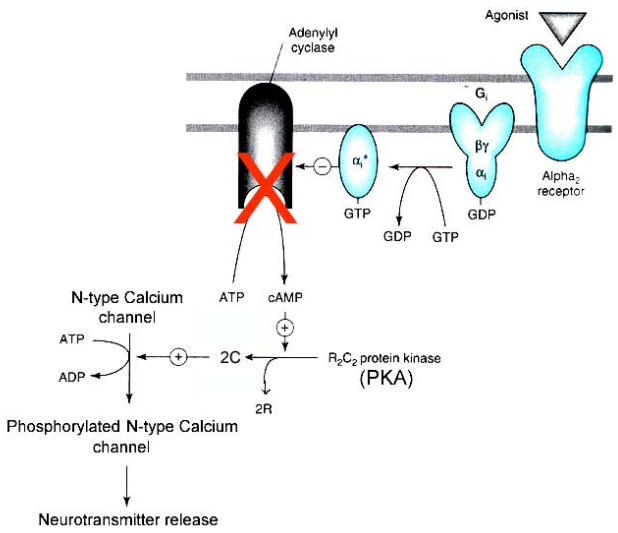
Modified From: Katzung, Basic and Clinical Pharmacology, 9th Ed.McGraw-Hill, New York, 2004.

2. α_2-adrenergic receptors negatively couple to adenylyl cyclase via Gαi subunit which inhibits cAMP formation.

Ex: Pre-synaptic α_2 receptor activation decreases neurotransmitter release (reduced calcium influx). Agonist ligand binds to pre-synaptic α_2 adrenergic receptor and inhibits adenylyl cyclase in the pre-synaptic cell which reduces cAMP and, in turn, reduces activation of phosphokinase A (PKA). Consequently, phosphorylation of N-type calcium channels on nerve terminals is reduced, thereby reducing calcium influx during membrane depolarization and reducing vesicular release of neurotransmitter.



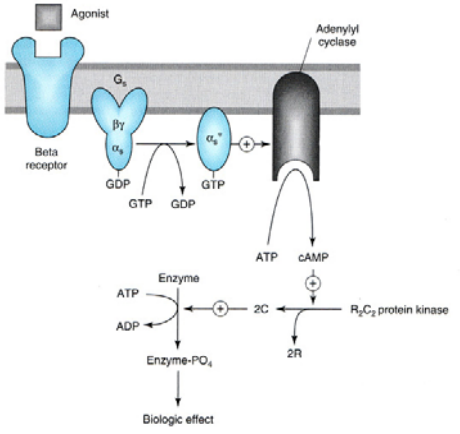
from: B.G. Katzung, In: Basic and Clinical Pharmacology, Examination and Board Review, 6th Ed. McGraw-Hill, New York, 2002



Modified From: Katzung, Basic and Clinical Pharmacology, 9th Ed. McGraw-Hill, New York, 2004

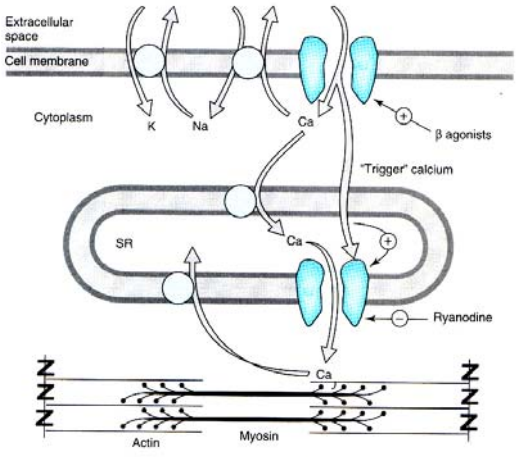
3. β_1-adrenergic receptors positively couple to adenylyl cyclase via Gαs-proteins – increases cAMP

EX: Positive chronotropy. Activation of adenylyl cyclase and increase of cAMP activation of PKA stimulates phosphorylation of calcium channels in the membrane of sinoatrial node cells leading to increased slow inward calcium current and thus faster nodal cell depolarization to the firing threshold. cAMP also directly activates funny current to increase slope of depolarization



Modified From: Katzung, Basic and ClinicalPharmacology, 9th Ed.McGraw-Hill, New York, 2004.

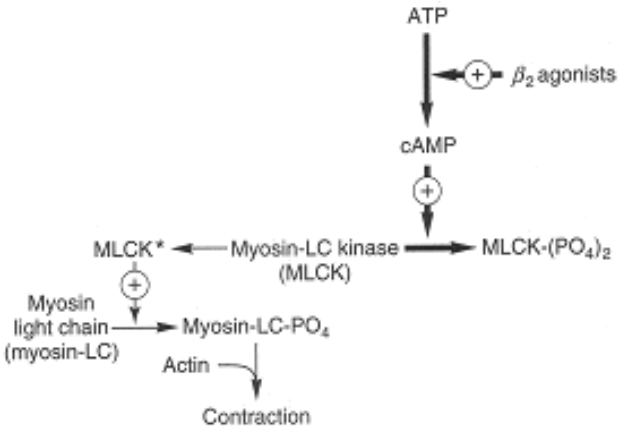
EX: Positive Inotropy: Increased cAMP leads to increased PKA-dependent phosphorylation of L-type calcium channels in myocyte membrane which leads to enhanced calcium influx and larger trigger signal for release of calcium from the sarcoplasmic reticulum into the intracellular space. Trigger calcium also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



from: B.G. Katzung, In: Basic and Clinical Pharmacology, Examination and Board Review, 6th Ed. McGraw-Hill, New York, 2002

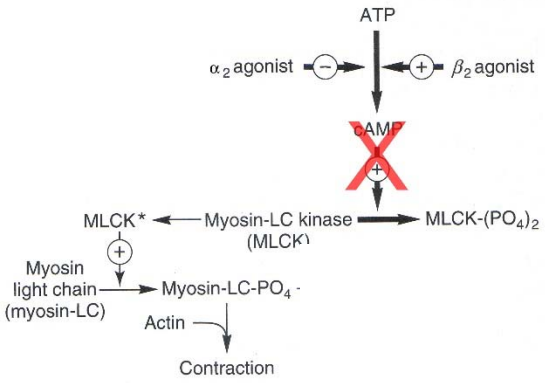
4. β_2-adrenergic receptors positively couple to adenylyl cyclase via Gαs protein - increases cAMP

EX: Vascular smooth muscle relaxation: cAMP activates PKA which phosphorylates and **inhibits** myosin light chain kinase (MLCK). Active MLCK normally phosphorylates the light chain of myosin enabling actin and myosin cross-bridge formation and smooth muscle contraction. Phosphorylation of the MLCK enzyme by PKA also reduces the affinity of MLCK for Ca-calmodulin resulting in further reduction of MLCK activity. Therefore, β_2 adrenergic receptor activation leads to reduced smooth muscle contraction. β_2-adrenergic receptors are highly expressed by smooth muscle of the bronchioles and some vascular beds and therefore regulate the degree of airway constriction as well as peripheral vascular resistance.



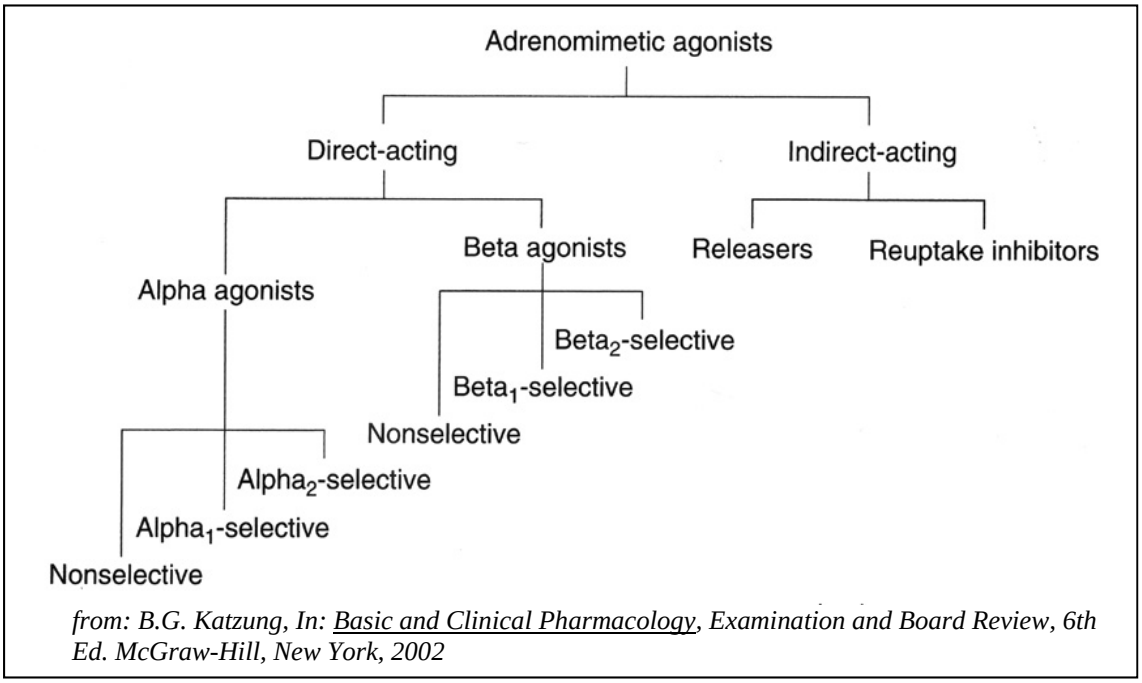
From: Katzung, Basic and ClinicalPharmacology, 9th Ed.McGraw-Hill, New York, 2004.

α_2-adrenergic receptors produce peripheral vasoconstriction through the opposite mechanism of β_2-adrenergic receptors. In this case, the Gαi subunit, to which the α_2 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.



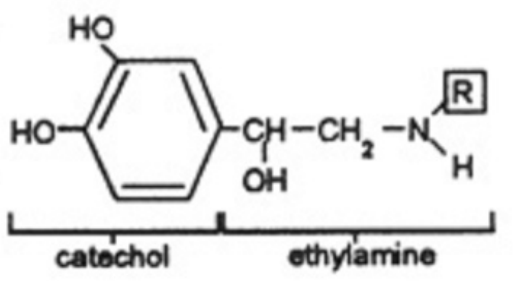
Modified From: Katzung, Basic and ClinicalPharmacology, 9th Ed.McGraw-Hill, New York, 2004.

VI. Adrenergic Agonists



from: B.G. Katzung, In: Basic and Clinical Pharmacology, Examination and Board Review, 6th Ed. McGraw-Hill, New York, 2002

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 β-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.

α_1-adrenergic: epinephrine > norepinephrine >> isoproterenol

α_2 adrenergic: epinephrine > norepinephrine >> isoproterenol

β_2-adrenergic: Isoproterenol > epinephrine >> norepinephrine

β_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.

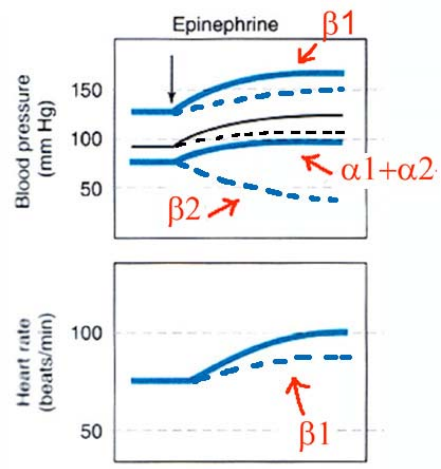
TPR has a predominant effect on diastolic pressure (prevailing arterial pressure after the systolic wave has passed is mediated by arterial vasoconstriction)

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 α_1, α_2, β_1 and β_2 receptors (β–receptor effects predominate at low concentrations), short acting, due to susceptibility to degradation.

Cardiovascular effects: at low infusion rates (<0.01 μg/kg/min, dashed lines in figure at right), β_2 receptor activation causes peripheral vasodilation, thereby decreasing diastolic BP; β_1 receptor activation has positive inotropic and chronotropic effects thereby increasing CO and systolic BP; at higher doses (>0.2 μg/kg/min, solid lines) effects of α_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.



Modified from: B.G. Katzung, In: Basic and Clinical Pharmacology, Examination and Board Review, 6th Ed. McGraw-Hill, New York, 2002

Bronchiole effect: β_2 receptor - bronchodilation, α_1 receptor - decrease in bronchial secretions

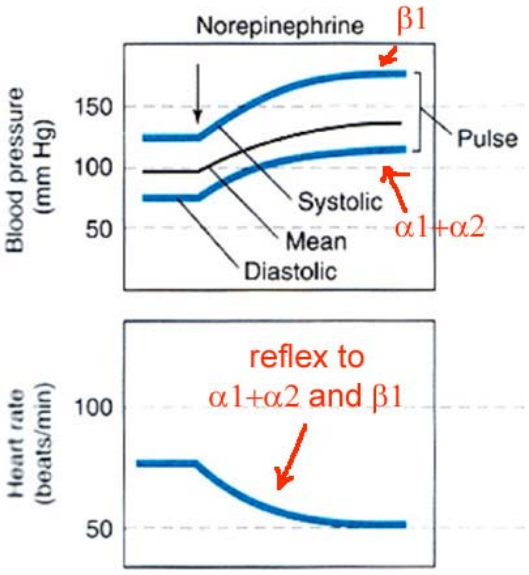
Toxicity: Arrhythmias, cerebral hemorrhage, anxiety, cold extremities, pulmonary edema

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 α_1, α_2 and β_1 receptors with little affinity for β_2 receptors, susceptible to degradation by metabolic enzymes, short half-life give by controlled infusion.

Cardiovascular effects: due primarily to α_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 β_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 β_2 receptors and so has limited effects on bronchiole smooth muscle.



Modified from: B.G. Katzung, In: Basic and Clinical Pharmacology, Examination and Board Review, 6th Ed. McGraw-Hill, New York, 2002

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 β_1 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 (>10μg/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)

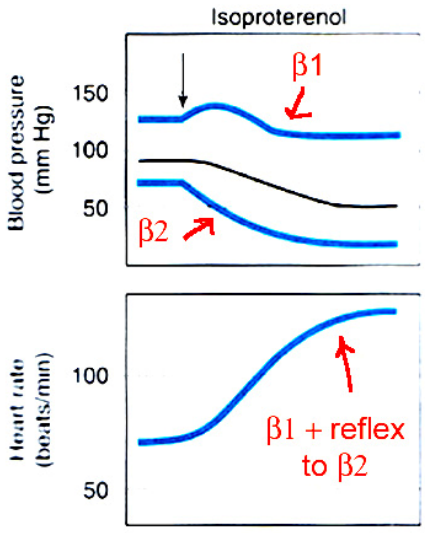
A. Non-selective β-adrenergic agonists: isoproterenol: potent β-receptor agonist with no appreciable affinity for α receptors.
Catecholamine structure means it is susceptible to degradation.

Cardiovascular effects: β_2 receptor activation promotes peripheral vasdilation, 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.



Modified from: B.G. Katzung, In: Basic and Clinical Pharmacology, Examination and Board Review, 6th Ed. McGraw-Hill, New

Contraindications: Angina, particularly with arrhythmias

B. Selective β_1-adrenergic receptor agonist - Dobutamine (adrenergic receptor affinity: $\beta_1 > \beta_2 > \alpha$), though considered by most to be a β_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 β_2-mediated vasodilation and reflex tachycardia. However, no agonist is purely selective so at higher doses, β_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 β-blockade

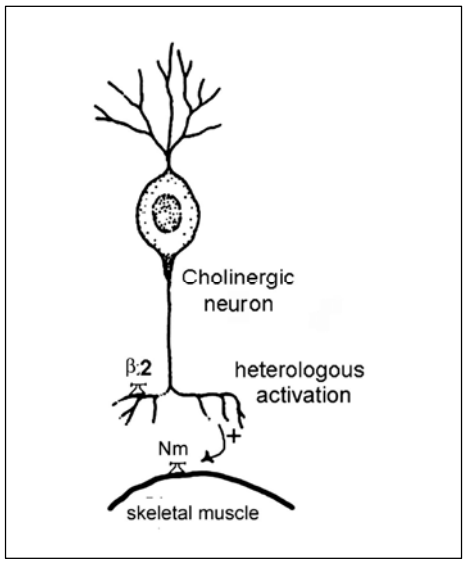
C. Selective β_2 adrenergic agonists: terbutaline, albuterol

Cardiovascular Effects: negligible in most patients due to lack of β_1 activity. However, can cause some β_1 agonist-like response

Bronchioles: Bronchodilation

Pregnant Uterus: Relaxation

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



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

D. Selective α_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

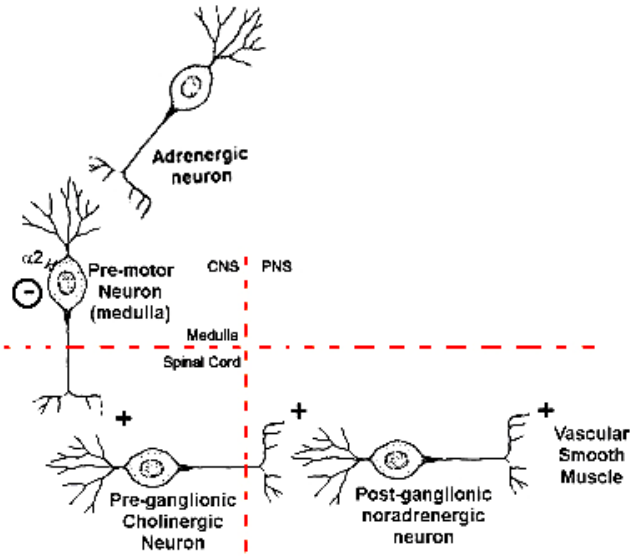
NOTE: Phenylephrine is not a catecholamine and therefore is not subject to rapid degradation by COMT. It is metabolized more slowly; therefore it has a much longer duration of action than endogenous catecholamines.

Contraindications: Hypertension, ….not effective in ventricular tachycardia

E. Selective α_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 α_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.

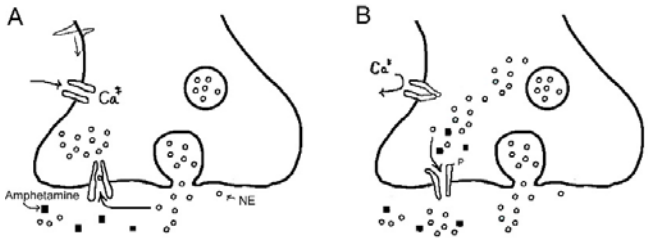


Toxicity: Dry mouth, sedation, bradycardia, withdrawal after chronic use can result in life-threatening hypertensive crisis (increases sympathetic activity).

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".

	Non-Selective (β_1 and β_2)	Cardioselective (β_1)	Partial Agonist (β_1 and β_2)
	PROPRANOLOL, TIMOLOL, NADOLOL	**ATENOLOL, METOPROLOL**	**PINDOLOL**
Heart Rate and Force of Contraction (β_1)	Decrease both rate and force of contraction	Decrease both rate and force of contraction	Decreases both rate and force of contraction. However, bradycardic response is limited due to partial agonist activity.
Peripheral Resistance (β_2)	Increase, due to unopposed vasoconstriction by α_1-receptors	Little effect because β_2-receptors are not blocked	May be slight decrease because of partial β_2 agonist properties
Renin Release (β_1)	Decreased release	Decreased release	Decreased release
Bronchioles (β_2)	Bronchoconstriction, particularly in asthmatics	Less bronchoconstriction in asthmatics, but still not recommended in these patients	Asthmatics have a reduced capacity to dilate bronchioles.
Glucose Metabolism (β_2)	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)	Little effect	Reduced response to epinephrine because partial agonist activity is not as potent as endogenously-released epinephrine

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 β_2 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, 2nd and 3rd degree heart block, cardiogenic shock

C. Cardioselective β_1-blockers: metoprolol, atenolol, esmolol, second generation β-blockers developed for their ability to reduce respiratory side effects.

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

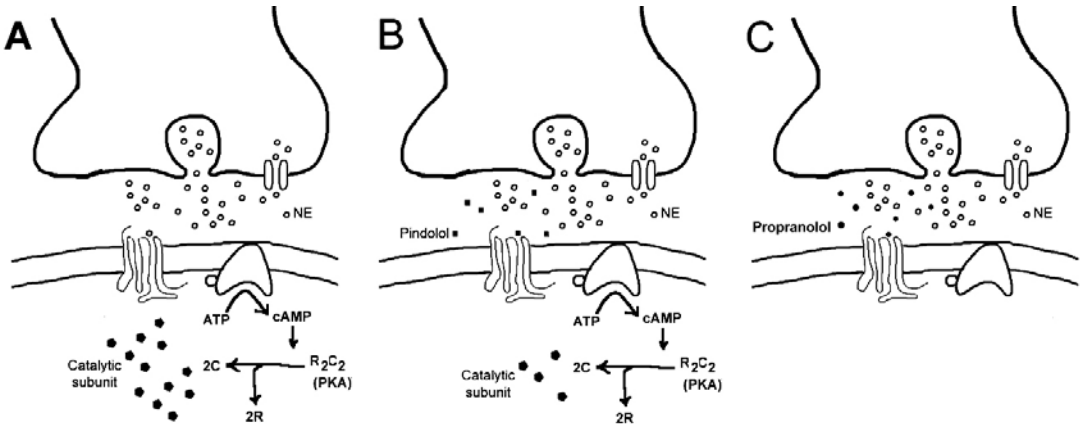
Therapeutic Use: Hypertension (metoprolol, atenolol), angina (metoprolol, atenolol), arrhythmia (esmolol-emergent control). Esmolol has very short half-life (~9 min) so is given i.v. in hypertensive crisis, unstable angina or arrhythmias when longer acting beta blockers may be problematic.

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

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

D. Partial Agonist: pindolol, partial agonist activity at both β_1 and β_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 β signal remains, while β 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.

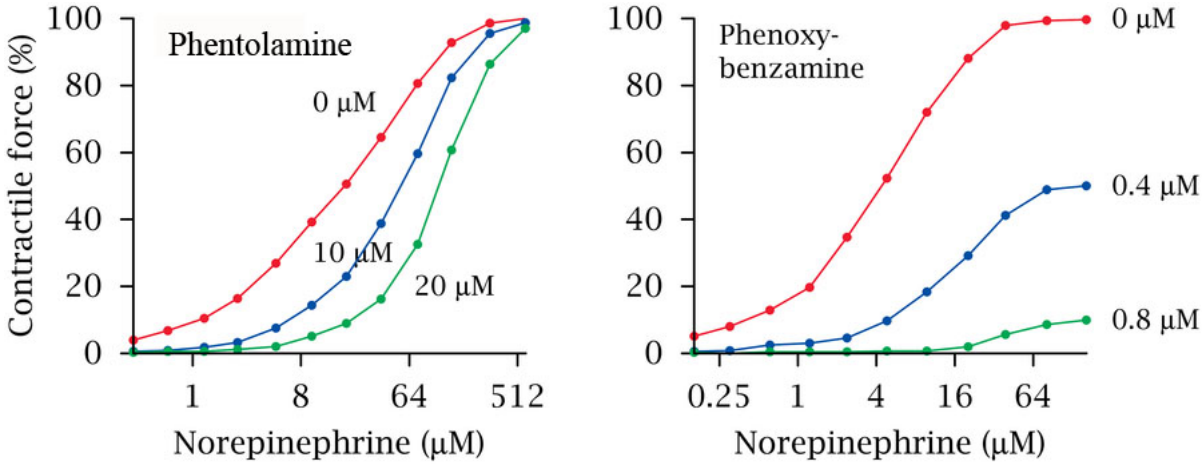
Therapeutic Use: Hypertension in those who are less tolerant of bradycardia and reduced exercise capacity caused by other beta blockers without partial agonist activity

Toxicity: same as for non-selective

Contraindications: Same as above

IX. α-adrenergic receptor antagonists

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



Cardiovascular Effects: Inhibit vasoconstriction therefore, decreases BP, increased inotropy and chronotropy due to blockade of pre-synaptic α_2-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 β_2 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

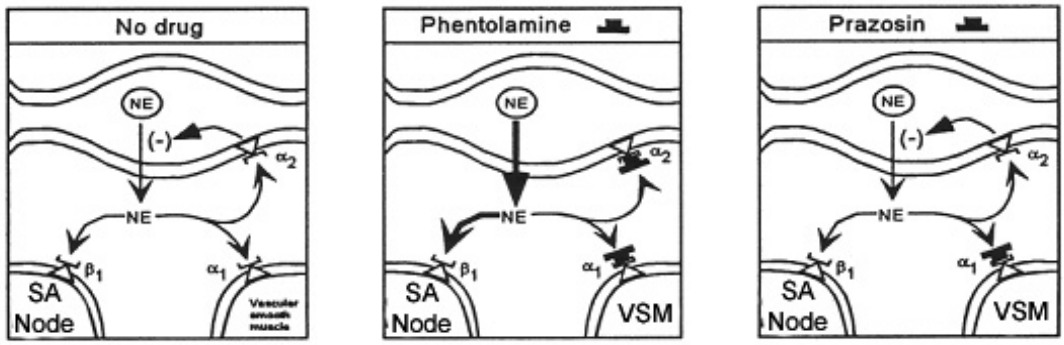
B. Selective α_1-receptor blockers: prazosin, doxazosin, and terazosin:

Cardiovascular Effects: Inhibit vasoconstriction, resulting in vasodilation and decreased BP, produces less cardiac stimulation than non-selective α-blockers due to preservation of α_2-adrenergic function (see figure below).

Modified from T.M. Brody, J. Lamer, K.P. Minnemon, IN: Human Pharmacology, Molecular to Clinic, Mosby 1998

Therapeutic Use: Hypertension, benign prostatic hyperplasia

Toxicity: Syncope, orthostatic hypotension



Generic Name	*Trade Name*	*Half-life*	*Mechanism of action*	*Elimination*	*Indication*
Epinephrine	**Adrenaline Chloride**	**short**	**α and β agonist**	**COMT**-urine	**Anaphylaxis, shock, cardiac arrest and heart block**
Norepinephrine	Levophed	**short**	**α-agonist, β1-agonist**	**MOA and COMT** - urine	**Acute hypotension due to shock**
Dopamine	**Dopamine**	**~2min**	**β-agonist, some α-agonist activity**	**MOA and COMT**	**Cardiogenic shock**
Isoproterenol	Isuprel	**short**	**β-agonist**	**COMT**-urine	**Transient heart block,** broncho-spasm during anesthesia
Dobutamine	Dobutrex	**2-3 min**	**β_1-agonist**	**COMT**-urine	**Short term Rx for low cardiac contractility**
Terbutaline	Brethine	2.9	**β2-agonist**	Urine	**Prevent and reverse bronchospasm in asthma, bronchitis and emphysema**
Albuterol	Ventolin	5 hr	**β2-agonist**	Urine	**Bronchial SM relaxation**
Phenylephrine	Neo-synephrine	**< 1 hr**	**α1-agonist**	MAO	**Pressor agent for anesthesia, nasal congestion, dilate pupil for eye exam, supraventricular tachycardia**
Clonidine	Catapres	12-16 hrs	**α2-agonist**	Urine	**Hypertension,** analgesia
Amphetamine	Adderall	10-13 hr	**Indirect sympathomimetic**	Urine	**ADHD**
Methylphenidate	Ritalin	2-3 hr	**Indirect sympathomimetic**	Urine	**ADHD**
Ephedrine	**Ephedrine**	3-6 hr	**Indirect sympathomimetic**	Urine	**Pressor agent with anesth.**

Methylphenidate	Ritalin	2-3 hr	**Indirect sympathomimetic**	Urine	**ADHD**
Pseudo-ephedrine	Sudafed	4.3-8 hr	**Indirect sympathomimetic**	Liver	**Nasal decongestion**
Tyramine	tyramine	**Normally very short**	**Displaces NE**	**MAO**	**Not therapeutic**
Propranolol	Inderal	**4 hr**	**β-blocker**	Liver	**Hypertension, angina due to atherosclerosis, MI**
Timolol	Blocaden (po) Timoptic (opth)	**4 hr**	**β-blocker**	Liver	**Glaucoma.**
Nadolol	Corgard	**20-24 hr**	**β-blocker**	Urine	**Long-term angina, hypertension**
Atenolol	Tenormin	6-7 hr	**β1-blocker**	Urine	**Hypertension, angina, MI**
Metoprolol	Lopressor, Toprol	3-7 hr	**β1-antagonist**	Liver	**Hypertension, long-term angina rx**
Pindolol	Visken	3-4 hr	**β-antagonist (with partial agonist activity)**	Urine	**Hypertension**
Esmolol	Breviblock	**~9 min**	**β1-blocker**	Esterases in RBC	**Supraventricular tachycardia**
Phenoxybenzamine	Dibenzyline	24 hr (iv)	**α-blocker**	Conjugates to receptor	**Pheochromo-cytoma**
Phentolamine	Regitine	19 min	**α-blocker-**	Urine	Test for pheochromo-cytoma, **rx for pheo. before surg.,** Catecholamine extravasation
Prazosin	Minipress	2.3 hr	**α-blocker**	Liver	Hypertension

Doxazosin	Cardura	22 hr	**α1-antagonist**	Liver	Prostatic hyperplasia, hypertension
Terazosin	Hytrin	12 hr	**α1-blocker**	Urine and fecal	**Prostatic hyperplasia, hypertension**
Epinephrine	**Adrenaline Chloride**	**short**	**α and β agonist**	**COMT**-urine	**Anaphylaxis, shock, cardiac arrest and heart block**
Norepinephrine	Levophed	**short**	**α-agonist, β1-agonist**	**MOA and COMT** - urine	**Acute hypotension due to shock**

CHOLINERGIC AGONISTS AND ANTAGONISTS

Date: August 21, 2017 (9:30-10:20 AM) **Recommended Reading: Basic and Clinical Pharmacology**, 13th Edition, Katzung, *et. al.*, pp. 105-120.

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.

13. Describe the symptoms of atropine poisoning and its treatment.

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

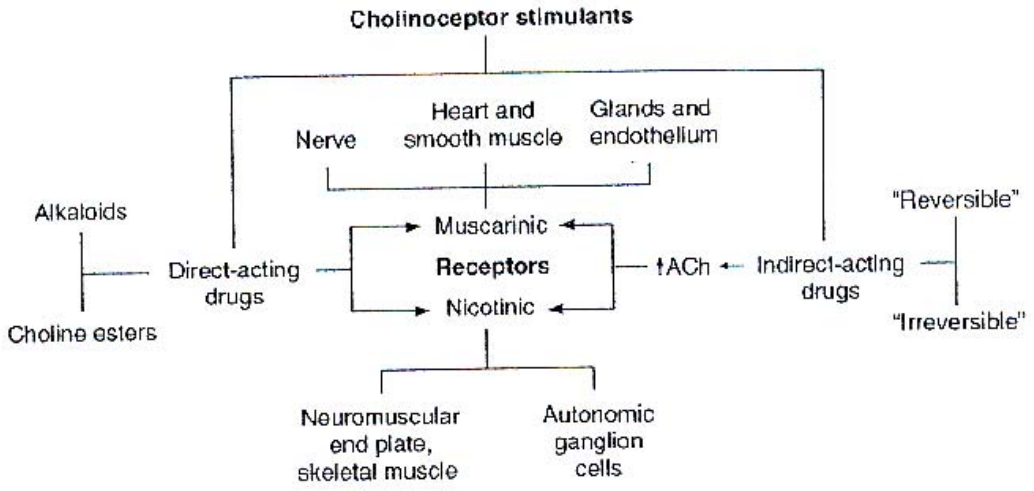
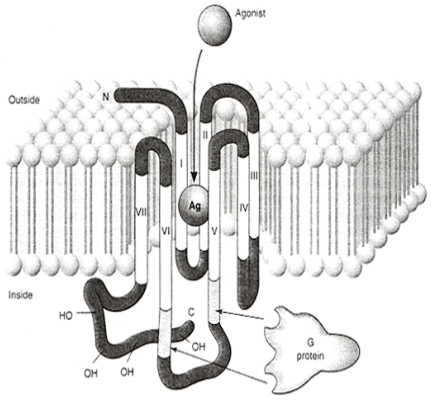


Fig. 7-1 From B.G. Katzung, In: Basic and Clinical Pharmacology Katzung 10th Ed. Pg. 94

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 (M_1, M_2, M_3). 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



From B.G. Katzung, In: Basic and Clinical Pharmacology 10th Ed

beds, and at cortical and subcortical sites in the central nervous system.

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

Muscarinic Receptors

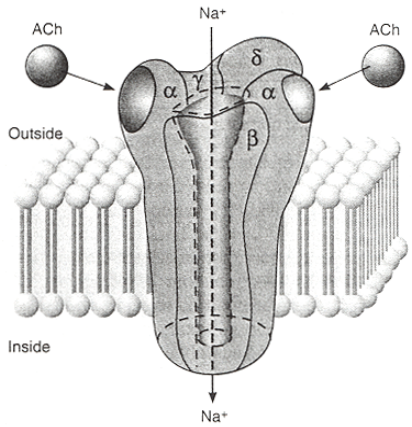
M1	Increased IP3, DAG and $[Ca^{2+}]$	Activates myenteric plexus
M2	Opens K channels	Decreases heart rate and contraction (decreases cardiac output)
	Decreased cAMP, decreased Ca^{2+}	Inhibits norepinephrine release from sympathetic nerve terminals
M3	Increased IP3, DAG and $[Ca^{2+}]$	Contacts circular ciliary muscle (pupillary constriction), ciliary muscle (near-vision accommodation), bronchiolar muscle, GI smooth muscle, uterine muscle, and bladder detrusor muscle (micturition)
		Relaxes vascular muscle (via nitric oxide from endothelium)
		Stimulates secretions of GI tract, eccrine sweat glands, tear glands, salivary glands, pancreas digestive fluids, and liver bile

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

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



From B.G. Katzung, In: Basic and Clinical Pharmacology 10th Ed

A. PROTOTYPICAL COMPOUNDS:

1. **NICOTINE** (Nicotrol): Stimulates N_N 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 electro convulsive shock therapy (more detail in Neuromuscular Relaxants lecture). Contraindicated in pts with family history of familial hyperthermia, or pts with skeletal muscle myopathies, or several days after multiple and wide spread skeletal muscle injury.

IV. MUSCARINIC AGONISTS (PARASYMPATHOMIMETIC AGENTS)

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

A. QUATERNARY NITROGEN ANALOGS:

1. ACETYLCHOLINE (prototype compound): $(CH_3)_3N^+-CH_2-CH_2-O-C(=O)-CH_3$

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-ß-Methylcholine): $(CH_3)_3N^+-CH_2-CH(CH_3)-O-C(=O)-CH_3$

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): $(CH_3)_3N^+-CH_2-CH_2-O-C(=O)-\mathbf{NH_2}$

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

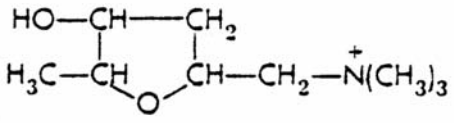
4. BETHANECHOL (Urecholine): $(CH_3)_3N^+-CH_2-CH(\mathbf{CH_3})-O-C(=O)-\mathbf{NH_2}$

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

C. NATURALLY OCCURING TERTIARY AMINES:

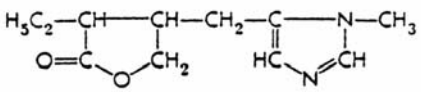
Several tertiary amine compounds with muscarinic agonist properties are available. Some of these are natural alkaloids, others have been prepared synthetically. The charge of the tertiary amine determines if the compound can cross the blood brain barrier.

1. MUSCARINE:

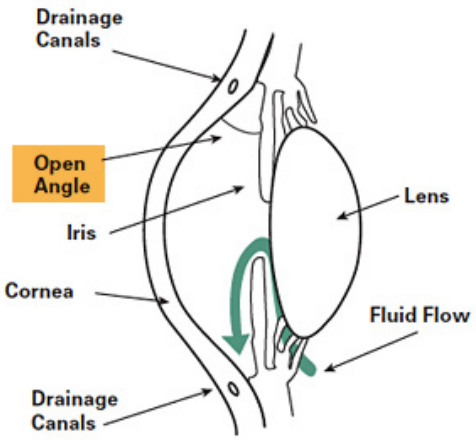


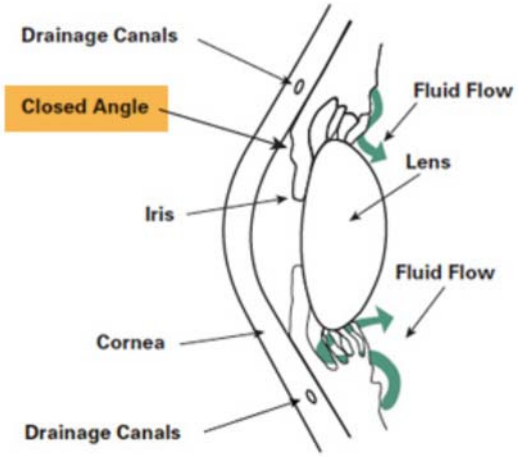
Alkaloid in wild mushrooms of the Clitocybe inocybe species. Prototype compound, though not used clinically. Historically one of the first cholinomimetic drugs to be studied. Pure muscarinic activity. Resistant to hydrolysis by acetylcholinesterase (no ester moiety). It is clinically important as a source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

2. PILOCARPINE:



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





V. INDIRECTLY ACTING CHOLINERGIC AGONISTS (CHOLINESTERASE INHIBITORS)

Acetylcholinesterase catalyzes the hydrolysis of acetylcholine

AChE
/
ACETYLCHOLINE → 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:

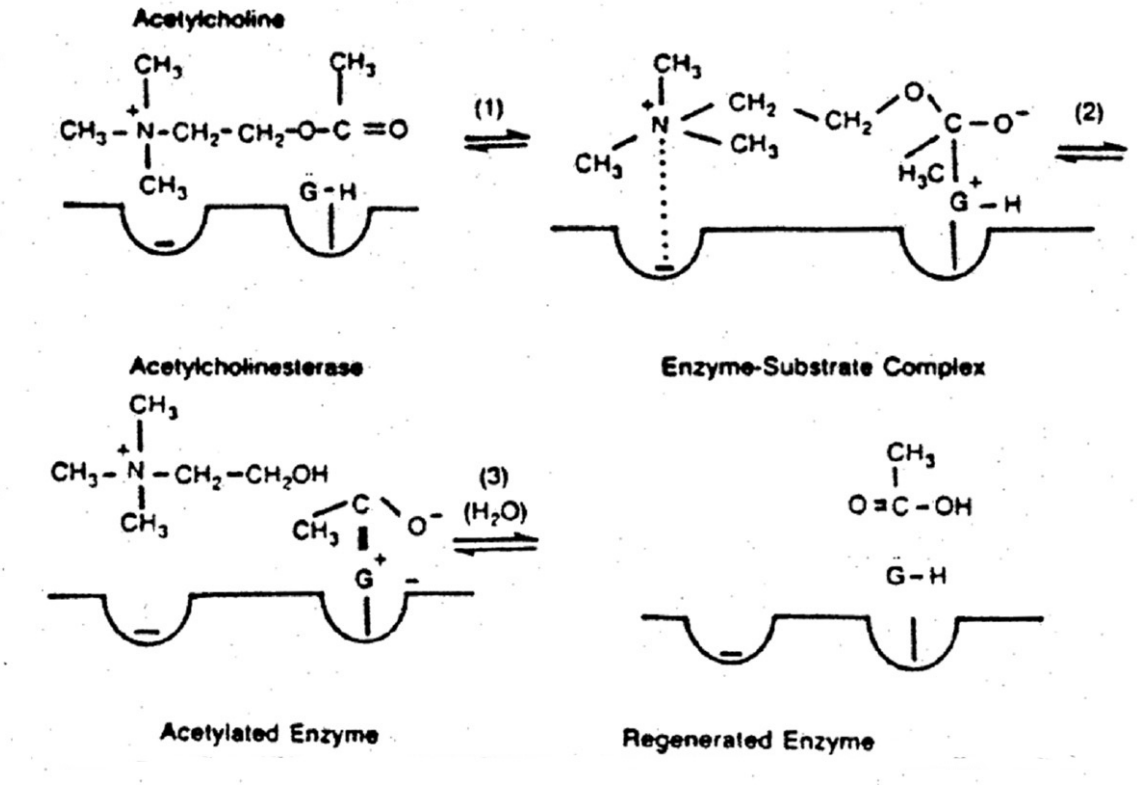
A. Acetylcholinesterase (AChE, true, specific, red blood cell cholinesterase).
Distribution: Neurons, motor endplate, red blood cells.
Function: Hydrolysis of acetylcholine liberated in synaptic cleft

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 cholinoceptive 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)



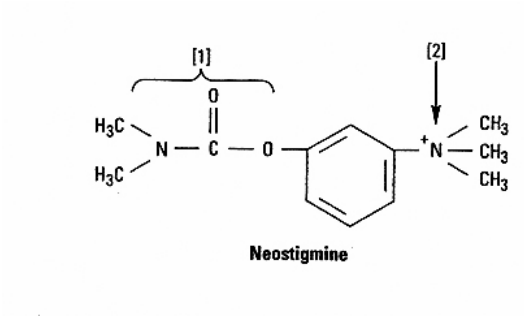
Acetylcholinesterase inhibitors bind competitively to the active sites on the acetylcholinesterase molecule with which acetylcholine normally interacts, prevent acetylcholine from interacting with the enzyme, and protect acetylcholine from being degraded.

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.

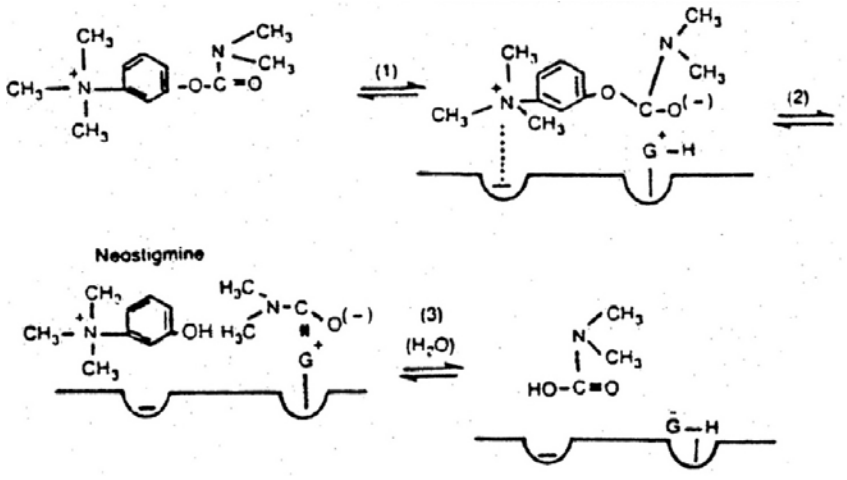
A. REVERSIBLE CHOLINESTERASE INHIBITORS: molecular mechanism

CLINICALLY USED ACETYLCHOLINESTERASE INHIBITORS

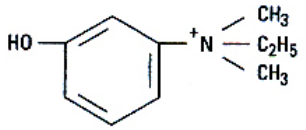
1. NEOSTIGMINE:



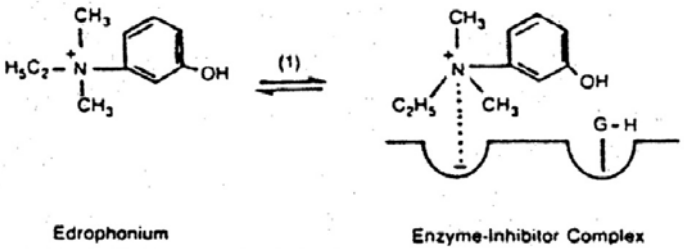
Contains a quaternary nitrogen, and thus poorly penetrates blood brain barrier. Inhibits acetylcholinesterase and has direct stimulatory effect on nicotinic receptors at the skeletal muscle endplate. Therefore used to reverse neuromuscular blockade (see neuromuscular relaxant lecture). Also used in the 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 acetycholinesterase is longer than acetylcholine's, as the bond it forms is more stable. As such, it can effectively block cholinesterase from binding acetylcholine for over an hour



2. EDROPHONIUM:



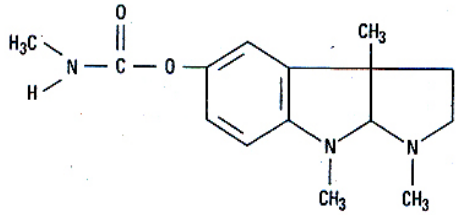
Similar in structure to neostigmine, but lacks an ester functional group. Inhibits cholinesterases and stimulates nicotinic receptors at the neuromuscular junction at lower doses than those which stimulate other cholinergic receptors. Has a very rapid onset of action, and a very short duration of action (10-15 min). Clinically used to establish diagnosis of myasthenia gravis or to make a differential diagnosis between progression of myasthenic weakness and a cholinergic crisis (i.e., excessive Ach) due to cholinesterase toxicity.



Exessive cholinesterase inhibition can cause neuromuscular block (see neuromuscular relaxant lecture), resulting in muscle weakness which can mimic and be mistaken for myasthenia gravis progression. Treatment with short acting cholinesterase inhibitor reduces symptoms if muscle weakness is due to disease progression. It will worsen symptoms if due to cholinesterase toxicity. Side effects include bradycardia and cardiac standstill. Contraindicated in mechanical block of intestine and urinary tract.

3. PHYSOSTIGMINE:

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

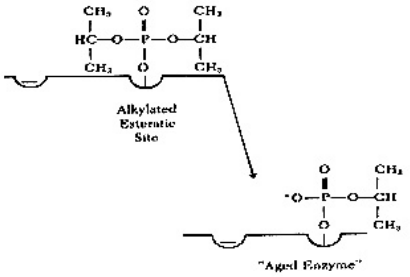


4. DONEPEZIL:

Indicated in the treatment of Alzheimer's disease. Reversible inhibitor of acetylcholinesterase in the CNS, high bioavailability, long-half life allows once a day oral dosing. Data suggest some improvement of cognition in patients with moderate to severe Alzheimer's Disesase.

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.



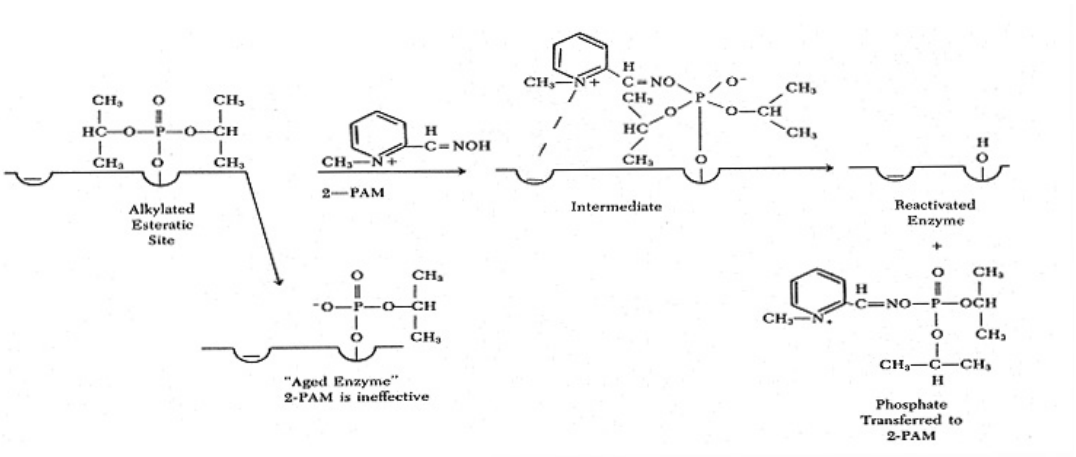
TOXICITY OF ORGANOPHOSPHATES (SLUDGE or DUMBBELLS)

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

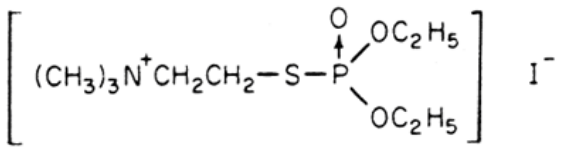
Treatment of severe organophosphate poisoning consists of:

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

MECHANISM OF ACTION OF PRALIDOXIMINE (2-PAM)



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

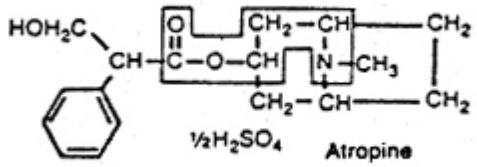


VI. MUSCARINIC ANTAGONISTS (PARASYMPATHOLYTIC AGENTS)

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

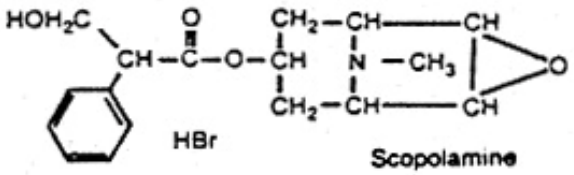
A. MUSCARINIC ANTAGONISTS:

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



Atropine

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.



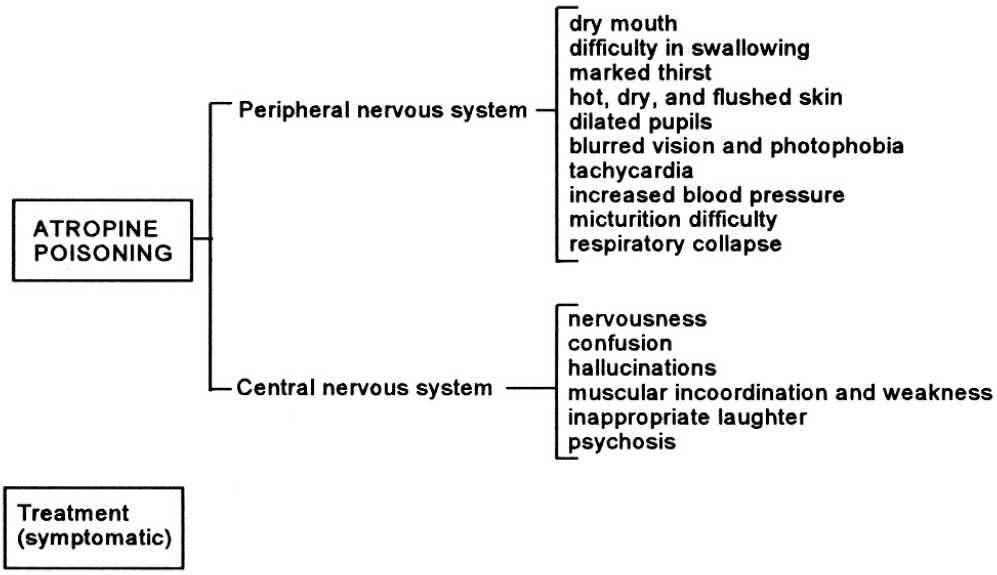
Scopolamine

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:



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

Modified from B.D. Bhagat, In: Mode of Action of Autonomic Drugs. Graceway Publishing Company, 1979.

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

Generic Name	Trade Name	Half-Life	Mechanism of action	Elimination	Rx
Nicotine	Nicotrol	1-2 hrs	**Activation of neuronal Nicotinic receptors**	Urine	**Withdrawal symptoms of smoking cessation**
Succinyllcholine	Anectine	5-8 min	**Depolarizing block of muscle nicotinic receptors**	**Butyrl cholinesterase**	**Neuromuscular block for electroconvulsive shock therapy or emergency intubation**
Acetylcholine	Not-used clinically	**~150 msec**	**Nicotinic and muscarinic agonist**	**AchE**	**None**
Methacholine	Provocholine	rela-tively short	**Muscarinic agonist**	AchE	**Diag. of subclinical asthma, or test for severity of asthma**
Carbachol	Miostat or Carbastat	Dura-tion 4-8 hrs topic-ally or 24 hrs intra-ocular	**Muscarinic and nicotinic receptor agonist**	AchE	**Miotic agent in ocular surgery, to reduce pressure following ocular surgery**
Bethanechol	Urecholine	~1 hr	**Muscarinic agonist**	unknown	**Urinary retention, bladder atony**
Pilocarpine	Salagen	**~1hr**	**Muscarinic agonist**	AchE	**Dry mouth from head and neck radiation or** Sjögren's syndrome**, Narrow angle glaudoma**
Neostigmine	Prostigmin	50-90 min	**AchE inhibitor**	AchE and plasma esterases	**Myasthenia gravis, reverse neuromusc. block**

Edrophonium	Tensilon, Enlon or Reversol	**~10 min**	**AchE inhibitor**	Bile	**Diag of myasthenia gravis, reversal of neuromusc. block**
Physostigmine	Antilirium	45-60 min	**Reversible AchE inhibitor**	AchE	**Delirium from anticholinergic drugs, glaucoma**
Donepezil	Aricept	~70hrs	**Reversible AchE Inhibitor**	Liver	**Alzheimer's Dx.**
Pralidoxime	2-PAM	**~75 min**	**Peripheral AchE reactivator**	Urine	**Respiratory muscle weakness in organophosphate poisoning**
Echothiophate	Phospholine	**Very long**	**Irreversible AchE Inhibitor**	unknown	**Open angle glaucoma**
Atropine	Atropine	2 hr	**Muscarinic antag**	Liver	**Excess secretions during surgery, the ↑ freq and urg. assoc with cystitis, hypertonic gut, organophosphate poisoning, bradycardia**
Scopolamine	Isopto	~9.5 hrs for trans-dermal, 24 for intra	**Muscarinic antagonist**	unknown	**Motion sickness, anti-salilagogue in surgery**
Glycopyrrolate	Robinul	0.5-2 hrs	**Muscarinic receptor antagonist**	urine	**Protects against excessive muscarinic activation during reversal of neuromuscular blockade, anti-salilagogue**

NEUROMUSCULAR RELAXANTS

Date: August 21st – 10:30-11:20 AM
Recommended Reading: Basic and Clinical Pharmacology, 13th Edition, Katzung, *et. al.*, pp. 455-471.

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.

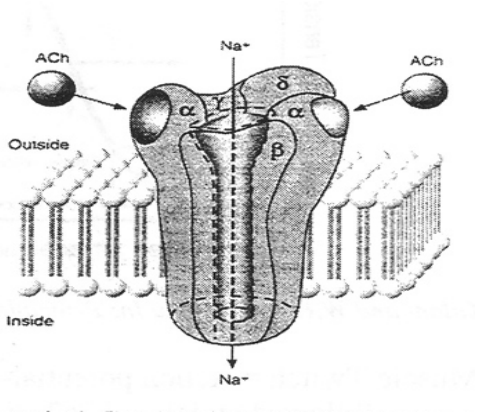
NEUROMUSCULAR RELAXANTS

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



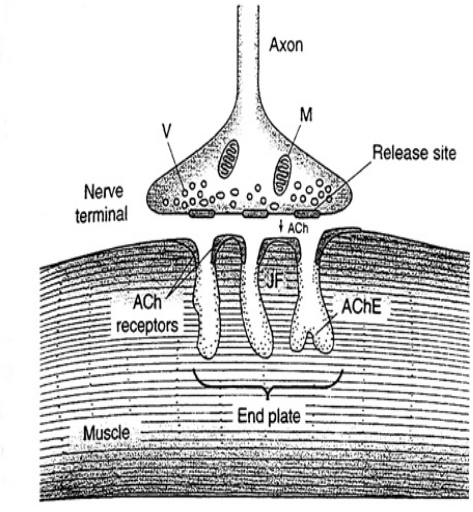
From: B.G. Katzung, Basic & Clinical Pharmacology, Appleton & Lange, 1998.

1. Nicotinic Receptors - Pentomeric 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 α, 1 β, 1 γ, 1 ε
   Ganglionic receptor – 2 α, 3 β

2. Acetylcholine is released from pre-synaptic 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.

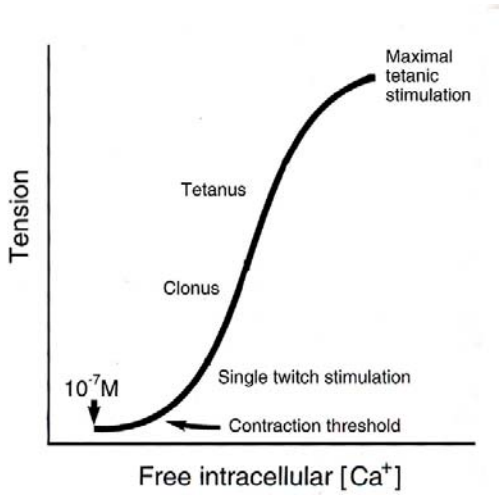


From B.G. Katzung, Basic and Clinical Pharmacology, 9th Ed., McGraw Hill, New York, 2004

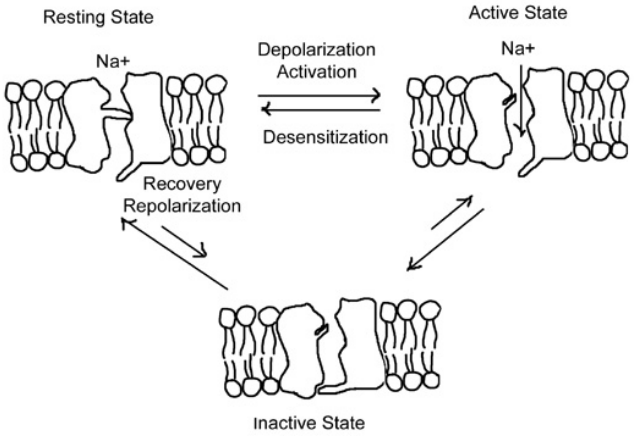
4. Muscle Twitch = Action potential-dependent increase in [Ca2+]i followed by fall in [Ca2+]i due to sequestration by sarcoplasmic reticulum

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

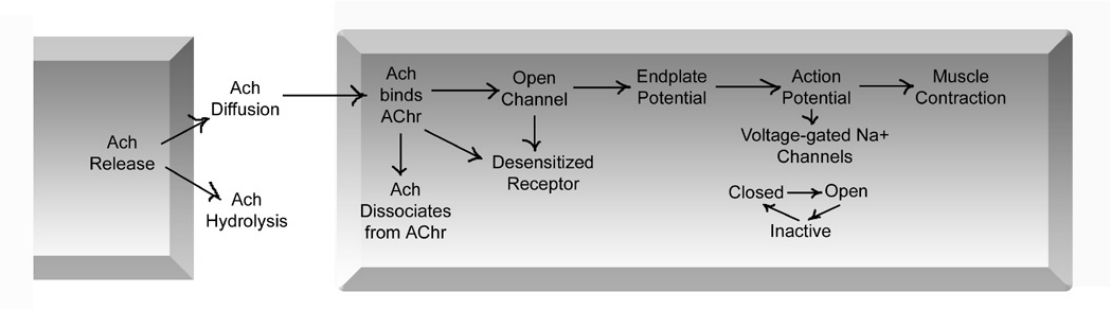


5. Propagation of the action potential generated by sufficient acetylcholine receptor (AchR) agonist binding is dependent upon availability of voltage-gated Na^+ channels in the resting state. There



KES

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)

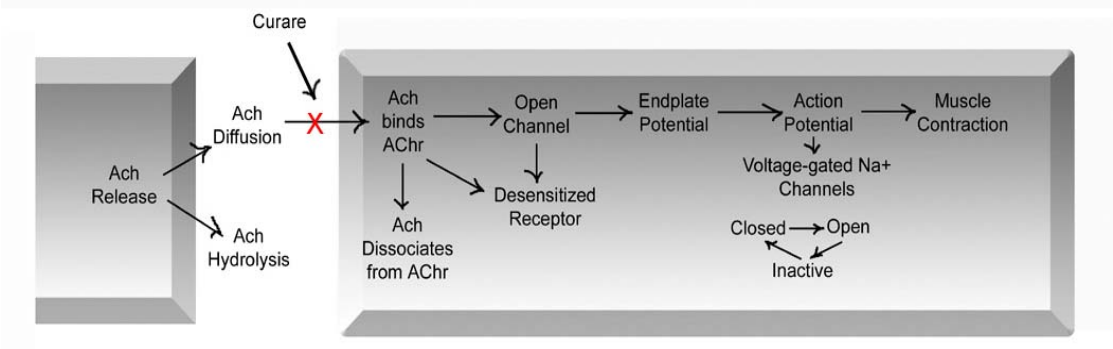
C. NON-DEPOLARIZING BLOCKING DRUGS - COMPETITIVE ANTAGONISTS (e.g. D-TUBOCURARINE, PANCURONIUM, VECURONIUM)

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

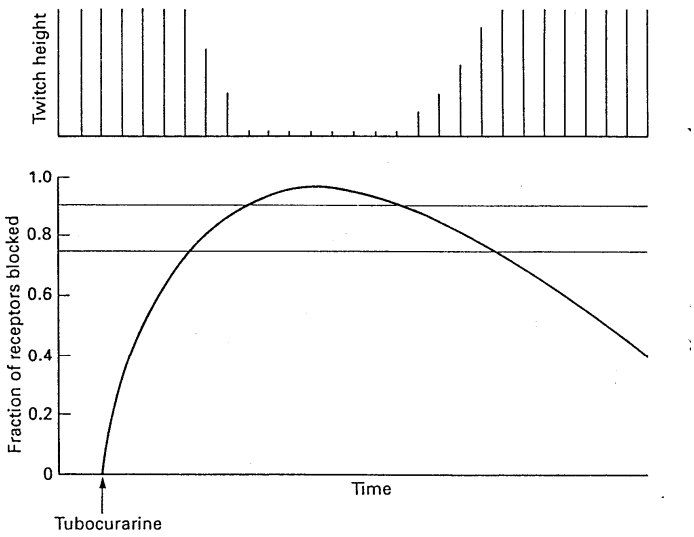
Competitive binding of curare-like drugs to the nicotinic receptor prevents opening of nicotinic receptor ion channel thus preventing membrane depolarization and end-plate potentials. Numerous curare type drugs have been developed. Choice of drug depends on preferred pharmacokinetic characteristics and 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 (tβ1/2) of a subset of commonly used non-depolarizing neuromuscular blockers.

A. Pharmacokinetics
   Rapid distribution
   $T_{1/2}$ 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!).

Pharmacokinetic Data			
Drug	**V_d** (ml / kg)	**C**l (ml / kg / min)	**$t_{\beta ½}$** (min)
Pancuronium	140 - 205	1.2 - 1.6	75 - 107
Tubocurarine	297 - 522	1.8 - 3.0	107 - 237
Vecuronium	270	5.2	65-75
Mivacurium	333	4.6	~ 3 - 5
Rocuronium	217	4.9	~ 60

Mode of Elimination			
Drug	Percentage Elimination		
	Renal	**Hepatic**	**Metabolic**
Pancuronium	30 - 80	10	15 - 40
Tubocurarine	40 - 60	40 - 60	0
Vecuronium	> 25	20	?
Rocuronium	10 - 20	80 - 90	-
Mivacurium			+++



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:

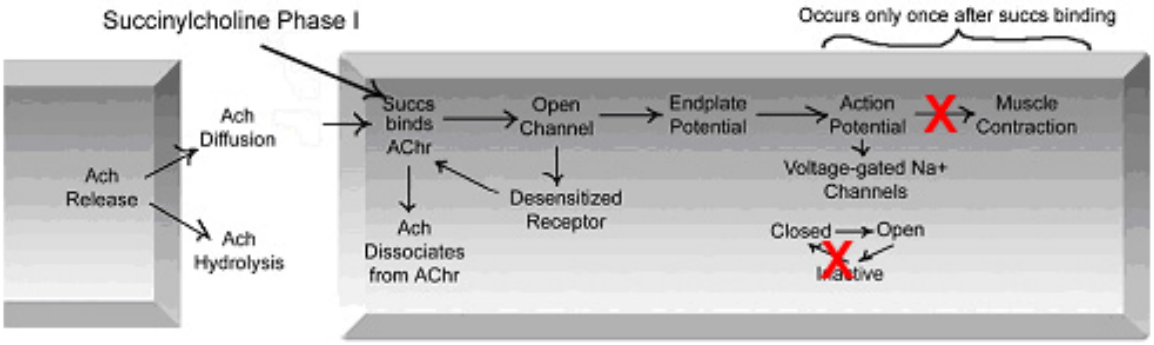
Inhalation anesthetics (enhances effect)
Antibiotics (enhance effect, particularly aminoglycosides)
Local anesthetics

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).



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

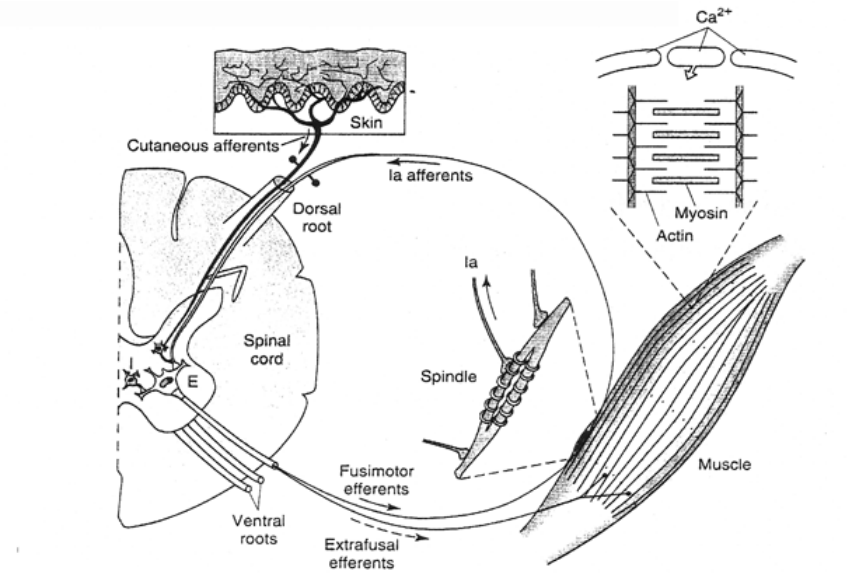
8. CONTRAINDICATIONS:

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

III. SPASMOLYTIC DRUGS

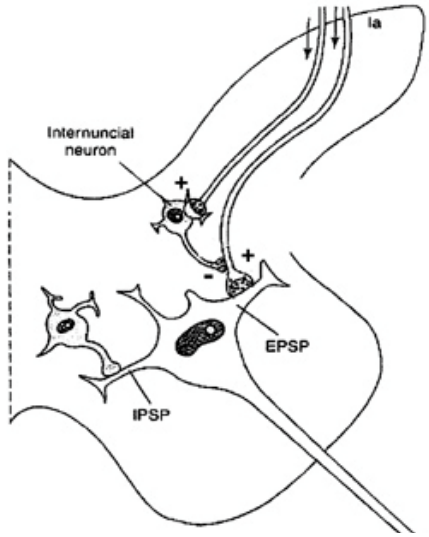
A. SKELETAL MUSCLE RELAXANTS:

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



Katzung, fig. 27-10, p. 442

2. Treatment of spasticity

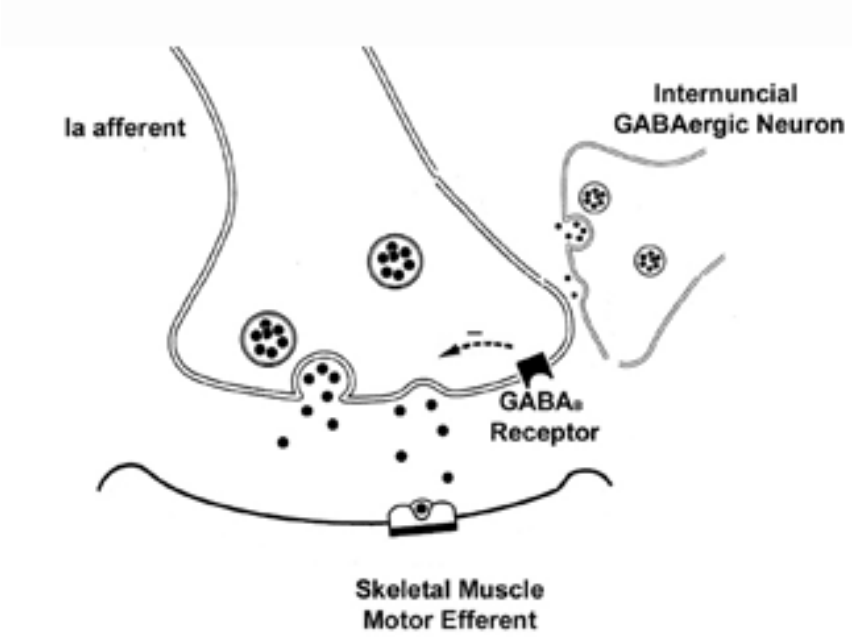


Katzung, fig. 27-11, p. 438

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$_B$ agonist

Reduces calcium influx, and therefore reduces the release of excitatory transmitters and substance P in spinal cord

Clinical usages:

Spinal spasticity

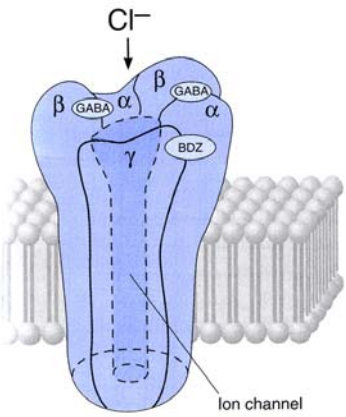
Spasticity due to multiple sclerosis

Side effects:

Drowsiness,

Mental disturbance

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



Mechanism of action:

Facilitate GABA mediated pre-synaptic 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 I N LECTURE: for more detail consult on-line reference www.rxlist.com/cgi/generic/albut2_cp.htm. Text in bold font are important.

Generic Name	**Trade Name**	**Duration of action**	**Mechanism of Action**	**Elimination**	**Rx**
Succinylcholine	Anectine	**Duration < 8 min**	**Depolarization Blockade of muscle nicotinic receptors**	**Metab by plasma cholinesterase**	**Tracheal intubation or ECT**
Pancuronium	Pavulon	**Duration 30-60 min**	**Non-depolarizing blockade of muscle Nicotinic receptors**	**Primarily renal excretion**	**Adjuvant in surgical anesthesia, sp. Abdominal wall relaxation & orthopedic procedures**
D-tubocurarine	Generic	**Duration >60 min**	**Non-depolarizing blockade of muscle nicotinic receptors**	**Liver clearance & renal elimination**	**Prototype** only used in lethal injection

Rocuronium	Zemuron	**Duration ~25 min.**	**Non-depolarizing blockade of muscle nicotinic receptors**	**Liver**	**Intubation, muscle relaxation during surgery or ventilation**
Mivacurium	Mivacron	**Duration 15-20 min**	**Non-depolarizing blockade of muscle nicotinic receptors**	**Plasma cholinesterase**	**Intubation, muscle relaxation during surgery or ventilation in pts w/ renal failure**
Vecuronium	Norcuron	**Duration 30-45 min.**	**Non-depolarizing blockade of muscle nicotinic receptors**	**Liver metab. & clearance, renal elimination**	**Adjuvant in surgical anesthesia, sp. Abdominal wall relaxation & orthopedic procedures**
Baclofen	Baclofen	1.5 hrs.	**Inhibits neurotransmitter release from skeletal muscle sensory afferent**	Urine	**Muscle spasticity assoc. with multiple sclerosis or spinal cord injury**
Diazepam	Valium	43 hr	**Benzodiazepine receptor agonist**	Liver	**Muscle spasm due to local injury (inflammation), muscle spasticity due to loss of descending inhibitory input, e.g. cerebral palsy**
Tizanidine	Zanaflex	2.5 hr	**Centrally acting α2 agonist**	Liver	**Muscle spasticity due to spinal cord injury or multiple sclerosis**
Dantrolene	Dantrium	8 hr	**Uncouples excitation-contraction of skeletal muscle (blocks ryanodine receptor)**		**Muscle spasm, Malignant hyperthermia**

Non Steroidal Anti-inflammatory Drugs (NSAIDs) I & II

Date: Monday August 21st, 2017 1-3 pm

Relevant reading:
Basic and Clinical Pharmacology- B.G. Katzung, 13th Edition, Chapter 36 618-625

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™)
Etodalac (Lodine™)

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

4. Non-NSAID Related Analgesic
Acetaminophen (Tylenol™/Paracetemol™)

Non Steroidal Anti-inflammatory Drugs (NSAIDs) I & II

Date: Monday August 21st, 2017 1-3 pm

Relevant reading:
Basic and Clinical Pharmacology- B.G. Katzung, 13th Edition, Chapter 36 618-625

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™)
Etodalac (Lodine™)

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

4. Non-NSAID Related Analgesic
Acetaminophen (Tylenol™/Paracetemol™)

(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 muscoskeletal 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

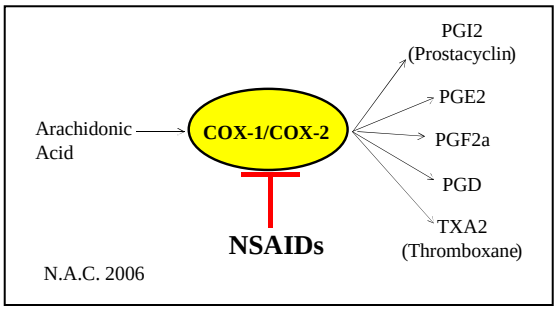
1. All NSAIDs work by inhibiting the activity of cyclooxygenase enzymes.

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 with the 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.

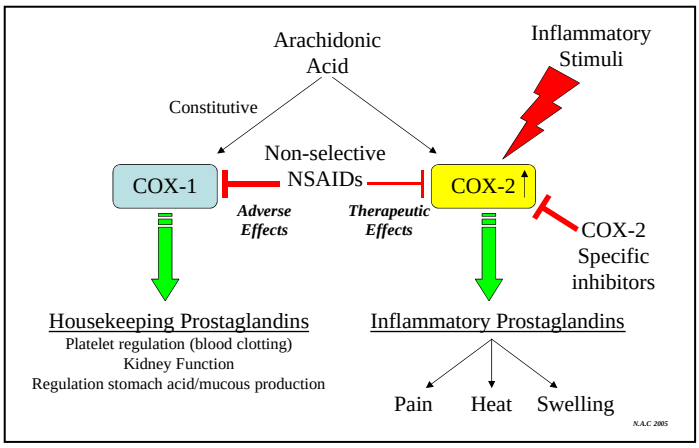
A3. Cyclooxygenase enzymes: Expression and Function

	COX-1	COX-2
Expression	**Constitutive**	**Inducible** in many cell types
Tissue Location	Ubiquitous	**Induced** by **inflammatory stimuli** in macrophages, monocytes, synoviocytes chondrocytes, fibroblasts, osteoblasts and endothelial cells -also expressed **constitutively** at low levels in **kidney**, **endothelium**, brain, ovaries, uterus & small intestines
Subcellular location	Endoplasmic Reticulum	Endoplasmic Reticulum
Functional Role	**General housekeeping**: Protection and maintenance of different tissues	**Pro-inflammatory responses**, Signaling & mitogenesis
Induction	Generally no induction	Induced by many pro-inflammatory and other stimuli e.g. LPS, TNF-α, IL-1, IFN-γ, EGF, PDGF, FGF, TGFβ
Inhibitors	Aspirin & NSAIDs	Aspirin, NSAIDs **and** selective COX-2 inhibitors

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 the production of these specific prostaglandins in the relevant cell type is **therapeutically beneficial** and results in **amelioration** of clinical symptoms.

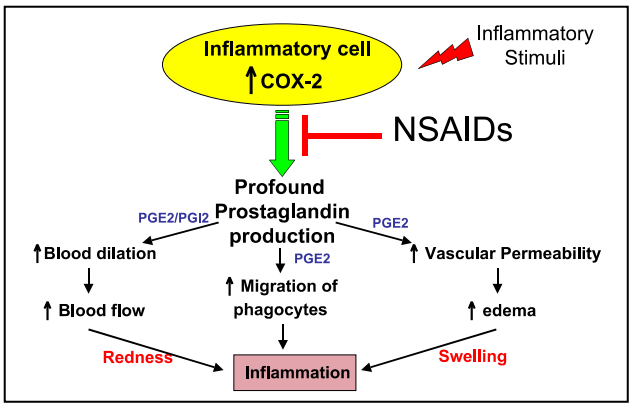
(B) Prostaglandins produced by COX-1 are primarily associated with the regulation of normal homeostatic physiological functions: Inhibition of the production of these COX-1-derived prostaglandins can lead to **adverse drug effects**.



A4.1 Disease-related functions of prostaglandins

(i) Inflammation

- COX-2 is specifically upregulated in inflammatory cells
- PGE2 & PGI2 (prostacylin) 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

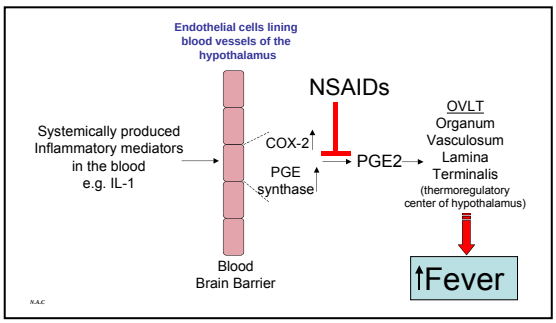


(ii) Pain

- 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

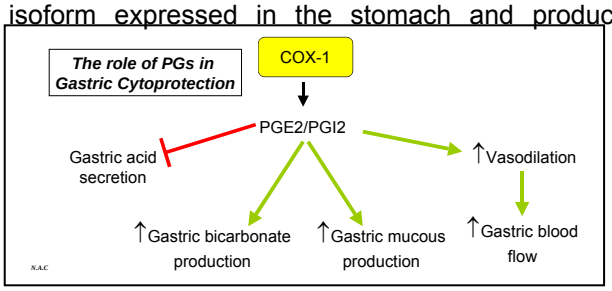
- systemically produced inflammatory mediators (e.g. IL-1/TNF-□) induce the expression of COX-2 in the endothelial cells lining the hypothalamus causing the production of PGE2, which then acts on the **Organum Vasculosum Lamina Terminalis** (OVLT: the thermoregulatory center of the hypothalamus) to cause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



A4.2 Homeostatic functions of prostaglandins- <u>associated with adverse NSAID effects</u>

<u>(i) Stomach and GI tract</u>

- COX-1 is the predominant enzyme isoform 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

  PGE2 & PGI2: inhibit production of gastric acid
  increase the production of gastric bicarbonate
  increase production of gastric mucous
  cause vasodilation & increase gastric blood flow

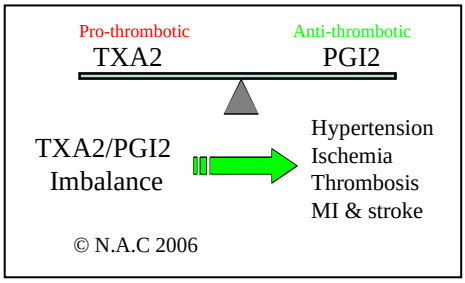
- **<u>Inhibition of COX-1 in the stomach is the cause of significant adverse effects of both Aspirin and the traditional NSAIDs</u>**

<u>(ii) Cardiovascular system</u>

- Prostaglandins are very important in the regulation of the cardiovascular system

- Platelets express only COX-1 and principally produce **<u>TXA2</u> (thromboxane),** which is a <u>vasoconstrictor</u> and promotes both platelet aggregation and activation.

- Endothelial cells express both COX-1 and COX-2, but **<u>lack</u>** TXA2 synthetase and hence are unable to produce TXA2. They produce primarily **<u>PGI2</u> (prostacyclin)**, which is a <u>vasodilator</u> and inhibits platelet aggregation.

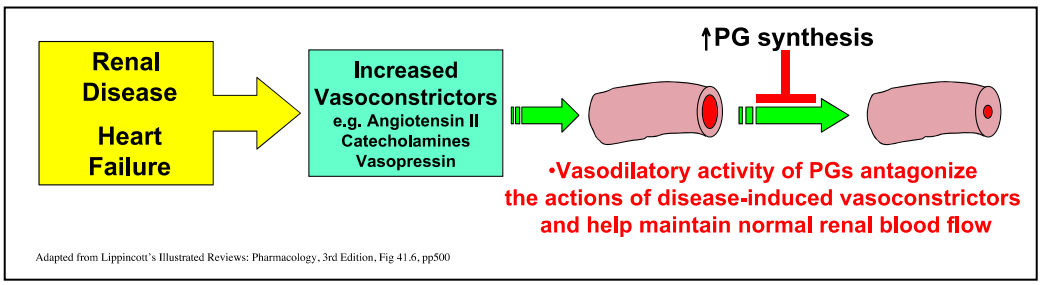


- The balance between the production of TXA2 & PGI2 regulates systemic blood pressure and thrombogenesis.

<u>(iii) Kidney</u>

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 vasodilatory 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.

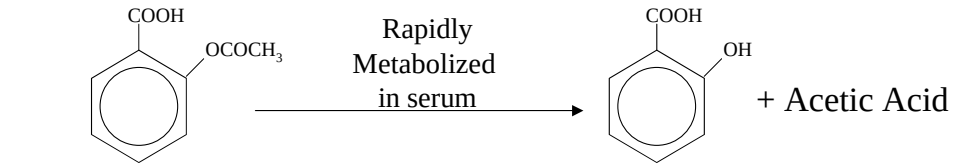
There are three distinct classes of NSAIDs:

a) Aspirin and other salicylates
b) Traditional NSAIDs e.g. ibuprofen and naproxen
c) Coxibs- selective COX-2 inhibitors e.g. celecoxib

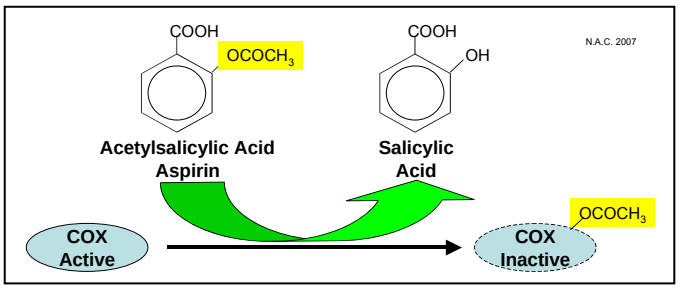
B2. Aspirin and other salicylates

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



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:

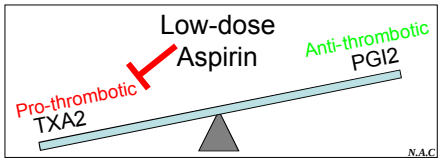
a) as a prohylactic treatment in the primary prevention of stroke and myocardial infarction in individuals at moderate to high risk of CVD
b) as a treatment in acute occlusive stroke
c) as secondary prevention of CVD after-
   (i) a myocardial infarction
   (ii) an occlusive stroke
   (iii) a transient 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

- Alkalinization 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)

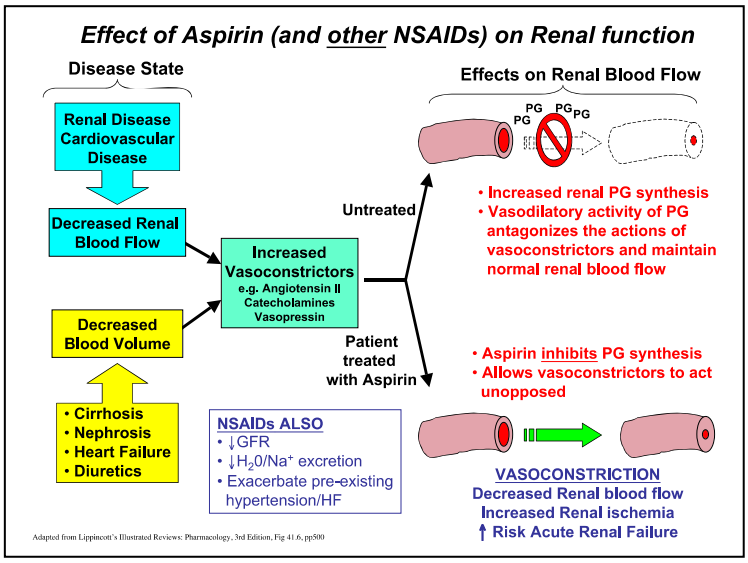
- **NSAID treatment can aggravate and promote development of gastric & duodenal ulcers**

- 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 transporetes 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 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 opiod 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, Dyspesia, 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 o chronic lower back pain, migraine, chronic muscoskeletal 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-exisiting CVD)
- Associated with higher doses and chronic treatment

(B) modest worsening of underlying hypertenstion
- Not associated with 1st occurrence heart failure, but can worsen pre-exisring 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)
- Asepctic 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®)
Rofecoxib (Vioxx®) – withdrawn Dec 2004 due to increased MI & stroke
Valdecoxib (Bextra®) – withdrawn April 2005 due to increased MI & stroke

B4.1 Features of 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

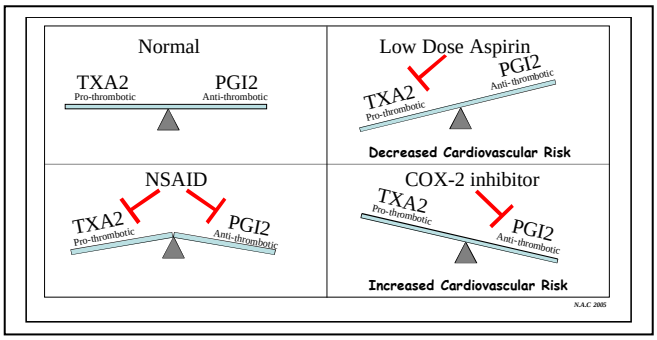
B4.2 COX-2 inhibitors and increased cardiovascular risk

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

Drug class	Type of NSAID	Specific Effect
Low-dose aspirin	All NSAIDs except celecoxib	Antagonize beneficial effects of low-dose aspirin (Prevents binding of aspirin to COX-1)
Oral anti-coagulants (e.g. warfarin)	All NSAIDs (Celecoxib-CYP2C9*)	↑anti-coagulant effect/Increased risk of bleeding (Platelet COX-1 inhibition/protein displacement)
Anti-hypertensives (e.g. ACE inhibitors β-blockers)	All NSAIDs	Decreased anti-hypertensive effect (NSAIDs promote renal vasoconstriction)
Diuretic agents (e.g. Furosemide)	All NSAIDs	↓ Diuretic effect/NSAIDs promote H_20 and Na^+ retention (Increased risk of high blood pressure)
Oral hypoglycemics (e.g sulfonylureas)	Salicylates	Potentiate hypoglycemic effects (Salicylates displace protein-bound sulfonylureas and independently enhance glucose utilization)
Uricosurics (e.g. Probenecid)	Salicylates	Decreased uricosuric effect (Salicylates increase plasma uric acid levels)
Lithium (narrow therapeutic window)	All NSAIDs	Increased Lithium toxicity (Decreased Renal Clearance)
Methotrexate	All NSAIDs	Increased Methotrexate toxicity (Protein displacement/Decreased Renal Clearance)
Aminoglycosides (e.g. gentamicin)	All NSAIDs	Increased Aminoglycoside toxicity (Decreased Renal Clearance)

N.A.C

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, wherease 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

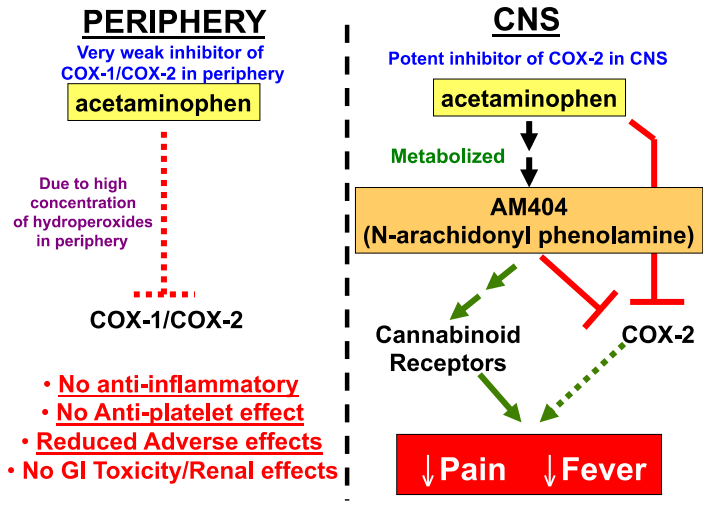
(vii) Overall the choice of NSAID requires a balance of:
a) clinical efficacy
b) Safety
c) Cost effectiveness

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



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

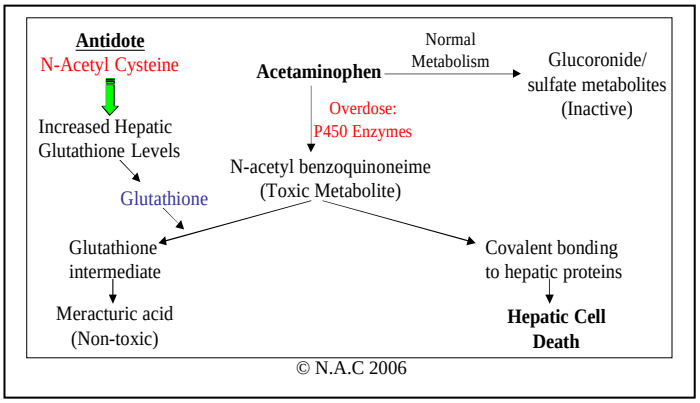
a) At normal doses (4g/day) Acetaminophen is essentially free of adverse effects

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, synoviocytes 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
Oxaproxin- 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:

Drug class	Type of NSAID	Specific Effect
Low-dose aspirin	All NSAIDs except celecoxib	Antagonize beneficial effects of low-dose aspirin (Prevents binding of aspirin to COX-1)
Oral anti-coagulants (e.g. Coumadin)	All NSAIDs (Celecoxib-CYP2C9*)	Increased risk of bleeding (Platelet COX-1 inhibition/protein displacement)
Anti-hypertensives (e.g. ACE inhibitors β-blockers)	All NSAIDs	Decreased anti-hypertensive effect (NSAIDs promote renal vasoconstriction)
Diuretic agents (e.g. Furosemide)	All NSAIDs	Increased risk of high blood pressure (NSAIDs promote H_20 and Na^+ retention)
Oral hypoglycemics (e.g sulfonylureas)	Salicylates	Potentiate hypoglycemic effects (Salicylates displace protein-bound sulfonylureas and independently enhance glucose utilization)
Uricosurics (e.g. Probenecid)	Salicylates	Decreased uricosuric effect (Salicylates increase plasma uric acid levels)
Lithium (narrow therapeutic window)	All NSAIDs	Increased Lithium toxicity (Decreased Renal Clearance)
Methotrexate	All NSAIDs	Increased Methotrexate toxicity (Protein displacement/Decreased Renal Clearance)
Aminoglycosides (e.g. gentamicin)	All NSAIDs	Increased Aminoglycoside toxicity (Decreased Renal Clearance)

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.