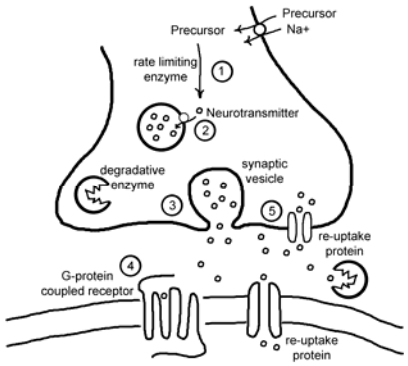
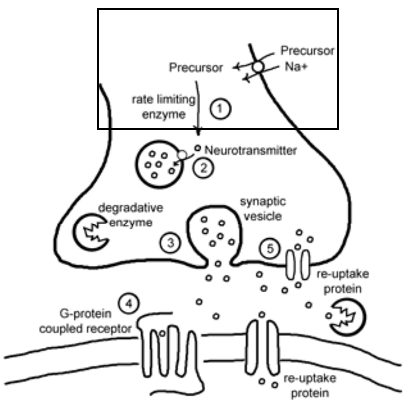
Pharmacology/Therapeutics I Block 2 Lectures

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.



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

iii Dietary intake of certain amino acids can influence precursor availability Ex**:** tryptophan. A diet low in tryptophan combined with high intake of amino acids that compete for tryptophan transporter reduces serotonin production.

iii 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

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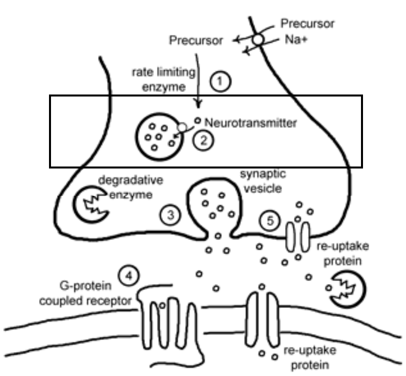
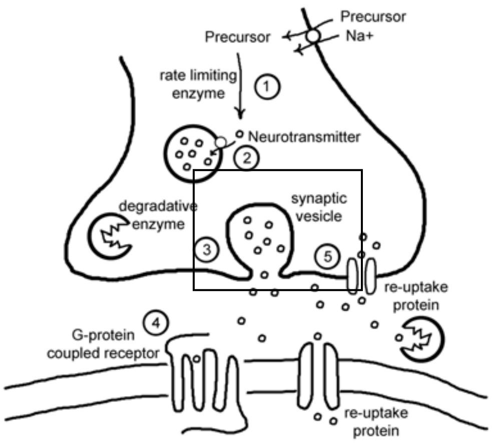


i Storage of neurotransmitters in synaptic vesicles protects them from degradation by cytosolic enzymes. Packaging of protein neurotransmitters in large vesicles at the cell body enables the transport of protein neurotransmitters down the axon to the nerve terminal.

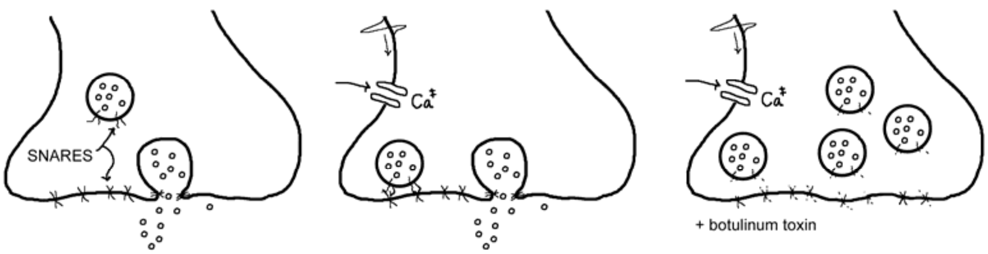
ii Neurotransmitters in the cytoplasm can be degraded when vesicular transport is inhibited resulting in neurotransmitter depletion.

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.



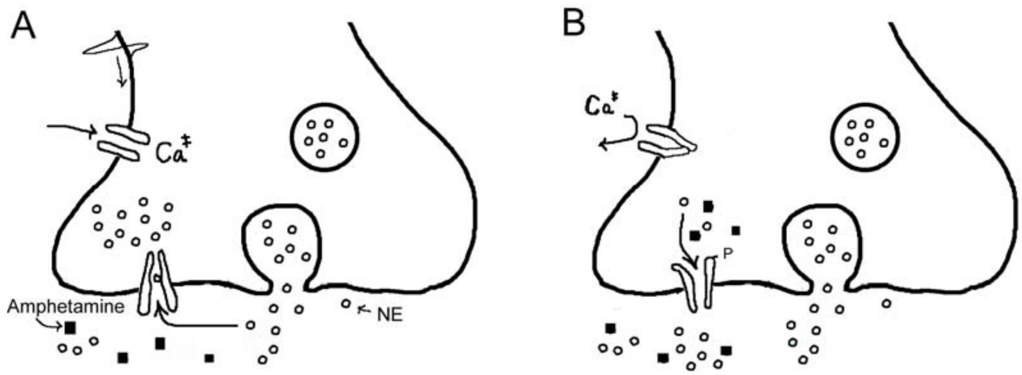
i. Toxins can degrade SNAREs and disrupt fusion of synaptic vesicles with the cell membrane. The pharmacological effect of such disruption depends upon the cell type that takes up the toxin

ii. **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.

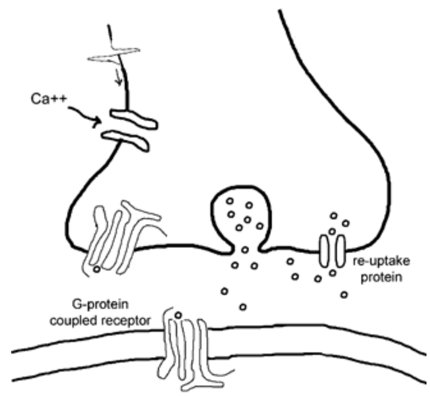


iii. Tetanus toxin targets neurons that inhibit motor neurons resulting in excessive muscle tone. This occurs first in the masseter muscle resulting in "lockjaw".

iv. 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.



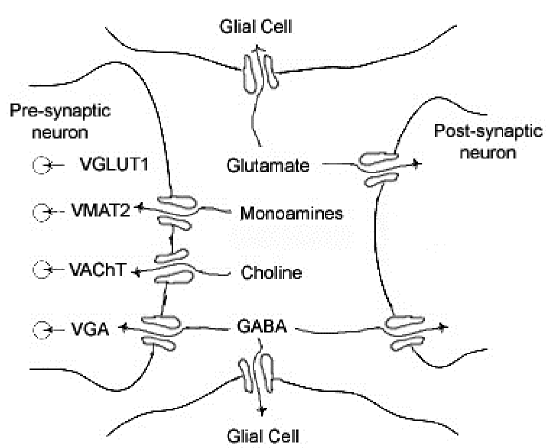
D. Binding of neurotransmitter to receptor (4) - Neurotransmitters bind to receptors localized on pre- and post-synaptic cell membranes.



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

ii. 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:



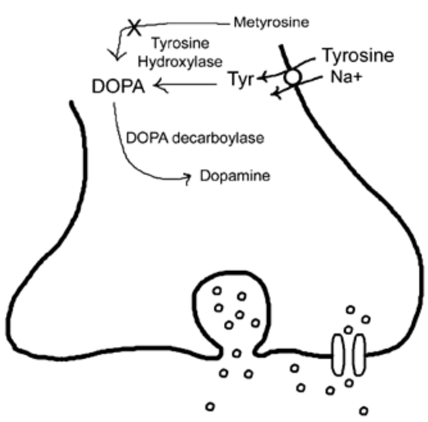
i. Re-uptake of the neurotransmitter out of the synaptic cleft can occur at the pre-synaptic nerve terminal, the post-synaptic cell or the surrounding glial cells. Primary reuptake site is dependent on the location of reuptake protein expression.

ii. Diffusion out of the synaptic cleft

iii. 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. .



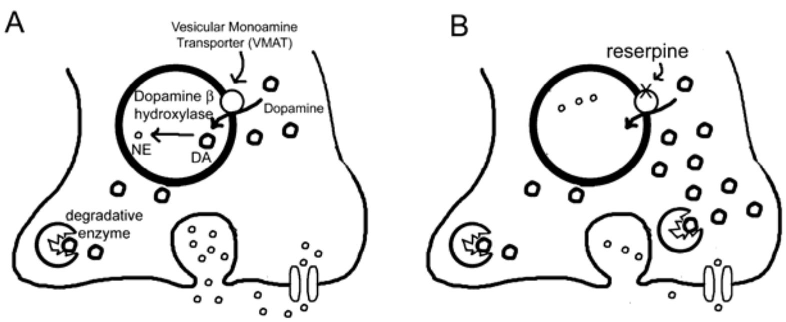
A. Synthesis **–** dopaminergic and noradrenergic neurons transport tyrosine into the cell via an amino acid transporter. Several enzymatic steps eventually lead to tyrosine's conversion to dopamine. Dopamine is the precursor to norepinephrine and epinephrine

i. Hydroxylation of tyrosine by tyrosine hydroxylase is the rate-limiting step in the production of catecholamines. **Metyrosine** competes with tryrosine for 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.

ii. **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.

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.

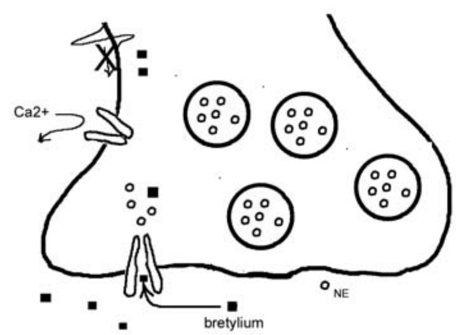
B. Storage- Dopamine is transported into synaptic vesicles by a vesicular transporter specific to monoamines, (i.e., serotonin, norepinephrine, histamine, dopamine). Dopamine is transformed to norepinephrine by dopamine β-hydroxylase. The dopamine β- hydroxylase enzyme is expressed within the vesicle.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

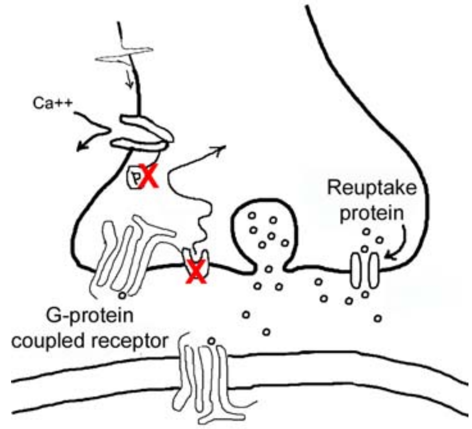
i. **Bretylium** inhibits excitability of the nerve terminal membrane and Ca2+-dependent fusion of the synaptic vesicle with the plasma membrane thus reducing neurotransmitter release. **Bretylium** has affinity for, and is taken up by reuptake transporters proteins that normally take up norepinephrine. 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

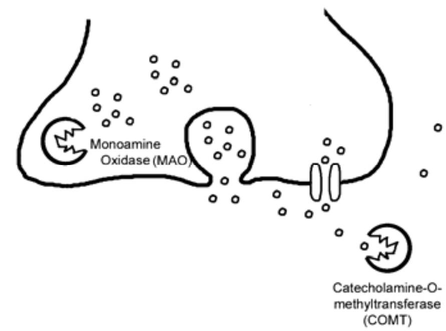
i. Post-synaptic receptor binding influences numerous cell functions that will be addressed in later lectures. Both agonists and antagonists of adrenergic receptors are used in the treatment of cardiovascular and respiratory diseases as well as mood disorders.

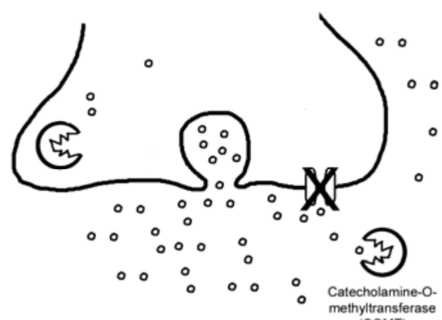
ii. Activation of pre-synaptic adrenergic receptors on nerve terminals influences neurotransmitter release, α–adrenergic receptors can inhibit, while β–adrenergic receptors can facilitate neurotransmitter release.



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

i. 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,

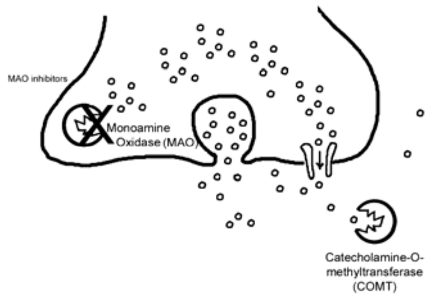


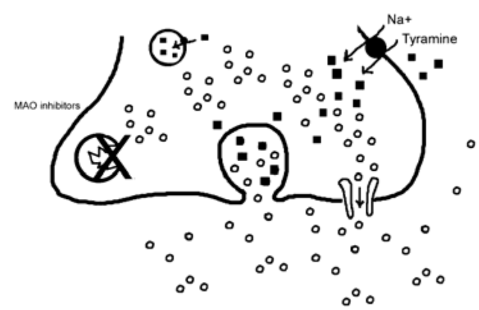


which is richly innervated by noradrenergic neurons.

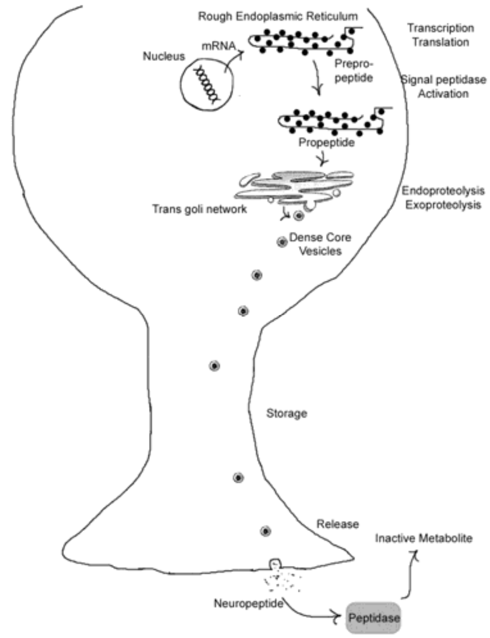
ii. Metabolism is less important for termination of endogenously released catecholamine since re-uptake from the synapse is so efficient. Circulating catecholamines such as those released by the adrenal gland or those administered exogenously are subject to metabolism by COMT. The efficiency of this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

iii. Metabolism also becomes a factor for catecholamines that have been taken back up into the cell. If they are not rapidly transported into the synaptic vesicle they become subject to rapid degradation by monoamine oxidase (MAO). **MAO inhibitors** lead to increased catecholamines in the cytoplasm. As norepinephrine accumulates in the cytoplasm, the transporter protein reverses direction leading to expulsion of norepinephrine into the synapse. Dietary sources of certain amino acids can produce adverse reactions when combined with MAO inhibitors. For example, **tyramine** can be taken up into noradrenergic cells. However, ingested tyramine is normally subject to significant first pass metabolism by MAO's in the liver. When MAOs are inhibited, such as during treatment for depression, ingested **tyramine** accumulates and is transported into adrenergic cells where it competes with norepinephrine for transport into synaptic vesicles resulting in even higher levels of cytoplasmic norepinephrine than with MAO inhibitors alone. The cytoplasmic accumulation of norepinephrine can reverse the concentration gradient across the plasma membrane and cause the reversal of the reuptake transporter. The resulting excessive release of norepinephrine can lead to a hypertensives crisis due to excessive vasoconstriction by norepinephrine in the periphery.





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 prepropeptide in the endoplasmic reticulum. Various cleavage processes mediated by peptidases ensue that lead to the production of active neuropeptide.

   i. Peptidase inhibitors can be used to block the cleavage of prepeptides thus preventing them from forming active neurotransmitter or hormones. Ex: <u>angiotensin converting enzyme (ACE) inhibitors, e.g., **lisinopril**,</u> block the conversion of angiotensin I to angiotensin II and thereby lower blood pressure in certain hypertensives patients.

B. Storage into vesicle – in contrast to other neurotransmitters, the neuropeptides are packaged into large “dense core vesicles”. This packaging occurs at the endoplasmic recticulum 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-</u>

peptidergic receptor agonists and antagonists have been developed to allow for penetration into the CNS. To date relatively few specific agonists and antagonists of neuropeptide receptors have been developed. Though several examples do exist.

i. 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 alcholism.

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.

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 tyrosine for transport into cell**

SYNAPTIC TRANSMISSION: TARGETS OF DRUG ACTION

Date: August 28, 2012, 8:30 – 9:20 am

KEY CONCEPTS AND LEARNING OBJECTIVES

1. Synaptic transmission is a signal transduction process that results from action potential-dependent release of a neurotransmitter from the pre-synaptic nerve terminal. The neurotransmitter initiates a signal by activating post-synaptic receptors that modify electrical or biochemical properties of the target cell.

    a. *understand the 5 steps involved in neurotransmission including the site where each step takes place within the neuron or synapse.*

2. Drugs are used to augment or inhibit neurotransmission by acting on pre- or post-synaptic mechanisms. Neurons that release different neurotransmitters may utilize similar processes and similar or the same proteins to catalyze reactions involved in neurotransmission. Thus, the ability of a particular drug to selectivity influence the function of a particular neuronal type depends upon whether the target is shared by other neuronal types, or alternatively whether the drug can gain entry into the cell.

    a. *Describe the* **pre-synaptic** *mechanisms by which drugs enhance or decrease transmission.*
    b. *Describe the* **post-synaptic** *mechanisms by which drugs enhance or decrease transmission.*
    c. *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.*
    d. *Understand how selectivity is maintained by differences in the accessibility of a drug to the cytoplasm of the target cell.*

3. Currently recognized neurotransmitters can be categorized into the following classes:

    - Biogenic amines – dopamine, serotonin, norepinephrine, epinephrine, acetylcholine
    - Amino Acids – glutamate, glycine, GABA
    - Peptides – SP, Ang II, LHRH, FSH, Vasopressin, Oxytocin, Neuropeptide Y
    - Nucleotides – ATP, ADP
    - Gases – NO, CO

Neurotransmitters within the different classes rely on different synthetic and catabolic enzymes, transporters, receptors etc, for their production, storage, action and inactivation.

a. *compare and contrast the main features of noradrenergic and peptidergic neurotransmission and understand how differences between the two processes influence strategies for their pharmacological manipulation*
b. *understand how the five steps in neurotransmission of adrenergic neurons can be manipulated using clinical pharmaceuticals*
c. *explain the effects of the following drugs or drug classes on adrenergic neurotransmission*

- ***metyrosine***
- ***reserpine***
- ***bretylium***
- ***cocaine***
- ***tricyclic antidepressants***
- ***monoamine oxidase inhibitors***
- ***SSRIs***
- ***Amphetamine***

AUTONOMIC NERVOUS SYSTEM AND ADRENERGIC AGONISTS

Date: August 29 and 30, 2012
Recommended Reading: **Basic and Clinical Pharmacology**, 11th Edition, Katzung, *et. al.*, pp. 127-166.

KEY CONCEPTS AND LEARNING OBJECTIVES

1. The autonomic nervous system is a peripheral involuntary motor system that regulates visceral motor activity. It is comprised of the sympathetic and parasympathetic nervous systems and has significant influence on the enteric nervous system as well.

   a. *Identify the distinguishing anatomical and chemical characteristics of the sympathetic, parasympathetic and somatic motor systems. e.g., origin, pathway, neurotransmitters released from pre and post-ganglionic cells.*
   b. *Recognize 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.*

2. With few exceptions, post-ganglionic neurons of the sympathetic nervous system release norepinephrine. The exceptions include neurons that innervate the sweat glands, which are cholinergic, and the adrenal medulla, which is innervated by pre-ganglionic sympathetic neurons, but acts as an exocrine gland that releases both epinephrine and norepinephrine into the circulation. The endogenous adrenergic neurotransmitters norepinephrine and epinephrine bind to adrenergic receptors to mediate their effects.

   a. *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.*
   b. *List the 5 main subtypes of adrenergic receptors and recognize the most common second messenger system to which they are coupled, and how the second messenger mediates the typical functional response of the target organs discussed in lecture.*
   c. *Recognize the two adrenergic receptors that are normally expressed on the pre-synaptic membrane of both noradrenergic and non-noradrenergic neurons and how their activation influences neurotransmitter release.*

3. Directly acting catecholamines and synthetic adrenergic agonist compounds have differing affinities for adrenergic receptors. If a drug has high affinity for a receptor, and if its binding of the receptor activates a second messenger system to which the receptor is coupled, the drug will likely produce a physiological effect. However, some drugs bind the same region as an endogenous agonist but have only a limited ability to stimulate the second messenger system. Therefore tests which assess a ligand's functionality rather than its affinity for the receptor must be used to determine an agonist's potency in producing a particular receptor mediated response.

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a. *Recognize the relative affinities of epinephrine, norepinephrine and the prototypical β-adrenergic receptor agonist, isoproterenol, for the different adrenergic receptors.*
b. *Recognize how these catecholamines influence cardiovascular and bronchial function and what receptors mediate their effects.*
c. *For the adrenergic receptor agonists discussed in class, recognize their relative affinity for the different adrenergic receptor and how this relates to their ability to mediate vascular contraction, bronchial smooth muscle relaxation and cardiac contractility.*
d. *Recognize the most common toxic side effects of the endogenous and synthetic adrenergic agonists discussed in lecture and understand why they occur* ***(those bolded*** *on slides).*
e. *Recognize the most important therapeutic uses for the endogenous and synthetic adrenergic agonists discussed in class. (****all*** *those discussed in lecture)*

4. Indirect acting sympathomimetics act by increasing neurotransmitter release from adrenergic neurons. Many are able to cross the blood brain barrier and thus have prominent CNS effects due to release of catecholamines in the CNS and stimulation of central adrenergic (and dopaminergic) receptors.

   a. *Recognize 4 commonly used indirect acting sympathomimetics*
   b. *Recognize the most important toxic side effects and most important therapeutic uses of indirect acting sympathomimetic drugs.*

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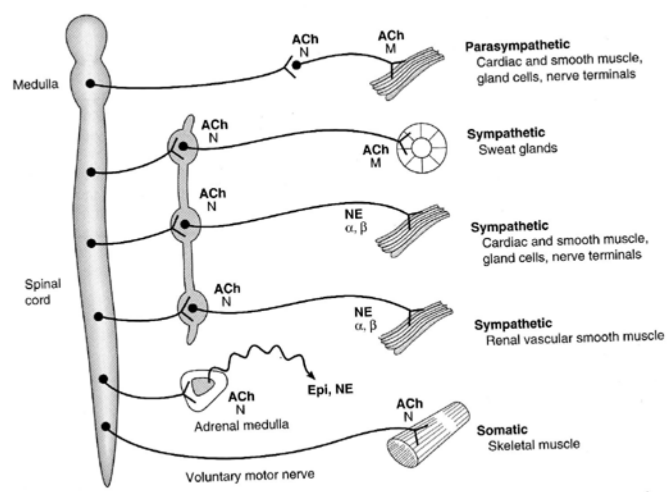
ADRENERGIC AGONISTS & ANTAGONISTS

GENERAL COMMENTS

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

I. Anatomy

A. Autonomic Nervous System – is defined as an involuntary motor system. It is composed of sympathetic (thoracicolumbar 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.*

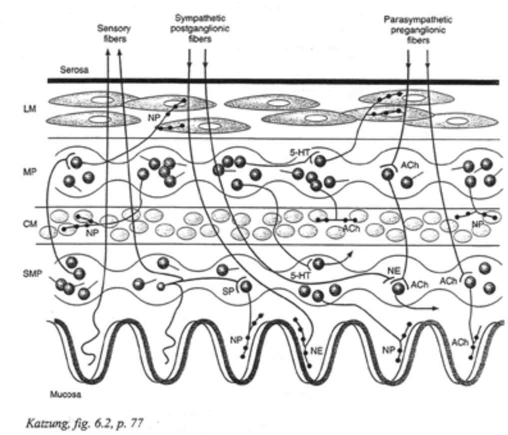
1. Sympathetic - thoracolumbar division (short pre-ganglionic cells and long-post ganglionic cells)

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

3. Enteric nervous system

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. Neurochemistry of the Autonomic Nervous system

A .Pre-ganglionic fibers release acetylcholine

B. Post-ganglionic parasympathetic fibers release acetylcholine

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

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

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

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

A. Parasympathetic - "Rest and Digest"

Eye – innervation of circular (or sphincter) muscles of pupil - constriction (miosis)

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

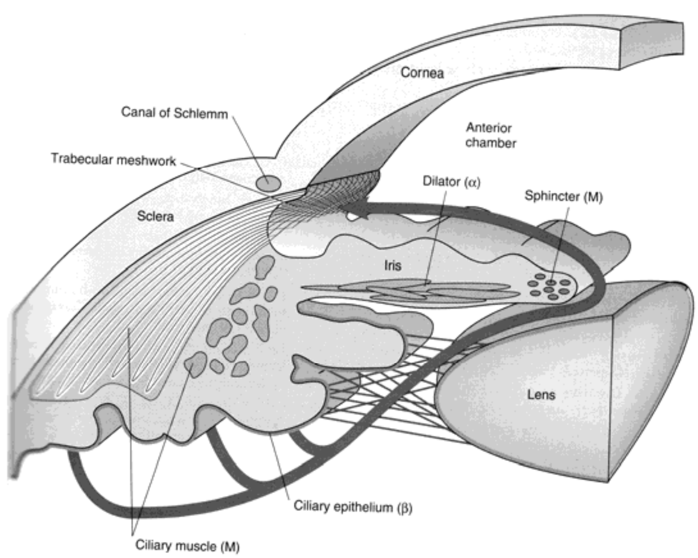
Bronchioles – innervates smooth muscle of bronchi – causes constriction

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

Bladder – innervates detrusor muscle, when activated causes bladder emptying

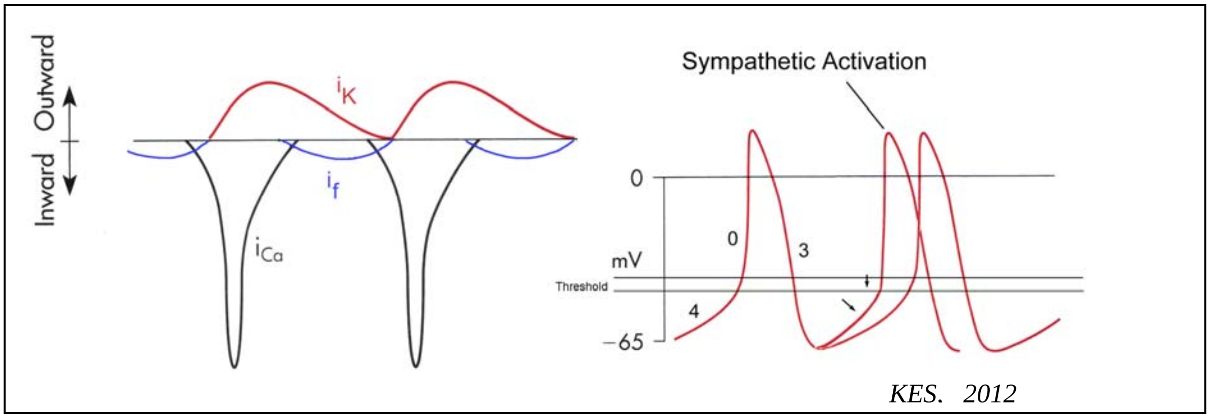
B. Sympathetic - "Fight or Flight", major effects:

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



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

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



Three currents contribute to sinoatrial node membrane potential,

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

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

Bronchioles – relaxation of smooth muscle lining the bronchioles

Blood vessels - contraction and relaxation - dependent on receptor population expressed in targeted vascular bed (e.g., $alpha_1$ vs. $beta_2$), as well as the ligand mediating the vascular response.

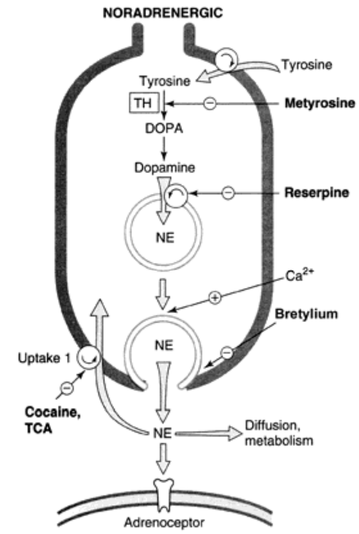
GI tract - decreased motility, can override normal enteric nervous system during fight or flight.

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

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

IV. Adrenergic Function

A. Adrenergic Neurotransmission



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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 monamine 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. 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

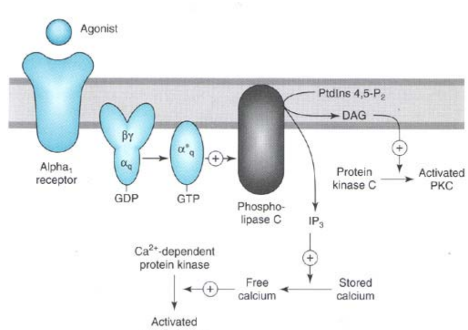
Types of adrenoceptors, some of the peripheral tissues in which they are found, and the major effects of their activation.

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.

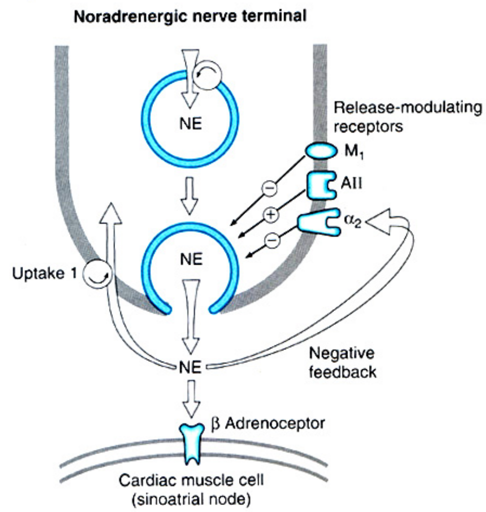


Modified From: Katzung, Basic and ClinicalPharmacology, 9th Ed.McGraw-Hill, New York, 2004.

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 (ryanodine receptor) that also acts as a calcium channel in the sarcoplasmic reticulum. When activated the ryanodine receptor releases stored calcium into the intracellular space, thereby increasing calcium concentrations and stimulating smooth muscle contraction.

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 inturn 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.



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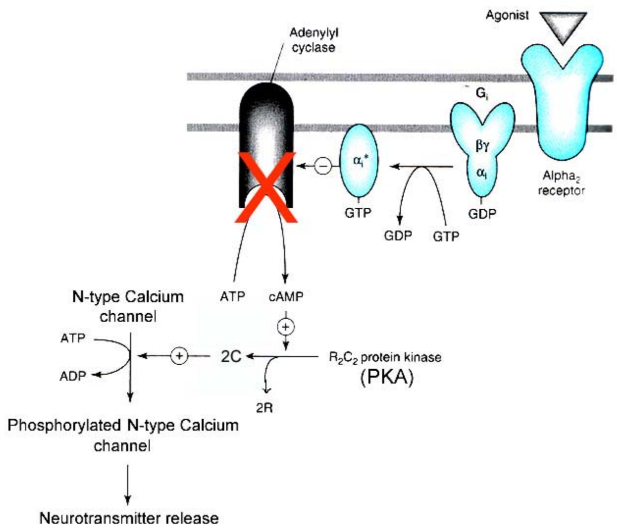

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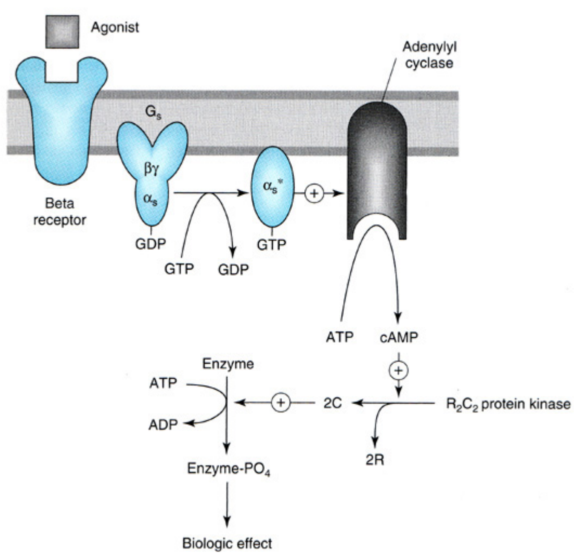
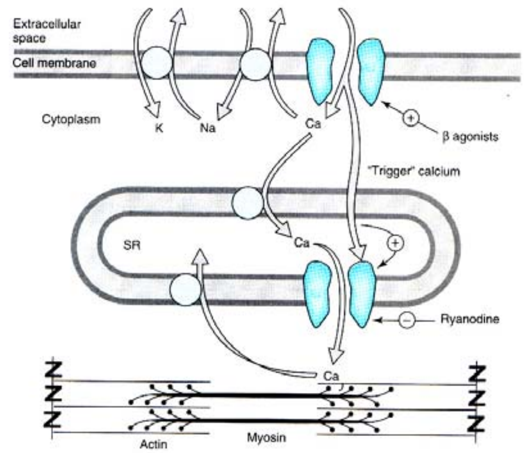
3. β_1-adrenergic receptors positively couple to adenylyl cyclase via Gαs-proteins – increases cAMP



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

EX: Positive chronotropy. Activation of adenylyl cylcase and increase of cAMP can activate PKA to promote phosphorylation of calcium channels in the membrane of sinoatrial node cells leading to increased inward calcium current and thus faster nodal cell depolarization to the firing threshold.

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



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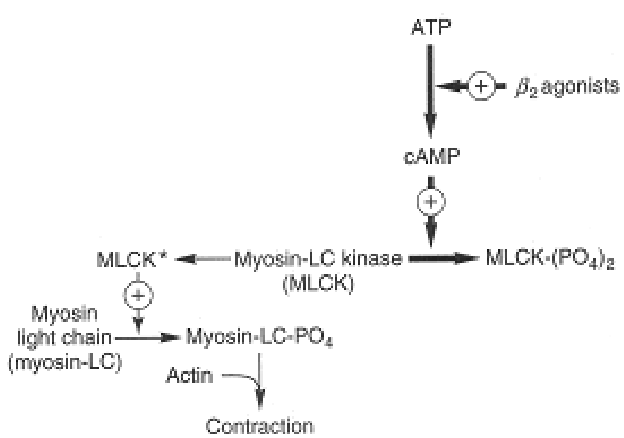
4. **β_2-adrenergic receptors**

positively couple to adenylyl cyclase via Gαs protein - increases cAMP

EX: Vascular smooth muscle relaxation: cAMP activates PKA which phosphorylates and **inactivates** myosin light chain kinase (MLCK). Normally MLCK phosphorylates the light chain of myosin enabling actin and myosin cross-bridge formation and smooth muscle contraction. Remember though that phosphorylation of the MLCK enzyme **inactivates** the enzyme so it cannot phosphorylate myosin light chain. In this case PKA **inactivates** MLCK. Therefore, β2 adrenergic receptor activation leads to reduced smooth muscle contraction. β2 adrenergic receptors are highly expressed on smooth muscle of the bronchi and some vascular beds and therefore regulates the degree of airway constriction as well as peripheral vascular resistance.



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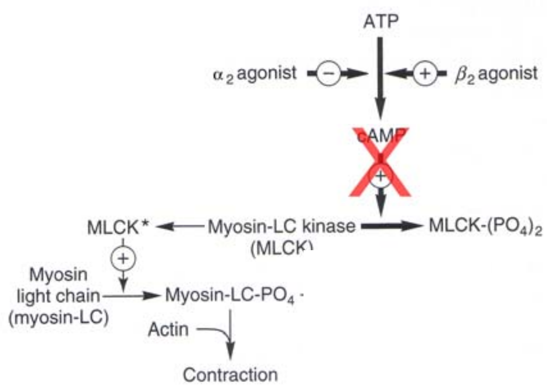
α2-adrenergic receptors produce peripheral vasoconstriction through the opposite mechanism. In this case, the Gαi subunit, to which the α2 adrenergic receptor is coupled, inhibits adenylyl cyclase, which, in turn, inhibits cAMP and PKA. PKA normally phosphorylates and inhibits the activity of myosin light chain kinase. Therefore, inihibiton of PKA leads to activation of MLCK and vascular smooth muscle constriction.



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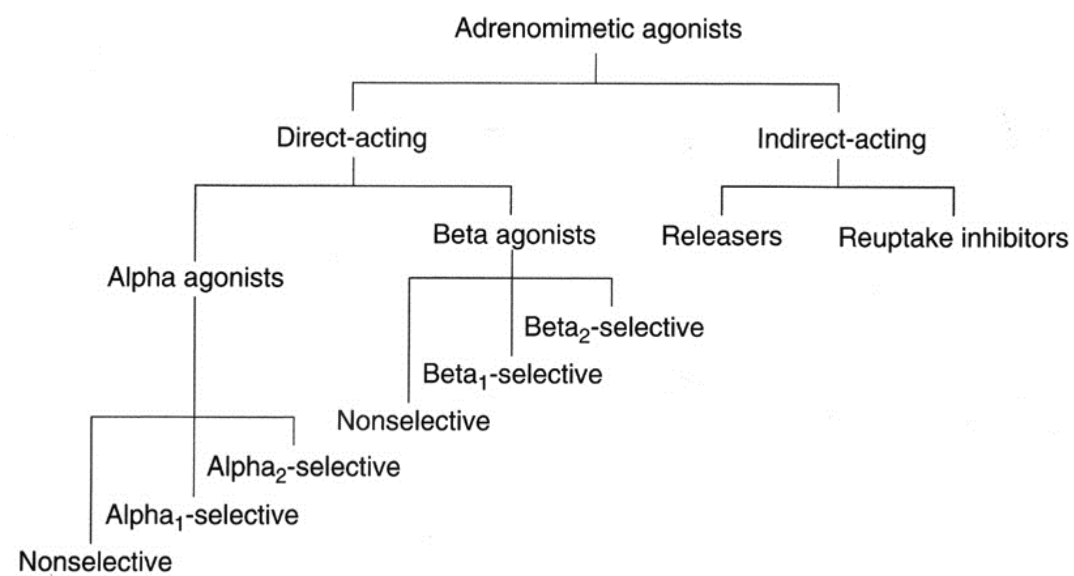
VI. Adrenergic Agonists



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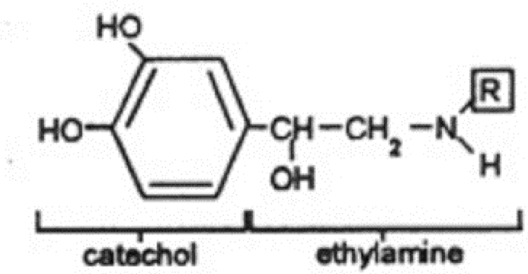
A. Direct Acting Sympathomimetics: Direct acting sympathomimetics (i.e., drugs that stimulate the sympathetic system) interact directly with adrenergic receptors to mediate their effects. Sympathomimetic agents have different affinities for adrenergic receptor subtypes. Thus, a specific compound may 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 lipophylic by altering the hydroxyl groups on the pheyl 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

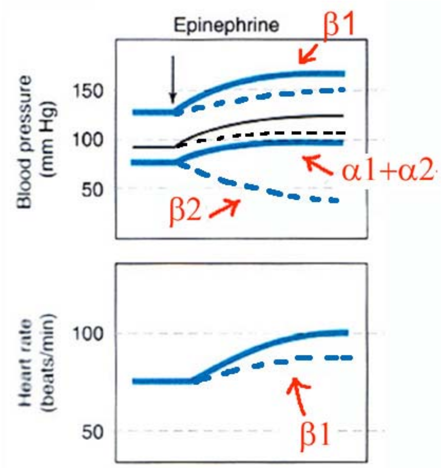
It is important to be able to predict the different hemodynamic effects produced by sympathomimetic agents given their receptor activity in order to effectively predict whether they will be beneficial or potentially hazardous in a particular clinical situation.

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 α1, α2, β1 and β2 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 therefore decreases diastolic BP; β_1 receptor activation has positive inotropic and chronotropic effects therefore increases CO and systolic BP; at higher doses (>0.2 μg/kg/min, solid lines) α_1 receptor activation predominates 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.



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

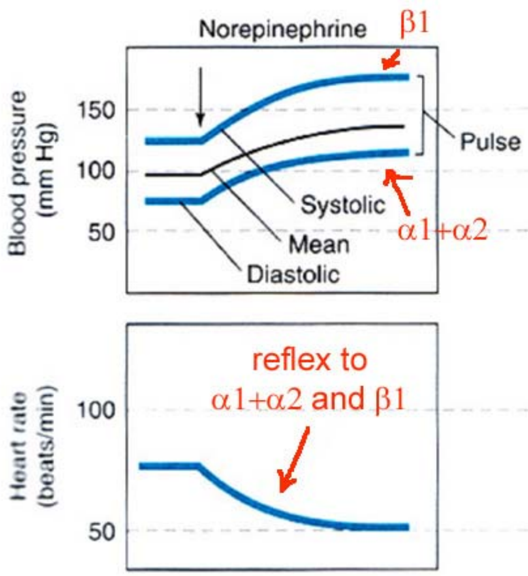
Toxicity: Arrhythmias, cerebral hemorrhage, anxiety, cold extremities, pulmonary edema

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 β1 receptor binding; large rise in pressure leads to reflex baroreceptor response and decrease in HR which predominates over the direct chronotropic effects; Overall increase in MAP; NE has limited affinity for β_2 receptors and so has limited effects on bronchiole smooth muscle.



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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, metabolized readily.

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.

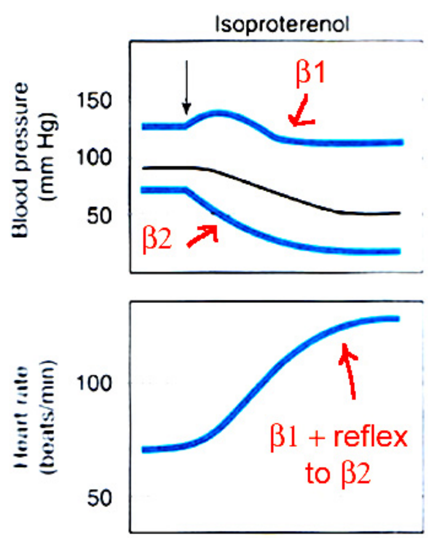
Cardiovascular effects: β_2 receptor activation promotes peripheral vasdilation, decreased diastolic BP; β_1 receptor - positive inotropy and chronotropy, leads to transient increased systolic BP. Overcome by vasodilatory effect; Overall small decrease in MAP which may contribute to further reflex HR increase.

Bronchioles: β_2 receptor – bronchodilation

Toxicity: Tachyarrhythmias

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

Contraindications: Angina, particularly with arrhythmias



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B. Selecitve β1-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 adrenregic agonists: terbutaline, albuterol

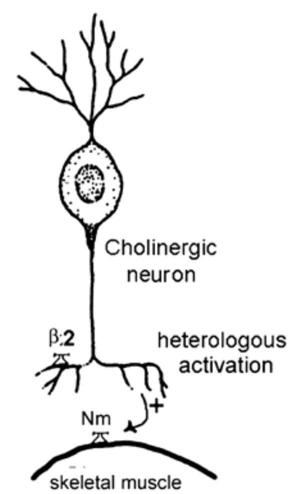
Cardiovascular Effects: negligible in most patients due to lack of β_1 activity. However, can cause some β_1 agonist-like response

Bronchioles: Bronchodilation

Pregnant Uterus: Relaxation

Toxicity: 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.

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



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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

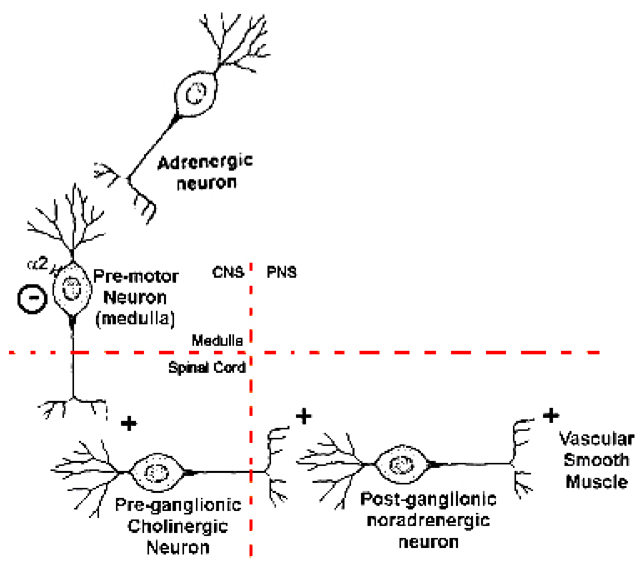
Therapeutic Use: Hypotension during anesthesia or shock, paroxysmal supraventricular tachycardia, mydriatic agent, nasal decongestant

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

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.



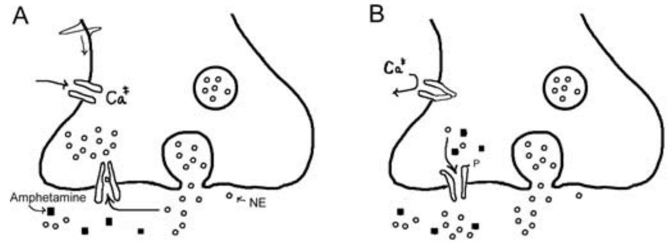
Activation of α_2-receptors on pre-motor neurons that normally provide tonic activation of sympathetic pre-ganglionic cells reduces pre-motor neural activity by unknown mechanism. Reduction of tonic excitatory input to the sympathetic cells reduces sympathetic output to vascular smooth muscle.

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 athrosclerosis, 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 release and thus reduced vasoconstriction, probably reduced sympathetic activation due to central effects in lipid soluble drugs. Possible peripheral vasoconstriction due to blockade of β_2 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.

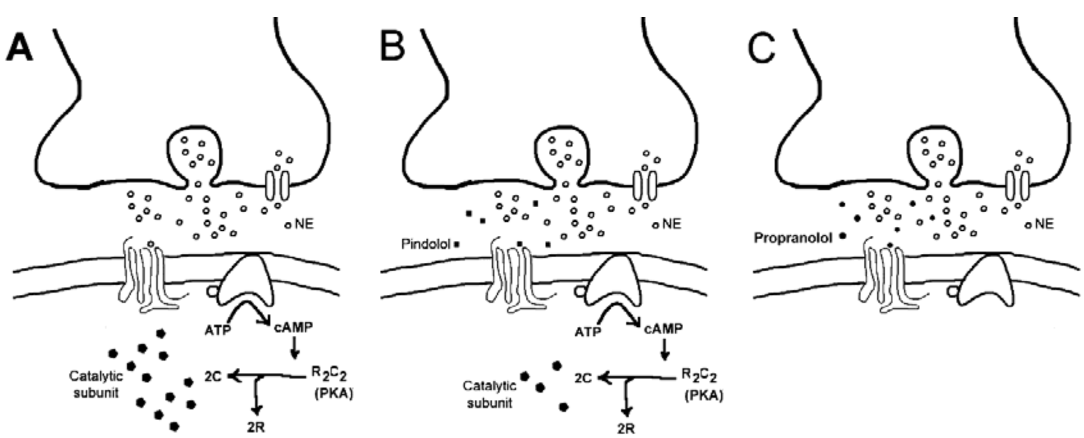
Cardiovascular Effects: Same as for non-selective β-blockers with limited effects on peripheral resistance.

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 hypertenisve crisis, unstable angina or arrhythmias when longer acting beta blockers may be problematic.

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

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

D. Partial Agonist: pindolol, partial agonist activity at both β1 and β2 adrenergic receptors; Therapeutic benefit is good when hypertension is due to high sympathetic output (A below) since blockade of endogenous agonist (i.e., NE and EPI) will predominate over partial agonist effect (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 (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.

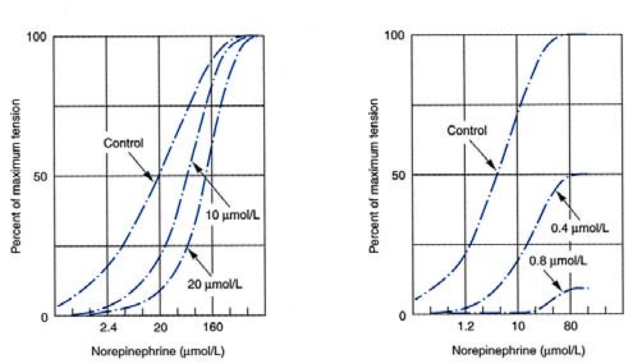
Therapeutic Use: Hypertension in those who are less tolerant of bradycardia and reduced exercise capacity caused by other beta blockers without partial agonist activity

Toxicity: same as for non-selective

Contraindications: Same as above

IX. α-adrnergic receptor antagonists

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



Effects of reversible and irreversible non-selective α-adrenergic receptor antagonists on dose-response curves to Norepinephrine *Figure 10-2 from Katzung***.**

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.)

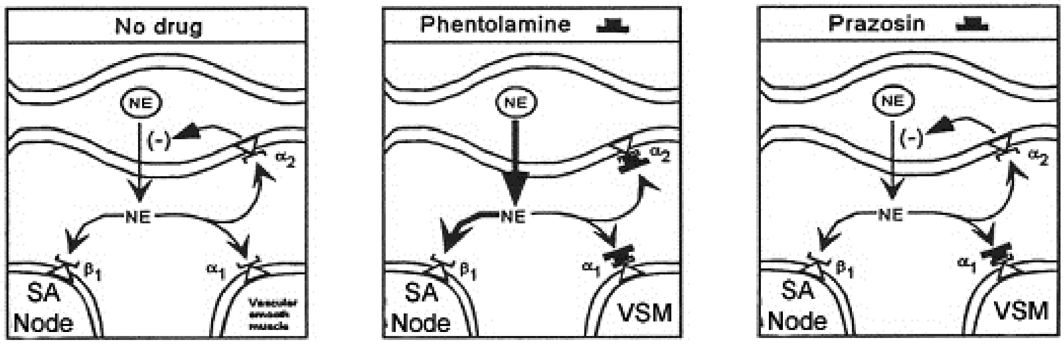
Therapeutic Use: Hypertension associated with perioperative treatment of pheochromocytoma, test for pheochromocytoma, dermal necrosis and sloughing with vasoconstrictor extravasation

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: Syncopy, orthostatic hypotension

X. **Drugs Covered in Lecture (Bold text is information you should know)** Do not memorize bold half-lives but have a general idea of the drug's half-life relative to other drugs in its class, e.g. Nadolol vs propranolol.

Generic Name	Trade Name	Half-Life	Mechanism of action	Elimination	Rx

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**
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)	**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**
Phenoxy-benzamine	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**

AUTONOMIC NERVOUS SYSTEM AND ADRENERGIC ANTAGONISTS

Date: August 31, 2012
Recommended Reading: **Basic and Clinical Pharmacology**, 11th Edition, Katzung, *et. al.*, pp. 127-166.

KEY CONCEPTS AND LEARNING OBJECTIVES

1. Beta-adrenergic receptors are found within the heart, eyes, vasculature, respiratory tract, digestive system and kidney. The receptor subtype expression varies depending upon the tissue. Beta-adrenergic receptor antagonists are one of the most important therapeutic agents used in current clinical practice for the treatment of cardiovascular disease.

   a. *Recognize the conditions that are most commonly treated with β-blockers and the mechanism by which β-blockers produce their beneficial effects in that condition.*
   b. *Identify the 6 β-adrenergic antagonists discussed in class and recognize to which of the 3 commonly recognized categories of β-blockers they belong.*
   c. *Understand how the 6 drugs differ from one another in their receptor subtype selectivity, relative duration of action and ability to cross the blood brain barrier and understand what advantage these attributes may provide in treating a particular patient population.*
   d. *Understand how the toxic side effects of the drugs differ with their receptor subtype selectivity.*

2. Alpha-adrenergic receptors are found primarily in vascular smooth muscle and act there to promote vasoconstriction. Consequently, the most prominent clinical use for α-adrenergic antagonists is in the treatment of disorders characterized by excessive vasoconstriction. More recently, α-adrenergic antagonists have been used to reduce constriction of non-vascular smooth muscle in the prostate and bladder.

   a. *Recognize the 5 prominent α-adrenergic antagonists used in clinical practice, their receptor subtype selectivity and the conditions for which they are used.*
   b. *Recognize the most serious side effects produced by selective and non-selective α-adrenergic receptor antagonists.*
   c. *Understand why selective α_1-adrenergic receptor antagonists are preferable for use in hypertension than non-selective α-adrenergic receptor antagonists.*

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

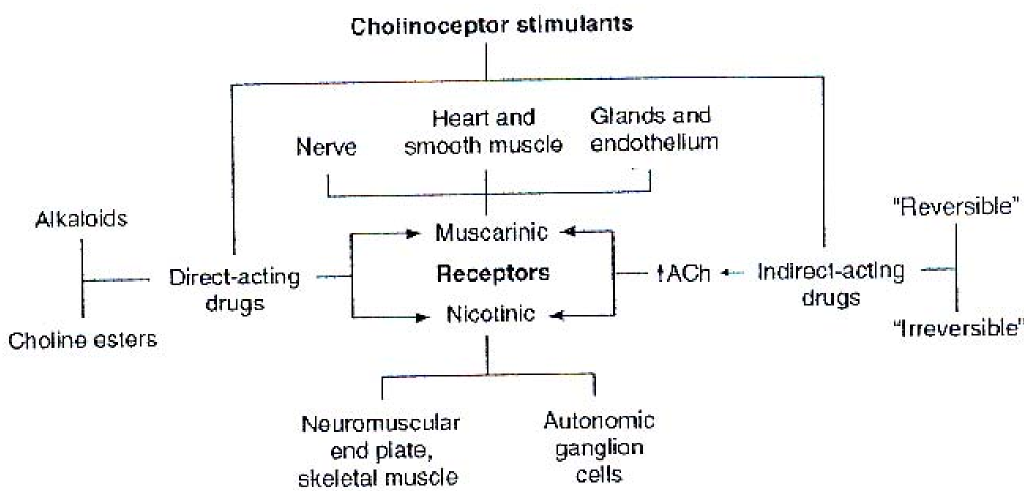
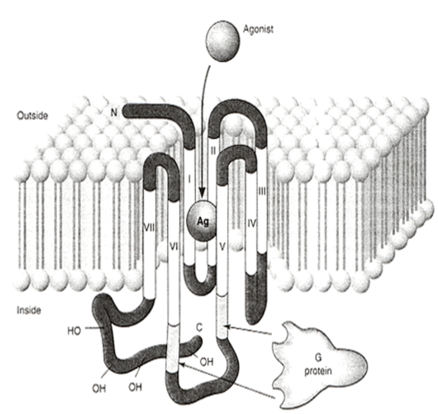


Fig. 7-1 From B.G. Katzung, In: Basic and Clinical Pharmacology Katzung 10th Ed. Pg. 94

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).



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

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

Muscarinic Receptors

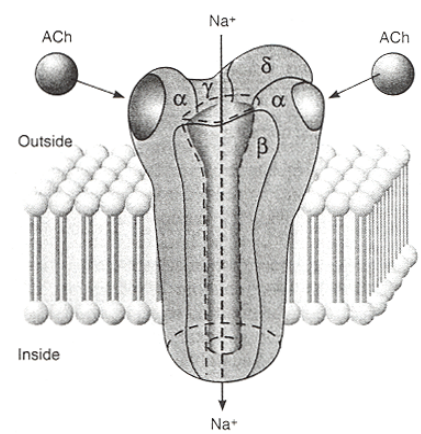
M1	Increased IP3, DAG and $[Ca^{2+}]$	Activates myenteric plexus
M2	Opens K channels	Decreases heart rate and contraction (decreases cardiac output)
	Decreased cAMP, decreased Ca^{2+}	Inhibits norepinephrine release from sympathetic nerve terminals
M3	Increased IP3, DAG and $[Ca^{2+}]$	Contacts circular 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, Nearsey and Wurster, In: Neuroscience, an outline approach Mosby Inc., St. Louis, 2002

The nicotinic receptors are pentomeric (five) transmembrane polypeptides, the subunits of which form a cation-selective channel permeable to sodium and potassium. Two main subtypes exist (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): $(CH_3)_3\overset{+}{N}\text{-}CH_2\text{-}CH_2\text{-}O\text{-}C(=O)\text{-}CH_3$

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

2. METHACHOLINE (Acetyl-ß-Methylcholine): $(CH_3)_3\overset{+}{N}\text{-}CH_2\text{-}CH(\mathbf{CH_3})\text{-}O\text{-}C(=O)\text{-}CH_3$

Differs from acetylcholine by methyl group on the β carbon. Hydrolyzed by acetylcholinesterase, but hydrolysis is slowed, has a longer duration of action than acetylcholine, has limited nicotinic effects, primarily muscarinic effects on smooth muscle, glands and the heart. The drug is used to diagnose bronchial hyperactivity in patients suspected of having asthma. Toxicity includes bronchiolar constriction. Contraindicated in pts given β-blockers since antidote to overdose is β-agonist.

3. CARBACHOL (Carbamylcholine):

$$(CH_3)_3\overset{+}{N}\text{-}CH_2\text{-}CH_2\text{-}O\text{-}\underset{\underset{\displaystyle O}{\|}}{C}\text{-}\mathbf{NH_2}$$

Carbamic group replaces the esteratic group of acetylcholine. The drug is 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):

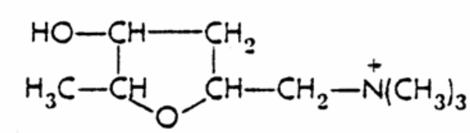
$$(CH_3)_3\overset{+}{N}\text{-}CH_2\text{-}\underset{\underset{\displaystyle \mathbf{CH_3}}{|}}{CH}\text{-}O\text{-}\underset{\underset{\displaystyle O}{\|}}{C}\text{-}\mathbf{NH_2}$$

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:

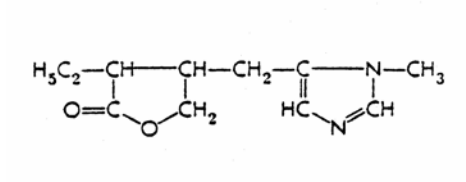
Several tertiary amine compounds with muscarinic agonist properties are available. Some of these are natural alkaloids, others have been prepared synthetically. The charge of the tertiary amine determines if the compound can cross the blood brain barrier.

1. MUSCARINE:

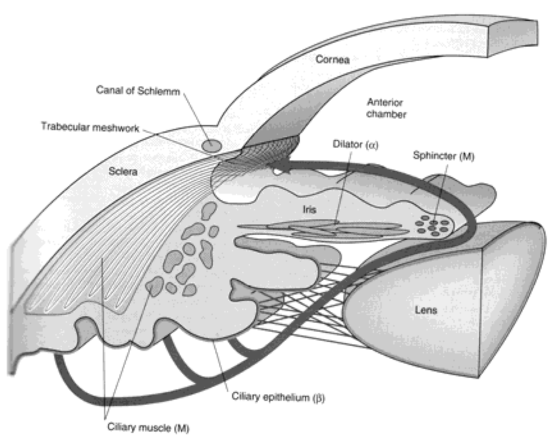


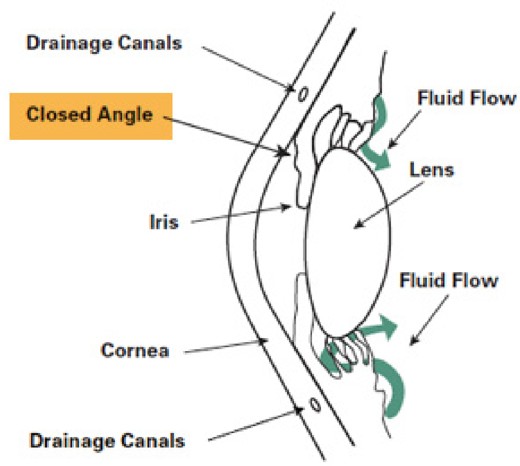
Alkaloid in wild mushrooms of the Clitocybe inocybe species. Prototype compound, though not used clinically. Historically one of the first cholinomimetic drugs to be studied. Pure muscarinic activity. Resistant to hydrolysis by acetylcholinesterase (no ester moiety). It is clinically important as a source 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 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.

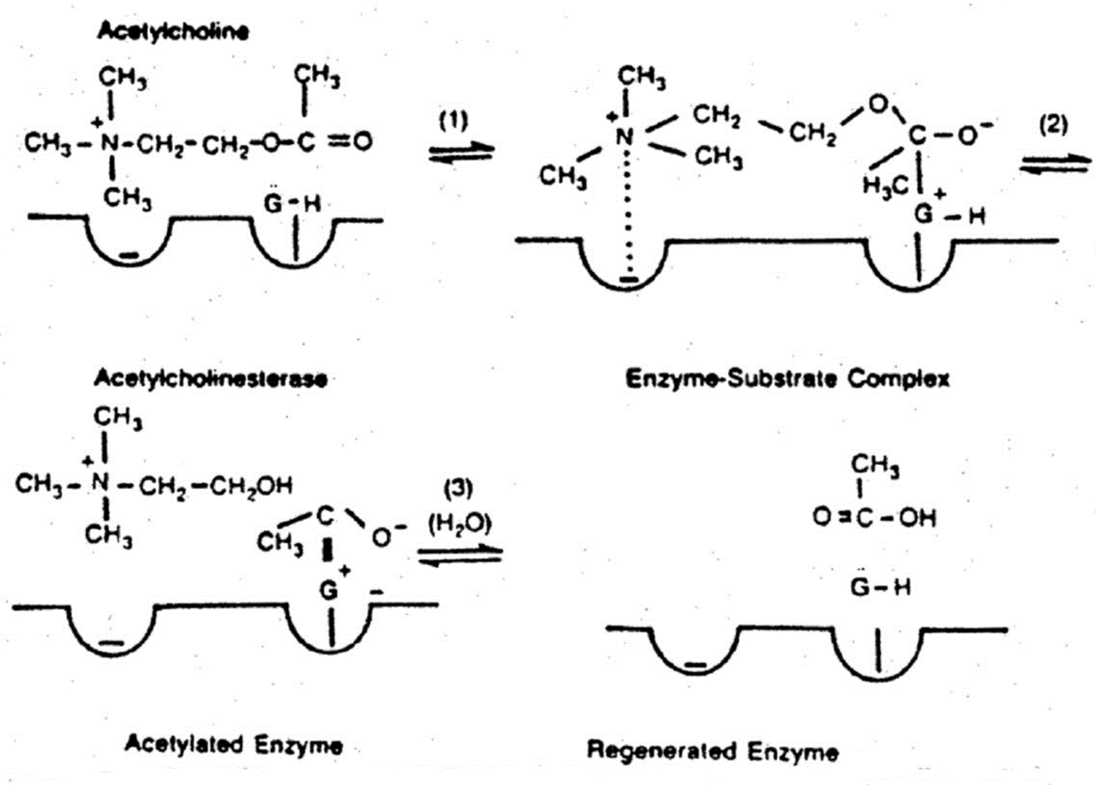
B. Butyrylcholinesterase (BuChE, pseudo, nonspecific, plasma cholinesterase).
Distribution: Plasma, glial cells, liver.
Function: Uncertain, however does hydrolyze certain exogenous drugs, e.g., succinylcholine.

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.

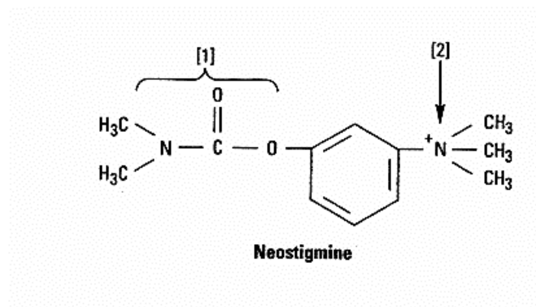
Two different general classes of acetylcholinesterase inhibitors have been identified, and distinguished by the extent to which they bind to the acetylcholinesterase molecule, and prevent its regeneration. They are identified in general terms as "reversible" and "irreversible" acetylcholinesterase inhibitors.


Acetylcholine
(1)
(2)
Acetylcholinesterase
Enzyme-Substrate Complex
(3)
(H2O)
Acetylated Enzyme
Regenerated Enzyme

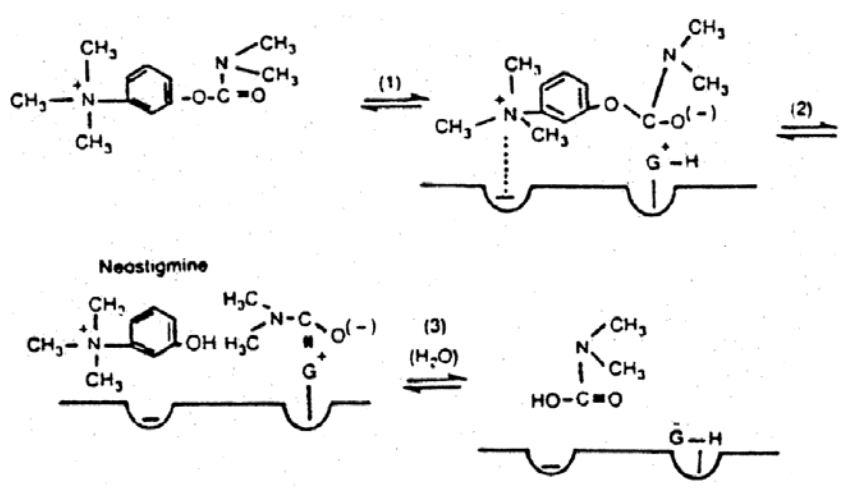
A. REVERSIBLE CHOLINESTERASE INHIBITORS: molecular mechanism

CLINICALLY USED ACETYLCHOLINESTERASE INHIBITORS

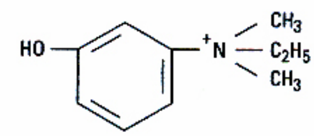
1. NEOSTIGMINE:



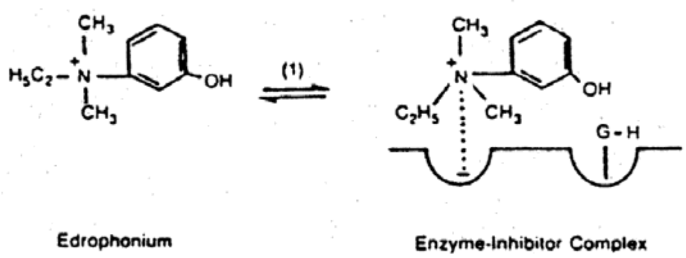
Contains a quaternary nitrogen, and thus poorly penetrates blood brain barrier. Inhibits acetylcholinesterase and has direct stimulatory effect on nicotinic receptors at the skeletal muscle endplate. Therefore used to reverse neuromuscular blockade (see neuromuscular relaxant lecture). Also used in the 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:



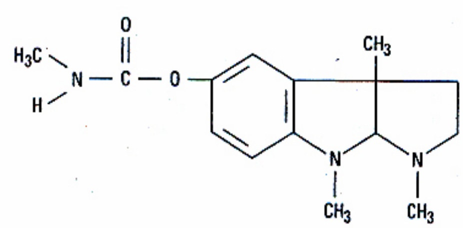
Similar in structure to neostigmine, but lacks an ester functional group. Inhibits cholinesterases and stimulates nicotinic receptors at the neuromuscular junction at lower doses than those which stimulate other cholinergic receptors. Has a very rapid onset of action, and a very short duration of action (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:

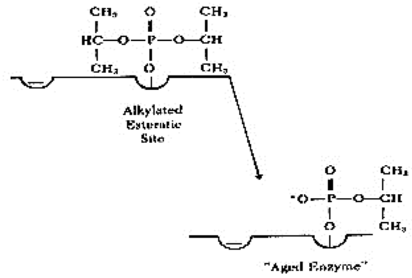
Alkaloid from the calabar bean, Physostigma venosum. Readily crosses the blood brain barrier. Inactivated by plasma cholinesterases but takes a long time. Duration of action up to 2 hours. Used in ophthalmology topically for treatment of glaucoma. Lowers intraocular pressure by increasing outflow of aqueous humor. Also used to counteract delirium with excess anticholinergic drugs. 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 Disease.

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.

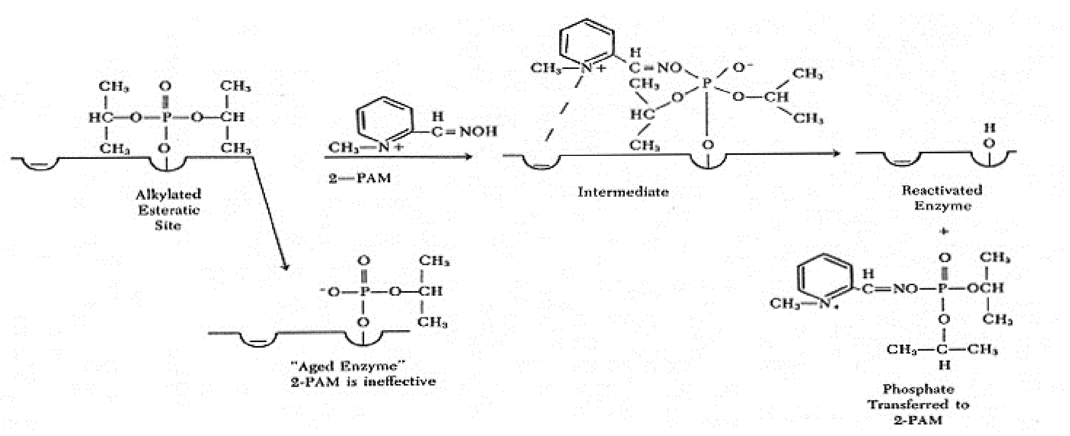
TOXICITY OF ORGANOPHOSPHATES (SLUDGE or DUMBBELLS)

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

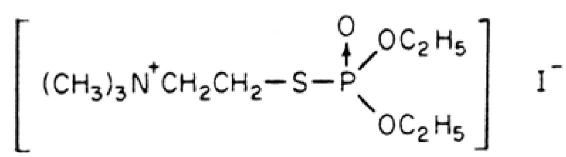
Treatment of severe organophosphate poisoning consists of:

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 days to a full week, requiring relatively infrequent administration. Can cause blurred vision and brow ache which typically resolve.

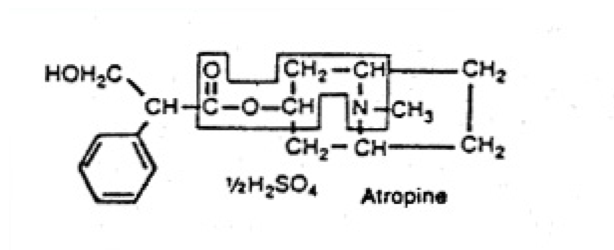


VI. MUSCARINIC ANTAGONISTS (PARASYMPATHOLYTIC AGENTS)

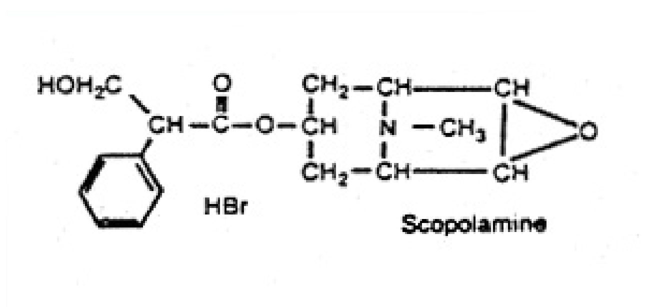
These compounds competitively block muscarinic receptors, inhibiting all parasympathetic functions and sympathetic cholinergic activity. These agents compete with acetylcholine for muscarinic receptors. The effect is reversible, but may persist for hours or days. At doses in excess of those employed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

A. MUSCARINIC ANTAGONISTS:

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



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

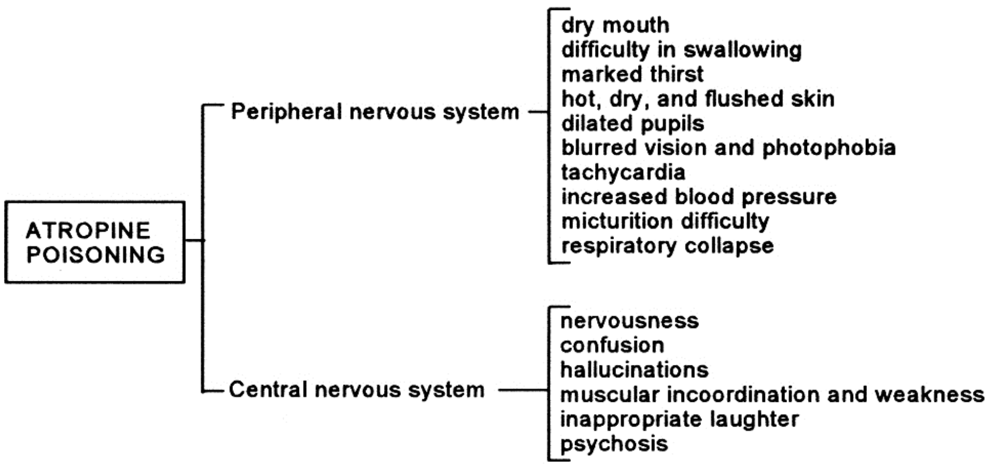


3. GLYCOPYRROLATE used following surgery in combination with cholinesterase inhibitors. Its antimuscarinic activity is used to prevent overstimulation of the gut during reversal of neuromuscular blockade (see neuromuscular blockade).

C. ATROPINE POISONING:

"blind as a bat, mad as a hatter, red as a beet, hot as a hare, dry as a bone, the bowel and bladder lose their tone, and the heart runs alone."

In cases of overdosage with atropinic agents, one observes characteristic symptoms of atropine poisoning:



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** Sjōgren'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 poisening, 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**

CHOLINERGIC AGONISTS AND ANTAGONISTS

Date: September 4, 2012 (8:30-9:20 AM) **Recommended Reading:** **Basic and Clinical Pharmacology**, 11th Edition, Katzung, *et. al.*, pp. 95-126.

KEY CONCEPTS AND LEARNING OBJECTIVES

I. CHOLINERGIC AGONISTS:

3. Cholinergic activation is achieved via stimulation of a variety of receptors. Some cholinergic agonists act on cholinoceptors directly; others act through indirect means.

   a. *Recogize the main structural and functional difference between nicotinic and muscarinic receptors, their mechanisms of action, and their location in the body.*
   b. *distinguish between parasympathetic and nicotinic effects in the body.*
   c. *Understand the general difference between the mechanism of action of directly and indirectly acting cholinergic agonists.*

2. Several key directly acting muscarinic and nicotinic agents are used clinically. Some are synthetic compounds; others are naturally occurring tertiary amines.

   a. *Know the differences in the pharmacological activity of key quaternary nitrogen analogs of choline (i.e., nicotinic vs. muscarinic activity).*
   b. *Know the 3 key quaternary analogs of acetylcholine discussed in lecture and their pharmacological actions in the body.*
   c. *Know the prototype tertiary amine muscarinic agonist discussed in lecture and its major chemical feature that distinguishes it from the quaternary analogs. Also know how this feature affects its clinical effects.*
   d. *Know the relative susceptibility of the quaternary analog agonists to enzymatic degradation.*
   e. *Recognize common clinical uses for the 4 muscarinic agonists discussed in glass.*

3. Indirectly acting cholinergic agonists inhibit cholinesterase. They exert their effect by inhibiting the breakdown of acetylcholine in the synaptic cleft, thus extending the time during which the neurotransmitter is available to bind its receptor.

   a. *Describe the two different types of cholinesterase in the body, their location, and their mechanism of action.*

b. *Recall 3 key representative reversible cholinesterase inhibitors discussed in lecture and know their relative duration of action, and primary clinical applications*

c. *Describe the mechanism of action of the irreversible cholinesterase inhibitors, and understand the reason behind the success of 2-PAM as an antidote to irreversible cholinesterase inhibition.*

d. *Describe the toxic pharmacologic effects obtained with, and the treatment required following, exposure to organophosphates.*

II. CHOLINERGIC ANTAGONISTS:

1. Muscarinic antagonists are also known as parasympatholytic agents. Representative compounds that will be covered in this lecture include atropine, scopolamine and glycopyrrolate. These agents are also related to poisonous compounds found in common plants and contribute to deadly toxic reactions.

a. *Describe the dose-dependent pharmacological effects of atropine.*
b. *Describe the symptoms of atropine poisoning, and its treatment.*
c. *Describe various clinical applications for atropinic agents.*
d. *Understand when, how and why glycopyrrolate is used during recovery from anesthesia*

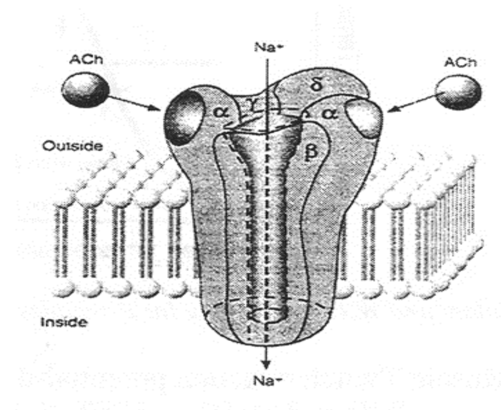
NEUROMUSCULAR RELAXANTS

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

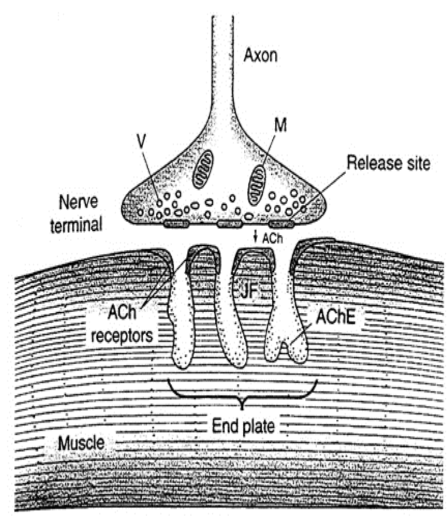
A. NEUROMUSCULAR JUNCTION NEUROTRANSMISSION



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 alpha, 1beta, 1 gamma, 1 epsilon□
Ganglionic receptor - 2□alpha, 3 beta□



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

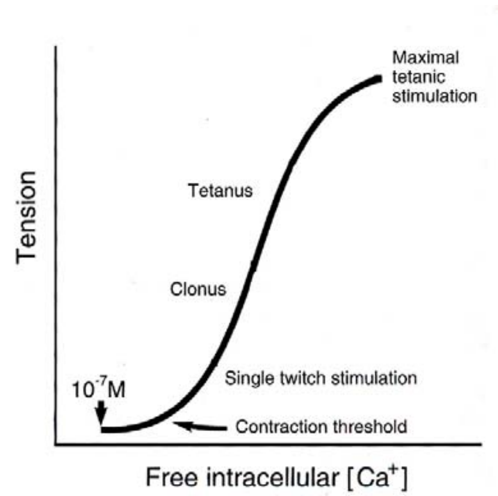
2. Acetylcholine is released from pre-synaptic vesicles into the synapse.

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.

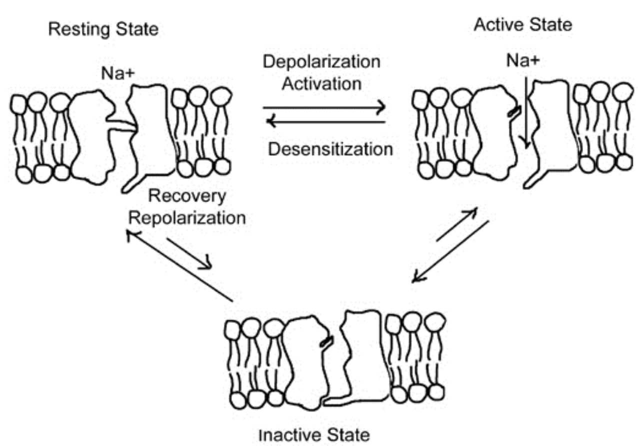
4. Muscle Twitch = Action potential-dependent increase in [Ca2+]i followed by fall in [Ca2+]i due to sequestration by sarcoplasmic reticulum

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

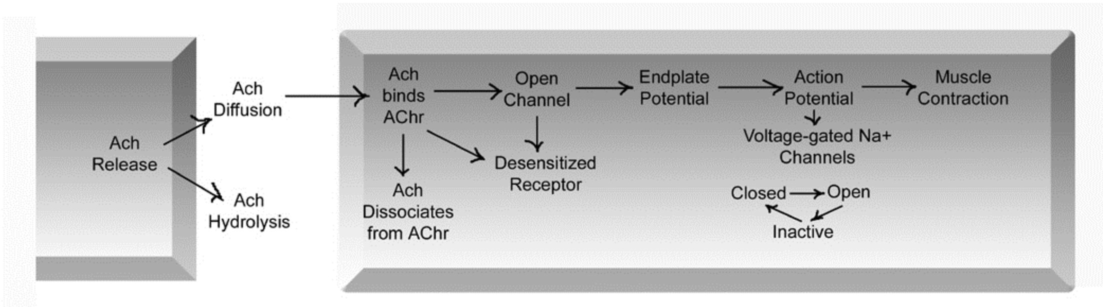


5. Propagation of the action potential generated by sufficient acetylcholine receptor (AchR) agonist binding is dependent upon availability of voltage-gated Na^+ channels in the resting state. There



KES, 2007

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)

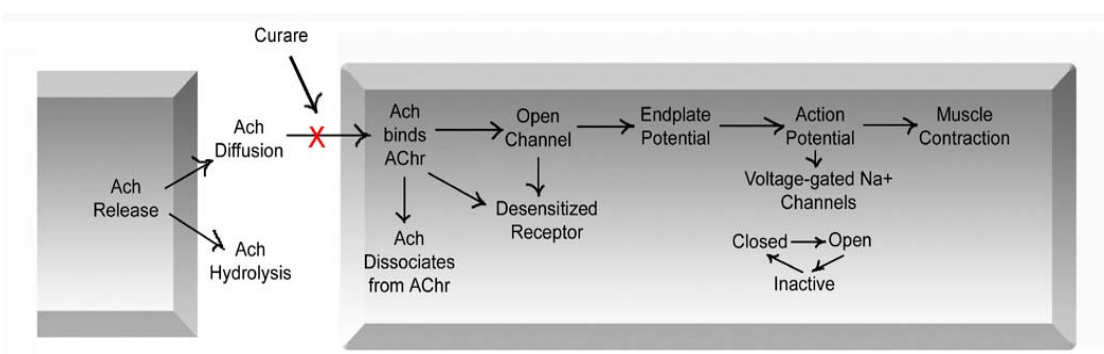
C. **NON-DEPOLARIZING BLOCKING DRUGS - COMPETITIVE ANTAGONISTS (e.g. D-TUBOCURARINE, PANCURONIUM, VECURONIUM)**

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 MANIFESTATIONS

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.

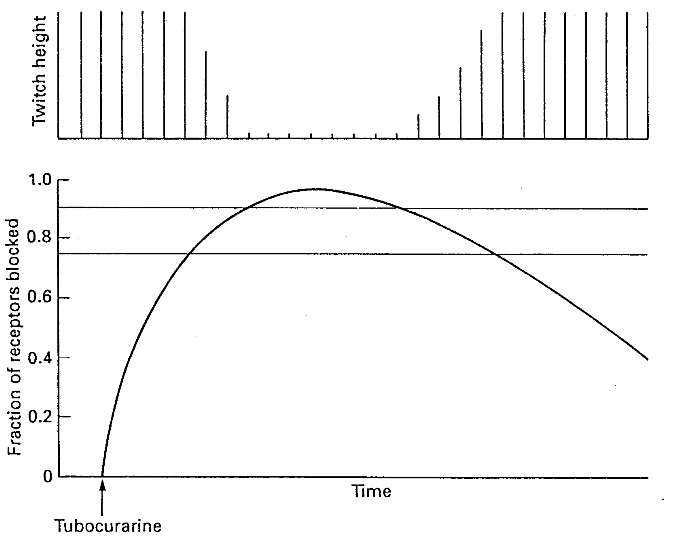
A. Pharmacokinetics
- Rapid distribution
- $T_{1/2}$ dependent on route of elimination
  - kidney > liver > plasma cholinesterase

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**1 (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 known as the receptor reserve. This concept is illustrated in the figure on the left. 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: mivacuronium)
Muscarinic blockade (increased HR and CO, pancuronium, rocuronium)

5. DRUG INTERACTIONS:

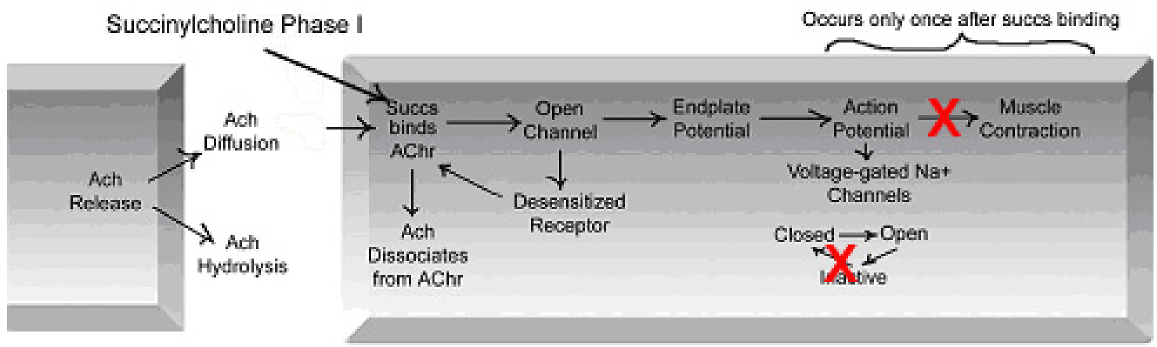
Inhalation anesthetics (enhances effect)
Antibiotics (enhance effect, particularly aminoglycosides)
Local anesthetics

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

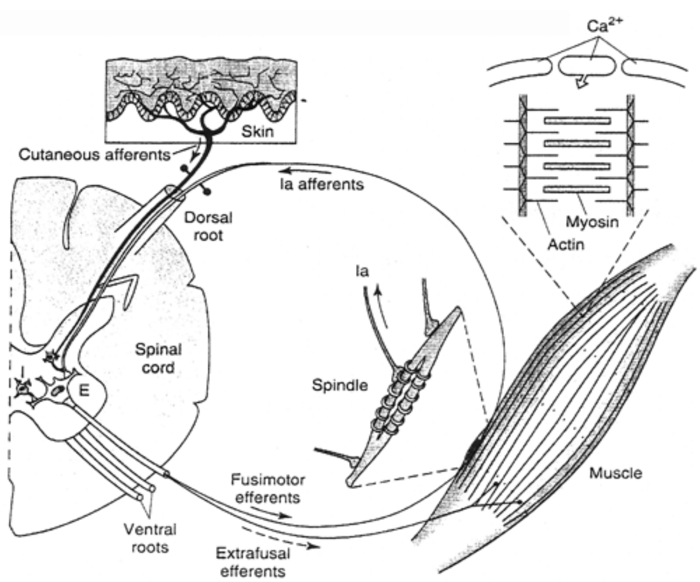
8. CONTRAINDICATIONS:

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

III. SPASMOLYTIC DRUGS

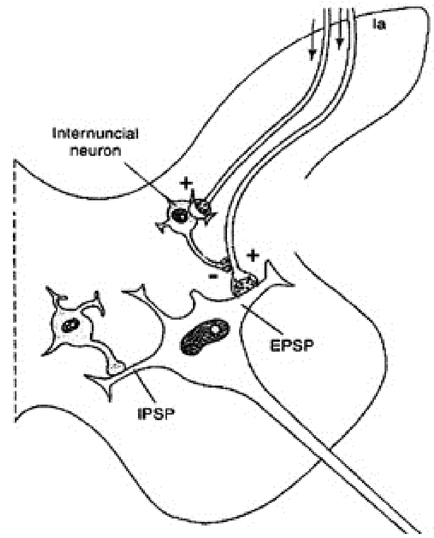
A. SKELETAL MUSCLE RELAXANTS:

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

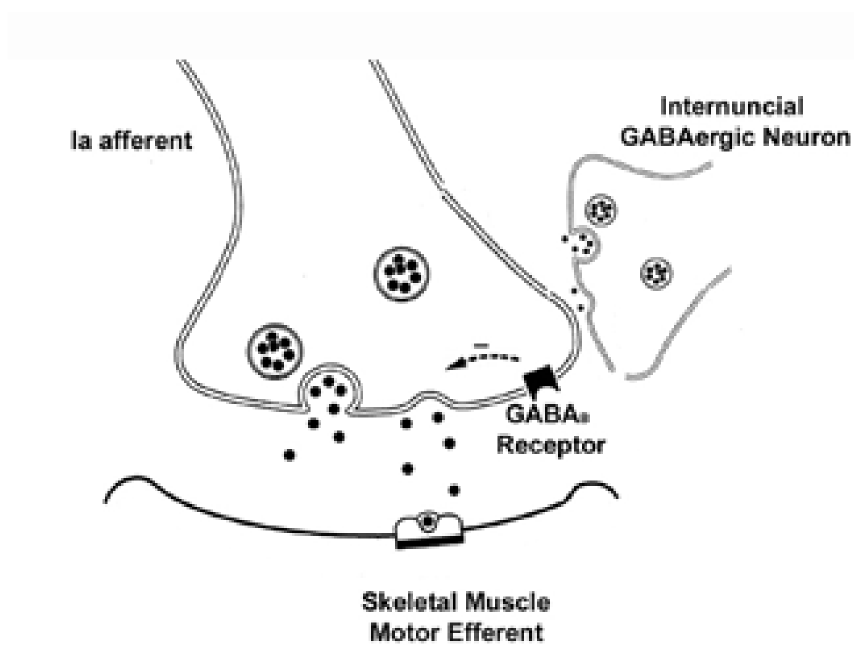


Katzung, fig. 27-11, p. 438

Reduce activity of Ia fibers that excite the primary motoneuron
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

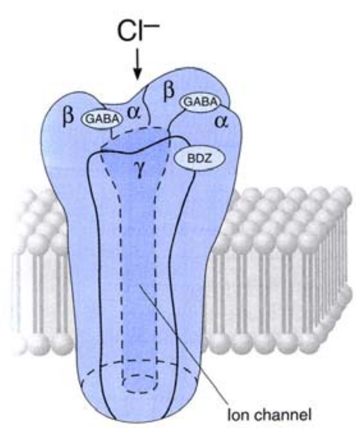
Side effects:
Sedation and drowsiness

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. <u>LIST OF DRUGS COVERED I N LECTURE:</u> for more detail consult on-line reference www.rxlist.com/cgi/generic/albut2_cp.htm. Text in bold font are <u>important.</u>

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**
Mivacuronium	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**

NEUROMUSCULAR RELAXANTS

Date: September 5 – 8:30-9:20 AM
Recommended Reading: **Basic and Clinical Pharmacology**, 11th Edition, Katzung, *et. al.*, pp. 127-166.

KEY CONCEPTS AND LEARNING OBJECTIVES

1. Neuromuscular blockers are used during specific surgical cases in which relaxation of large muscle groups are required for adequate retraction, or during intubation, artificial ventilation and electroconvulsive shock (ECS) therapy. Muscle paralysis is achieved by blocking neurotransmission and propagation of membrane depolarization in the post-synaptic membrane of the neuromuscular junction.

    a. *understand the mechanisms by which skeletal muscle nicotinic receptor activation stimulates skeletal muscle contraction including the agonists, receptors, and post-synaptic mechanisms that initiate contraction.*

2. Two different classes of neuromuscular blocking agents are used during surgery to produce paralysis. Non-depolarizing agents compete with acetylcholine for the post-synaptic nicotinic receptor. In contrast, depolarizing agents cause prolonged stimulation of the motor end plate leading to disorganized motor muscle contraction and subsequent paralysis.

    a. *Compare the two distinct mechanisms by which depolarizing and non-depolarizing neuromuscular blockers mediate their effects on the motor end plate.*
    b. *Compare the pharmacokinetics of the two classes of neuromuscular blockers.*
    c. *Recognize how cholinesterase inhibition affects the paralysis produced by each type of neuromuscular blocker.*
    d. *Compare the mechanisms by which the action of both classes of neuromuscular blockers are terminated.*
    e. *Understand the characteristics of non-depolarizing or depolarizing neuromuscular blockers that make them better suited for specific uses*
    f. *Describe the prominent side effects of each class of skeletal muscle relaxant.*
    g. *Know the antidote for either class of neuromuscular blockers.*

3. Presently, the only depolarizing neuromuscular blocker approved for use in the US is succinylcholine. The effects and mechanism of action of succinylcholine change with increasing length of exposure.

    a. *Describe the characteristics of phase I and phase II block with depolarizing neuromuscular blockers and understand why phase II should be avoided.*

4. Numerous non-depolarizing agents are available and commonly used in clinical practice. In general they differ in their onset of action, duration of action and mode of elimination. The choice of agent often depends upon the procedure for which they are used as well as the patient's medical history.

a. *Understand the characteristics of the following non-depolarizing neuromuscular blockers and why certain characteristics make the 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 length orthopedic surgery.*

Pancuronium
Rocuronium
Mivacurium
Vecuronium

5. Skeletal muscle relaxants are used for the relief of spastic muscle disorders, a state of increased muscle tone that results from an imbalance between excitatory and inhibitory neural control of muscle tone. "Spasticity" commonly results from inadequate supraspinal control resulting from upper motor neuron lesions as in cerebral palsy, multiple sclerosis or stroke. Treatment presents a difficult therapeutic problem, since often relief can be achieved only at the price of increased muscle weakness.

a. *Diagram the stretch reflex arc including the excitatory and inhibitory synapses.*
b. *Understand the physiological basis of muscle spasticity.*

6. GABAergic inhibitory neurons provide important control of somatic motor excitation at the level of the spinal cord. Pharmacological manipulations of GABA receptors are used to combat muscle spasticity.

a. *Describe the mechanisms by which baclofen and benzodiazepines alter somatic motor neuron excitation.*
b. *Describe their major side effects and understand how the route of delivery can reduce side effects.*

7. Two more novel approaches to combat muscle spasticity include the use of α2-adrenergic receptor antagonists and a selective blocker of calcium release from the sarcoplasmic reticulum.

a. *Understand the basic mechanisms by which Tizanidine and Dantrolene reduce muscle spasticity*
b. *Recognize the major side effects of both drugs.*
c. *Know the important alternative use of dantrolene in clinical practice.*

#18 - **Pharmacology of Headache Disorders**

Matthew McCoyd, MD
Assistant Professor
Department of Neurology

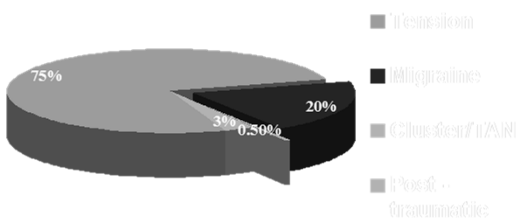
Objectives

- **Differentiate between primary and secondary headache disorders**
- **Describe pharmacological management of primary headache disorders**
- **Understand mechanism of actions of migraine specific medications**
- **Recognize side effects of various headache abortive and preventive medications**

Primary Headache Disorders

- **Migraine**
- **Cluster headaches or other trigeminal autonomic cephalgias**
- **Tension headaches**
- **Others primary headaches**

Lifetime Prevalence of Headache Disorders



Secondary Headaches

- Post-traumatic headaches
- Neuralgias (e.g. trigeminal neuralgias)
- Substance abuse or withdrawal
- Facial, neck, eye, sinus, ear, nose, teeth, mouth, or muscular pain
- Vascular disorders
- Other intracranial pathologies such as neoplasms
- Systemic infections
- Central nervous system infections
- Disorders of cerebrospinal fluid
- Sleep disorders
- Toxic, metabolic, medications

Red Flags

- Worst headache
- Atypical headache
- Progressive headache
- Headache with exertion
- Altered mental status
- Meningeal signs
- Fever
- Immunocompromised patient
- New onset focal neurologic findings
- Positional headache
- New onset of headache after age 50 or during pregnancy

Tension Headache

- Most common type of headache
- More prevalent in women
- May be continuous for months or years
  - Episodic: less than 15 days a month
  - Chronic: > 15 days a month
- Pressing/tightening quality
- Mild or moderate intensity
- No aggravation by routine activity
- No nausea or vomiting
- No photophobia or sonophobia

Cluster Headache

- More common in spring and fall
- Commoner at night
- 1 in 100
- No family history
- More prevalent in men
- Cluster period lasts 2-4 weeks
- Severe unilateral, orbital, supraorbital and/or temporal pain
- Lasts 15 to 180 minutes untreated
- Frequency: 1 qod to 8/day
- Associated signs (unilateral to pain): lacrimation, nasal congestion, rhinorrhea, ptosis, miosis, eyelid edema, conjunctival injection

Migraine

- Paroxysmal disorder
- Syndrome of subjective symptoms, not objective signs
- Clinical variability
- Variability of course
- No laboratory or pathological findings

Migraine
Criteria for diagnosis*

A. At least 5 attacks

B. Headache lasting 4-72 hours

C. Headache has at least two of the following characteristics:

1. Unilateral location
2. Pulsating quality
3. Moderate to severe intensity
4. Aggravation by walking stairs or similar routine physical activity

* Migraine without aura

Common Pathway for Pain Regardless of Underlying Etiology of the Headache

- Not completely understood
- Three key factors
  - Cranial blood vessels
  - Trigeminal innervation of the vessels
  - Reflex connections of the trigeminal system with the cranial parasympathetic outflow
- HA pain of the scalp and face is transmitted via trigeminal nerve
- Serotonin receptors are the main focus of pain management

Migraine Is a Neurovascular Disorder

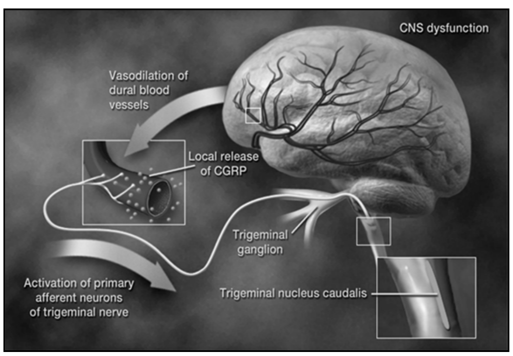
- Genesis of migraine is neurologic
- Likely that hyperexcitability of central nervous system confers susceptibility to migraine attacks
- Migraine associated with regional reduction in cerebral blood flow and cortical spreading depression
- Trigeminovascular system involved in generation of migraine pain

Aurora SK, Welch KMA. *Curr Opin Neurol*. 2000;13:273-276
Aurora SK. *Curr Pain Headache Rep*. 2001;5:179-182
Olesen J et al. *Ann Neurol*. 1990;28:791-798
Goadsby PJ et al. *Ann Neurol*. 1990;28:183-187

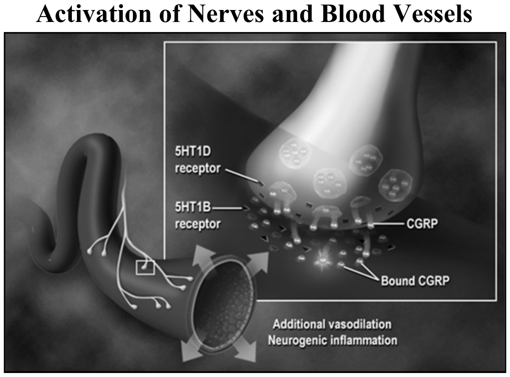
Pain Generators

- Large cranial vessels
- Proximal intracranial vessels
- Dura mater
  - These vessels are innervated by branches of the ophthalmic division of the trigeminal nerve, whereas the structures of the posterior fossa are innervated by branches of the C2 nerve roots

The Migraine Process: Activation of the Trigeminal Nucleus Caudalis (TNC)



The Migraine Process: Activation of Nerves and Blood Vessels



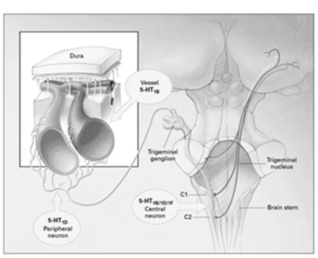
The Role of Serotonin in Migraine

- Migraine reflects events within the vessel wall, the vessel lumen, and the brain
- Localization of 5-HT_1 receptors to cephalic vessels explains preferential development of migraine
- Stimulation of 5-HT_{1D} receptors cause neuronal inhibition of central nervous system (CNS) neurons, and 5-HT_{1B} dural cerebral vessel smooth muscle relaxation
- Selective drug binding to 5-$HT_{1B/D}$ receptors is critical to therapeutic efficacy in migraine

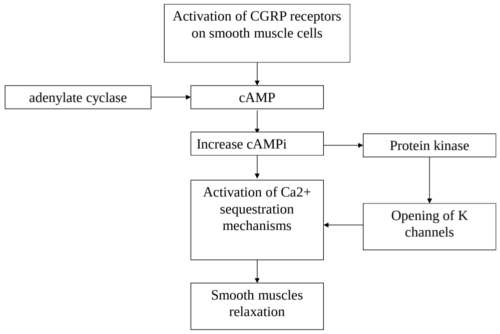
Headache Therapies

- Acute
  - Targets the blood vessels
  - Goal is to eliminate symptoms
- Preventive
  - Targets the brain
  - Goal is to reduce frequency of attacks

Possible Sites of Action of Triptans in the Trigeminovascular System



Cellular mechanisms of vasodilatation to CGRP



Pharmacological targets for potential antimigraine agents

- **Serotonergic receptors**
  - **5-HT$_{1B/1D}$ receptors**
  - **5-HT$_{1F}$ receptors**
  - **5-HT$_{2B}$ receptors**
  - **5-HT$_{3}$ receptors**
- **alpha adrenoceptors**
- **β-adrenergic receptors**
- **Calcium channel**
- **Platelet serotonin release**
- **CGRP antagonists e.g. olcegepant**
- **Dopaminergic antagonists**

Classification for 5-HT Receptors

Receptor	Effects mediated
• 5-HT$_{1A,1B,1D}$	**Neuronal inhibition of central nervous system (CNS) neurons, smooth muscle relaxation, contraction of some vascular smooth muscle** – **1A antagonist ergotamine** – **1B agonist triptans, ergotamine** – **1D agonist triptans, antagonist ergotamine**
• 5-HT$_{2}$	**Neuronal depolarization; vasoconstriction of most blood vessels, bronchoconstriction, contraction of gastrointestinal smooth muscle, platelet aggregation** – **2A antagonist cyproheptadine, atypical antipsychotic s** – **2C antagonist methysergide, fluoxetine**
• 5-HT$_{3}$	**Neuronal depolarization leading to activation of autonomic reflexes, neuronal excitation in the CNS** – **Antagonist metaclopramide, mirtazapine, memantine**
• 5-HT$_{4}$	**Gastrokinetic action (cholinergically mediated ileal contraction) myocardial stimulation, esophageal relaxation (in animal studies)** – **Agonist metaclopramide**

Antimigraine Mechanisms of the $5HT_{1B/1D}$ Receptor Agonists

Location	Mechanism of Action
Vascular	Selective constriction of pain-producing intracranial extracerebral blood vessels
Neurogenic	Reduction of trigeminal sensory nerve activation and inhibition of vaso-active neuropeptide release
Central	Inhibition of neurotransmitter release from activated trigeminal nerves in the brainstem and upper cervical spine column

Hargreaves et al,.Can J Neurol Sci.1999

Levels of Evidence

- ***Level I***
  Independent, blind comparison with a "gold standard" of anatomy, physiology, diagnosis, or prognosis among a large number of consecutive patients suspected of having the target condition
- ***Level II***
  Independent, blind comparison with a "gold standard" among a small number of consecutive patients suspected of having the target condition
- ***Level III***
  Independent, blind comparison with a "gold standard" among nonconsecutive patients suspected of having the target condition
- ***Level IV***
  Included studies that did not meet criteria for at least Level III evidence

Strength of Evidence (quality of evidence)

- ***Grade A***
  Multiple well-designed randomized clinical trials, directly relevant to the recommendation, yielded a consistent pattern of findings
- ***Grade B***
  Some evidence from randomized clinical trials supported the recommendation, but the scientific support was not optimal. For instance, few randomized trials existed, the trials that did exist were somewhat inconsistent, or the trials were not directly relevant to the recommendation. An example of the last point would be the case where trials were conducted using a study group that differed from the target group of the recommendation
- ***Grade C***
  The US Headache Consortium achieved consensus on the recommendation in the absence of relevant randomized controlled trials

Migraine Abortive Medications

- Simple Analgesics
- NSAIDs
- Anti-emetics
- Lidocaine
- Migraine-specific medications
  - Triptans
  - Ergotamine
  - DHE

Avoid butalbital-containing medications and narcotics

Acute Medications with Established Statistical and Clinical Benefit Grade A

- Triptans
- DHE
- Acetaminophen/aspirin + caffeine for non-disabling headaches
- Aspirin/ ibuprofen/naproxen sodium
- Butorphanol Intranasal *addictive*

Triptans

Index drug: Sumatriptan

- All triptans are agonists at $5HT_{1B/D}$ receptors
- Range of agents available (currently 7)
- Variety of strengths, dosage forms – SC, PO, nasal
- Range of half-lives 3-26 hours
- Vary in lipophilicity, selectivity for cerebral vessels
- Most provide approx 66% headache response at 2 hours
- Most provide approx 30% pain-free response at 24 hours

Pharmacokinetic characteristics of triptans

Variable	Sumatriptan Imitrex®	Almotriptan Axert®	Eletriptan Relpax®	Frovatriptan Frova®	Naratriptan Amerge	Rizatriptan Maxalt®	Zolmitriptan Zomig®
Half-life (hr)	2.0	3.5	5.0	25.0	5.0-6.3	2.0	3.0
Time to max concentrations (hr)							
During attacks	2.5	2.0-3.0	2.8	3.0	2.0-3.0	1.0	4.0
At other times	2.0	1.1-3.8	1.4-1.8	3.0	2.0-3.0	1.0	1.8-2.5
Oral bioavailability (%)	14	69	50	24-30	63-74	40	40
Metabolism & Excretion							
Primary route	MAO	CYP3A4	Renal 50%	Renal 50%	Renal 70%	MAO	CYT450
Secondary route	-	MAO, CYP2D6	CYT450	CYP1A2	CYT450	-	MAO

Non-oral Alternatives

- **Nasal Sprays**
  - **Dihydroergotamine (Migranal®)**
  - **Sumatriptan (Imitrex®)**
  - **Zolmitriptan (Zomig®)**
- **Injections**
  - **Dihydroergotamine SC, IM, IV (D.H.E. 45®)**
  - **Sumatriptan SC (Imitrex®)**

Caveats in use of Triptans

- **Avoid within 24 hrs of use with ergotamine**
- **Avoid if patient on MAO inhibitor**
- **Avoid if patient has, or is at risk for ischemic heart disease**
- **Avoid with uncontrolled hypertension, renal disease**
- **Avoid in cases of basilar migraine, hemiplegic migraine**

Triptan Sensations

- Warm/Hot sensations
- Tightness
- Tingling
- Feelings of heaviness or pressure
- Occur in nearly any part of the body
- Most commonly reported in face, limbs, and chest
- Occur with all
  - $5\text{-}HT_{1B/1D}$ agonists

Serotonin Syndrome

Central Serotonergic Hyperstimulation

- Motor Symptoms
  - Myoclonus
  - Tremor
  - Hyperreflexia
  - Incoordination
- Mental status changes
  - Agitation
  - Hypomania
  - Confusion
- Autonomic Symptoms
  - Diaphoresis
  - Fever
  - Shivering

Contraindications and Precautions triptans

- Ischemic cardiac, cerebrovascular, or peripheral vascular disease
- Uncontrolled hypertension
- Hypersensitivity
- Use within 24hrs of another $5HT_1$ agonists and/or ergots
- Hemiplegic/basilar migraine
- Prior evaluation of patients with risk factors for CAD
- Severe hepatic impairment
- SSRI precaution

Ergot alkaloids

- Ergotamine, dihydroergotamine
- Powerful vasoconstrictors derived from rye fungus claviceps purpurea
- C. purpurea also contains LSD, isolated 1938
- Known since medieval times; St Anthony's Fire
- Epidemics of hallucinations with peripheral gangrene
- Last recorded outbreak in France 1954
- Potent binding to $5HT_{1B}$, $5HT_{1D}$, $5HT_{1F,}$ and $5HT_2$ receptors
- Affinity for alpha, beta and dopamine receptors
- May work via inhibition of neurogenic inflammation

Ergotamine & DHE receptor profile

Adrenergic receptors	Dopaminergic receptors	Serotoninergic receptors
Alpha 1	DA1	5-HT1A
Alpha 2	DA2	5-HT1B
Beta		5-HT1F
		5-HT2A
		5-HT2C
Alpha1 > Alpha 2> Beta; DA2 > DA1		

Ergot Alkaloids

- Ergotamine
  - rarely used since introduction of triptans
  - available in US only in suppository form
  - potent arterial vasoconstrictor
  - extremely nauseating
  - causes uterine contractions
- DHE
  - IV, SC and nasal spray formulations
  - arterial and venous vasoconstrictor
  - less emetic
  - less uterine contraction than ergotamine

Contraindications and Precautions
Ergots

- Ischemic cardiac, cerebrovascular, or peripheral vascular disease,
- Collagen vascular disease or vasculitis
- Cardiac valvular disease
- Uncontrolled hypertension
- Use within 24hrs of triptan therapy
- Hemiplegic/basilar migraine
- Prior evaluation of patients with risk factors for CAD
- Renal or hepatic impairment
- Pregnancy, breastfeeding
- Age > 60

Migraine Preventive Medications

- Anticonvulsants
- Antihypertensives
- Tricyclic antidepressants
- NSAIDs
- Opiates
- Muscle relaxants
- Serotonin antagonists

Goals of Preventive Treatments

- Reduce attack frequency
- Reduce attack severity
- Reduce attack duration
- Improve response to acute treatment
- Improve function and reduce disability
- Possibly treat co-morbid conditions

Prophylactic Medications
General principles

- Initiate therapy with medications that have the highest level of evidence
- Begin with lowest effective dose and increase gradually
- Aim to achieve a good response with minimal side effects
- Allow 8-12 weeks trial period
- Watch for adverse effects and drug interactions
- Avoid during pregnancy
- If successful therapy, may taper after one year

Preventive Therapy for Migraine

Drug	Dose	Selected Side Effects
B-adrenergic receptor antagonists Propranolol Metoprolol	 40-240 100-200	Reduced energy, tiredness, postural symptoms, drowsiness, weight gain, impotence
Amitriptyline	25-75	Drowsiness, weight gain, dry mouth
Divalproex	800-1200	Tiredness, weight gain, hair loss, liver and hematologic abnormalities, teratogenecity
Flunarizine	5-15	Tiredness, weight gain, depression, parkinsonism
Serotonin antagonists Pizotiline Methysergide	 0.5-3 1-6	Drowsiness, weight gain Drowsiness, leg cramps, retroperitoneal fibrosis, hair loss
Verapamil	160-320	Constipation, leg swelling, atrioventricular conduction disturbances
SSRI		Anxiety, insomnia
Gabapentin	900-2400	Tiredness, dizziness
Topiramate	25-200	Confusion, paresthesia, weight loss
Tizanidine		Fatigue

Group 1†	Group 2‡	Group 3§	Group 4¶	Group 5‖
Amitriptyline	B-blockers	A: Antidepressants	Methysergide	Acebutolol
Divalproex sodium	Atenolol/metoprolol/nadolol	Doxepine		Carbamazepine
Propranolol/timolol		Fluvoxamine		Clomipramine, clonazepam
Topiramate				
	Ca-blockers	Imipramine		Clonidine
	Nimodipine/verapamil	Mirtazepine		Indomethacin
		Nortriptyline		Nicardipine
	NSAIDs	Paroxetine		Nifedipine
	Aspirin/fenoprofen/flurbiprofen	Protriptyline		Pindolol
	Ketoprofen	Sertraline trazodone		
	Mefenamic acid	Venlafaxine		
	Neproxen	Cyproheptadine		
	Other	B: (side effect concerns)		
	Feverfew	Methylergonovine (methylergometrine)		
	Magnesium vitamin B2	Phenelzine		

Alternative Therapies

- Avoid triggers
- Relaxation, biofeedback
- Physical therapy
- Dietary/vitamin supplementation:
  - Vitamin B2, B6
  - St.John's Wort
  - Ginger
  - Gingko biloba
  - Fever few
  - Magnesium supplementation
  - Coenzyme Q10
- Botulinum toxins (*)
- Nerve blocks
- Neurostimulation

Cluster Headache Acute therapies

- Limited by headache duration 30- 90 minutes
- Oral medications of little use
- Effective medications
  - Inhaled oxygen 100
  - Injectible sumatriptan
  - Nasal spray triptans
  - Intranasal lidocaine
  - Intranasal DHE
- Prednisone

Cluster Headache Preventative Therapies

- Calcium channel blockers: verapamil (bradycardia, drop in blood pressure, pedal edema, weight gain)
- Anticonvulsants: valproic acid (weight gain, tremor, hair loss, thrombocytopenia, pancreatitis) topiramate (nephrolithiasis, cognitive impairment, tingling sensation, glaucoma)
- Lithium carbonate (nephrogernic diabetes insipidus, thyroid disease, tremor)

Pharmacology of Tension Headaches

- Acute tension headache:
  - NSAIDs
  - Acetaminophen
- Chronic tension headache
  - Prophylaxis approach, e.g. tricyclic antidepressants, tizanidine)
  - Management of co-morbidities especially psychological
  - Biofeedback therapy
  - Sleep hygiene
- Avoid overuse of OTCs due to risk of medication overuse headaches (MOH)
- Avoid narcotic use due to risk of MOH and substance dependence

Pharmacology of Secondary Headaches

- Treatment of underlying etiology
- Simple analgesics:
  - Acetaminophen
  - NSAIDs
  - Combination agents
  - Tramodol (centrally-acting, opioid-like)
- Avoid narcotics

END

OPIOIDS

Reading Assignment:

OPIOID RECEPTORS
MariaWaldhoer,SelenaE.Bartlett,and
JenniferL.WhistlerKatzung.
Annu. Rev. Biochem. 2004. 73:953–90

KEY CONCEPTS AND LEARNING OBJECTIVES

1. Be familiar with the "opioids system".

   a. Describe the major opioid receptors, tissue expression, and their signal transduction.
   b. Describe the major ligands for these receptors

2. Be familiar with the physiology of pain experience

3. Understand the role of opioid transmission in the pain experience and how agonists induce analgesia.

4. Understand the concepts of opioid tolerance, dependence, and addiction.

5. Be able to compare and contrast each of the drugs listed in table 1

Table 1)

Category	Generic name
Strong analgesic	Morphine
	Meperidine
	Methadone
Moderately strong analgesic	Oxicodone
	Codeine
Agonist-antagonists	Pentazocine
	Buprenorphine
Antagonist	Naloxone

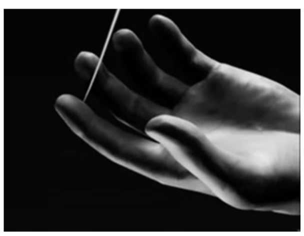
Opioids Analgesic

Dr. Saverio Gentile, Ph.D.
Department of Molecular Pharmacology & Therapeutics
Loyola University Chicago
Stricht School of Medicine
sagentile@lumc.edu
Tel: 708-216-3263

Peter Paul Rubens
Prometheus Bound,
c.1610/11
Philadelphia Museum of Art

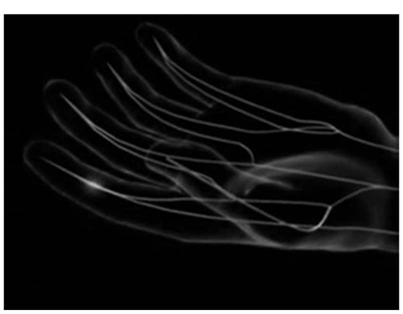
Tissue Damage

When tissue is damaged, there is an immediate release of inflammatory chemicals called excitatory neurotransmitters, such as histamine and bradykinin. Bradykinin stimulates the release of prostaglandins and substance P, a potent neurotransmitter that enhances the movement of impulses across nerve synapses.



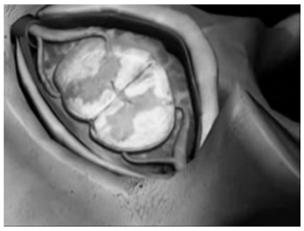
Transduction

Transduction occurs as the energy of the stimulus is converted to electrical energy.
Nociceptor→ action potential.



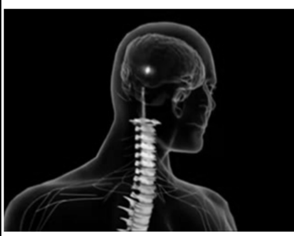
Transmission

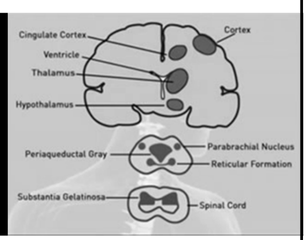
Pain stimuli travel quickly to the substantia gelatinosa in the dorsal horn of the spinal cord, then cross over to the opposite side of the spinal cord and ascend to the higher centers in the brain via the spinothalamic tracts and on to the thalamus and higher centers of the brain, including the reticular formation, limbic system, and somatosensory cortex.



Perception

When pain stimuli reach the cerebral cortex, the brain interprets the signal; processes information from experiences, knowledge, and cultural associations; and perceives pain. Thus, perception is the awareness of pain. The somatosensory cortex identifies the location and intensity of pain, and the associated cortex determines how an individual interprets its meaning.





Generally pain is divided into two types:

ACUTE PAIN

It is a normal, predicted physiological response to a noxious chemical, thermal or mechanical stimulus
It is of sudden onset, lasting → hrs-ds (not > 6 ms)
Disappears once the underlying cause is treated.
Beneficial in a sense that it is a warning of actual or potential physical harm; signaling that damage has occurred & that something needs to be done.

Examples of acute pain :
- Heart attack
- Acute appendicitis
- Bone fracture
- Muscle sprain
- Prolapsed disc

CHRONIC PAIN

It is the pain that starts acute & continues beyond normal time expected or persists or recurs for various other reasons
It outlived its usefulness & is no longer beneficial to patient.

Examples of chronic pain:
- Cancer
- Neuropathy
- Inflammation
- Distensions
- Eruptions

Goals of pain managment

Reducing Pain → treat the cause

Focused on reducing the pain

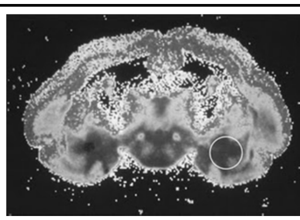
Minimize pain, limit disability & maximize person's function
Multidisciplinary; blends physical, emotional, intellectual & social variables

Opioids

can be

Extracted | Synthesized | Endogenous

Expression of μ-type opioids in Human CNS

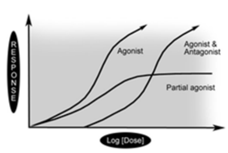


Agonist: A compound that will bind to a receptor to positively activate a pharmacological response. Opioid agonists include morphine, heroin (diamorphine) and oxycodone.

Antagonist: A compound that binds to a receptor without activating any pharmacological response; as if the receptor were unoccupied. Naloxone and Naltrexone are opioid antagonists.

Partial Agonist: A compound that will bind to a receptor to positively activate a LIMITED pharmacological respone. Opioid partial agonists include pentazocine and buprenorphine.

Agonist-antagonist: opioid analgesics are a heterogeneous group of drugs with moderate to strong analgesic activity comparable to that of the pure agonist opioids such as codeine and morphine but with a limited effective dose range. The group includes drugs which act as an agonist or partial agonist at one receptor and an antagonist at another



Drugs for pain management

Category	**Generic name**	**Trade name**
Strong	Morphine	(various)
	Methadone	Dolophine®
	Meperidine	Demerol®
Moderately Strong	Codeine	(various)
	Oxycodone	Roxicodone®; Percodan® + Aspirine Percocet® + acetominophen
Receptor agonist-antagonist	Pentazocine	Talwin® + aspirin Talacen® + acetinophen
	Buprenorphine	Buprenex®
Antagonist	Naloxone	Narcan®

Receptor	Subtypes	Location	Function
Delta (δ) (OP1)	δ1, δ2	**Brain** -Pontine nuclei -Amygdala -Olfactory bulbs -Deep cortex	-Analgesia -Antidepressant effects -Physical dependence
Kappa (κ) (OP2)	κ1, κ2, κ3	**Brain** -Hypothalamus -Periaqueductal gray -Claustrum **Spinal cord** - Substantia gelatinosa	-Spinal analgesia -Sedation -Miosis -Inhibition of ADH release -dysphoria
Mu (μ) (OP3)	μ1, μ2, μ3	**Brain** -Cortex (lamina III-IV) -Thalamus -striosomes -periaqueductal gray **Spinal cord** -substantia gelatinosa Intestinal tract	**μ1**: -Supraspinal analgesia -physical dependence **μ2**: -Respiratory depression -miosis -euphoria -reduced GI mobility -physical dependence **μ3**: ???
Nociceptin receptor (OP4)	ORL1	**Brain** -Cortex -Amygdala -hippocampus -septal nuclei -habenula -hypothalamus **Spinal cord**	-anxiety -depression -appetite

Definitions

Analgesia: absence of pain without loss of consciousness

Antidepressant: alleviate mood disorder

Physical dependence: chronic use of a drug that has produced tolerance

Sedation: administration of drugs to facilitate a medical procedure or diagnostic procedure

Miosis: constriction of the pupil to less to 2 mm

Dysphoria: unpleasant or uncomfortable mood, such as sadness. Opposite of Euphoria.

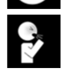
Central Nervous system effects

Analgesia: Pain consist of both sensory and affective (emotional) components. Opioids analgesic are unique in that they reduce both aspects of the pain experience.

Euphoria: Intravenous morphine users experience a pleasant floating sensation with lessened anxiety and distress. However, dysphoria, an unpleasant state characterized by restlessness and malaise, may occur.

Sedation: In standard analgesic doses, morphine (all opioids) disrupts normal REM and non-REM sleep patterns.

Cough suppression: Well recognized opioid action. Codeine is used to treat patients soffering from pathological cough and in patients in whom iit is necessary to maintain ventilation via endotracheal tube.

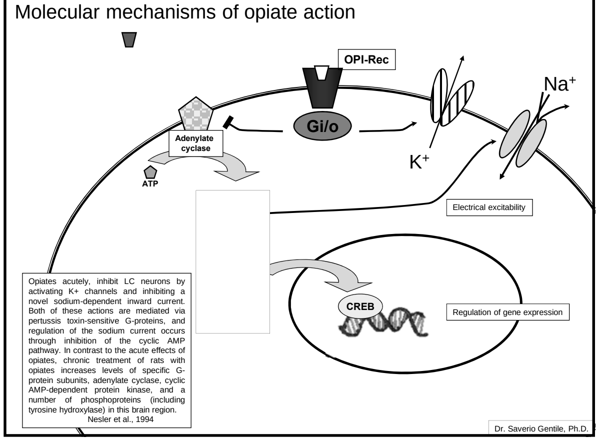


Miosis: Pharmacologic action to which no tolerance develops. Good to diagnose opioid overdose.

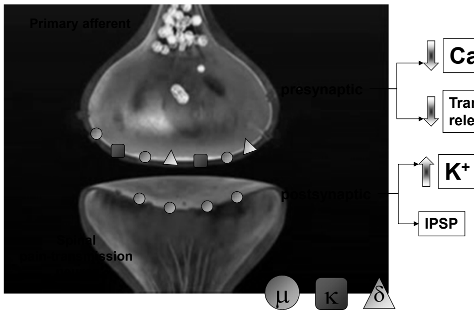
Temperature: Body temperatire is partially regulated by the action of endogenous opioids in the brain. Morphin administered to the antherior hypothalamus produced hyperthermia. Stimulation of k-receptor = hypothermia.

Respiratory depression: Opioid analgesic can produce significant respiratory depression by inhibiting brainstem respiratory mechanism. This is one of the most difficult clinical challenges in the treatmet of severe pain. Research to overcome this problem is focused on delta type receptor pharmacology.

Molecular mechanisms of opiate action

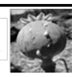


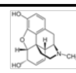
Pre-and-post synaptic expression of Opioids Receptors: LOCATION
LOCATION
LOCATION



Morphine
(strong)

Prototypical opioid
Note: Discovered by the Byzantines





Indication

Morphine can be used as an analgesic to relieve:

- pain in myocardial infarction
- pain in sickle cell crisis
- pain associated with surgical conditions, pre- and postoperatively
- pain associated with trauma
- severe chronic pain, e.g., cancer
- pain from kidney stones (renal colic, ureterolithiasis)
- severe back pain

Side Effects

- Constipation (μ-rec myenteric plexus)
- Addiction (psychological and physiological)
- Tolerance
  . Rec. phosphorylation=conformational changes
  . de-coupling from G-prot.=desensitization
  . Receptor internalization=reduced number
  . cAMP upregulation= counterugulatory

Withdrawal

Cessation of dosing with morphine creates the prototypical opioid withdrawal syndrome, which unlike that of barbiturates, benzodiazepines, alcohol, or , is not fatal by itself in neurologically healthy patients without heart or lung problems; it is in theory self-limiting in length and overall impact in that a rapid increase in metabolism and other bodily processes takes place, including shedding and replacement of the cells of many organs. Nonetheless, suicide, heart attacks, strokes, seizures proceeding to status epilepticus, and effects of extreme dehydration do lead to fatal outcomes in a small fraction of cases.

Overdose

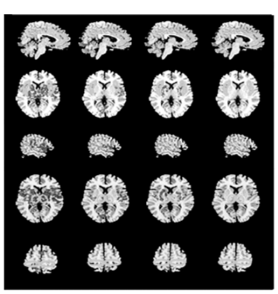
A morphine overdose occurs by intentionally or accidentally taking too much of it. A large overdose can cause asphyxia and death by respiratory depression if the person does not get medical attention or an antidote (Naloxone) immediately.

Note: Morphine and Hepatitis C

Researchers at the University of Pennsylvania have demonstrated that morphine withdrawal complicates hepatitis C by suppressing IFN-alpha-mediated immunity and enhancing virus replication.

References: Gupta K, Kshirsagar S, Chang L, *et al.* (2002).
Roshanpour M, et al. (2009).
Koch T, Höllt V (2008).
Wang CQ, Li Y, Douglas SD, *et al.* (2005).

Opioids Induce Analgesia by Reducing the Amount of Information



NeuroImage
Volume 45, Issue 3, 15 April 2009, Pages 940-949

ANESTHESIA & ANALGESIA

Summary of group functional magnetic resonance imaging (fMRI) results (*n* = 9 subjects) showing voxel maps of significant differences in voxels between "pain" and "no pain" conditions, for each of the four treatment conditions (control, VR only, opioid only, and combined VR + opioid). Regions of interest are outlined in green. Alone, VR and opioid each appear to attenuate pain-related neural activity in the five regions of interest, whereas the combination of VR+ opioid appears to further reduce pain-related activity compared with either treatment condition alone. VR = virtual reality distraction; ACC = anterior cingulate cortex; SS2 = secondary somatosensory cortex; SS1 = primary somatosensory cortex.

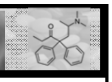
Drug	Interaction
Triprolidine histamine H1 antagonist used in allergic rhinitis; asthma; and urticaria	The CNS depressants, Triprolidine and Morphine, may increase adverse/toxic effects due to additivity. Monitor for increased CNS depressant effects during concomitant therapy.
Trovafloxacin broad spectrum antibiotic It was withdrawn from the market due to the risk of hepatotoxicity.	Morphine may reduce serum levels of Trovafloxacin decreasing the efficacy of the antibiotic. IV doses of morphine should be administered at least 2 hours after a dose of Trovafloxacin given in a fasting state or 4 hours after if given in a fed state.
Rifampin A semisynthetic antibiotic	Rifampin decreases the effect of morphine/codeine

Food Interactions

- •Avoid alcohol.
- •Take with food.
- •To avoid constipation: increase your daily intake of fiber (beans, whole grains, vegetables).

Methadone
(strong)

-Binds μ–Rec and NMDA (Glutamate Rec.)
-Low cost



It is an opioid analgesic that is primarily a mu-opioid agonist.
It has actions and uses similar to those of morphine.
It also has a depressant action on the cough center and may be given to control intractable cough associated with terminal lung cancer.
Methadone is also used as part of the treatment of dependence on opioid drugs, although prolonged use of methadone itself may result in dependence.

The methadone abstinence syndrome, although qualitatively similar to that of morphine, differs in that the onset is slower, the course is more prolonged, and the symptoms are less severe.

1. Mu-type opioid receptor
Actions: **agonist**

2. Delta-type opioid receptor
Actions: **agonist**

3. Glutamate [NMDA] receptor subunit 3A →
Actions: **antagonist**

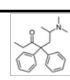
Some data also indicate that methadone acts as an antagonist at the N-methyl-D-aspartate (NMDA) receptor. The contribution of NMDA receptor antagonism to methadone's efficacy is unknown. Other NMDA receptor antagonists have been shown to produce neurotoxic effects in animals.

4. Neuronal acetylcholine receptor subunit alpha-10 →
Actions: **antagonist**

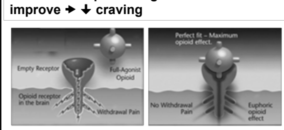
Ionotropic receptor with a probable role in the modulation of auditory stimuli. The channel is permeable to calcium which may activate a potassium current which hyperpolarizes the cell membrane. In the ear, this may lead to a reduction in basilar membrane motion, altering the activity of auditory nerve fibers and reducing the range of dynamic hearing. This may protect against acoustic trauma

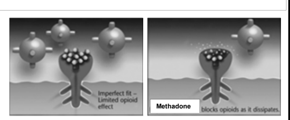
Methadone
(strong)

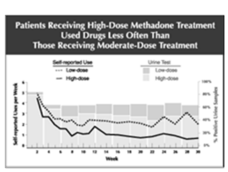
-Binds μ–Rec and NMDA (Glutamate Rec.)
-Low cost



Firm occupancy of opioid receptors by methadone ↓ desire for other opioid intake, because it is producing an ↓ effect that stop withdrawal manifestations. With time addicts improve → ↓ craving







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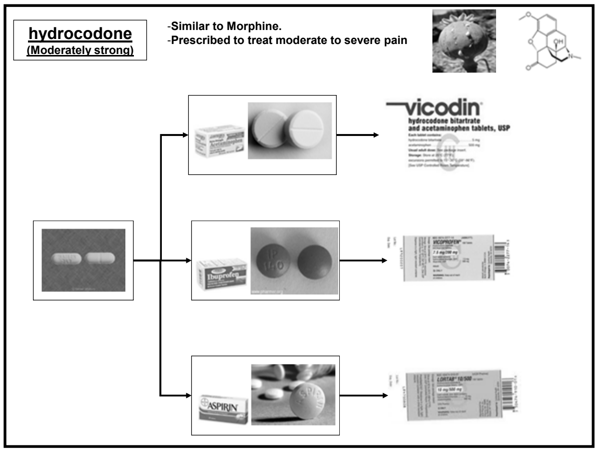
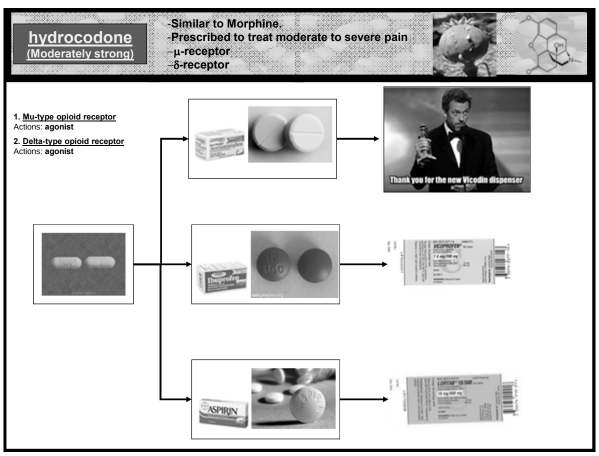
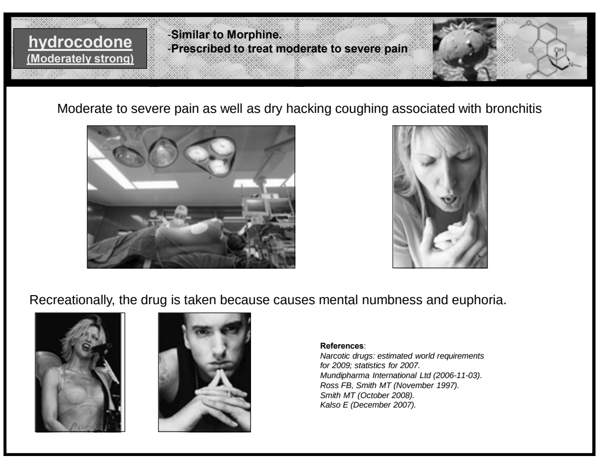
References:
http://www2.cochrane.org/reviews/
^ "Dolophine Drug Description". http://www.rxlist.com/cgi/generic/methdone.htm.
^ "Methadone". http://web.archive.org/web/20080227025738/http://www.nlm.nih.gov/medlineplus/druginfo/medmaster/a682134.html.
^ "Methadone". http://www.drugs.com/methadone.html.
^ "Methadone". http://www.medicinenet.com/methadone-dispersible_tablet/article.htm.


hydrocodone
(Moderately strong)
-Similar to Morphine.
-Prescribed to treat moderate to severe pain
vicodin
hydrocodone bitartrate
and acetaminophen tablets, USP
ASPIRIN


hydrocodone
(Moderately strong)
-Similar to Morphine.
-Prescribed to treat moderate to severe pain
-μ-receptor
-δ-receptor
1. Mu-type opioid receptor
Actions: agonist
2. Delta-type opioid receptor
Actions: agonist
Thank you for the new Vicodin dispenser
ASPIRIN


hydrocodone
(Moderately strong)
-Similar to Morphine.
-Prescribed to treat moderate to severe pain
Moderate to severe pain as well as dry hacking coughing associated with bronchitis
Recreationally, the drug is taken because causes mental numbness and euphoria.
References:
Narcotic drugs: estimated world requirements for 2009; statistics for 2007.
Mundipharma International Ltd (2006-11-03).
Ross FB, Smith MT (November 1997).
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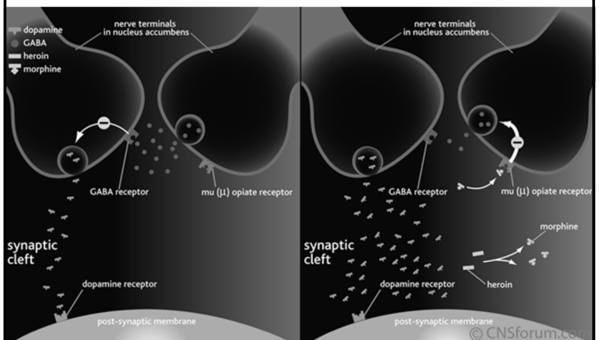
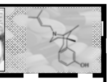
The mechanism of action of at the mu (m) opiate receptors



Euphoria

Pentazocine
agonist-antagonist narcotic



1. **Mu-type opioid receptor**
   Actions: **antagonist**
2. **Delta-type opioid receptor**
   Actions: **agonist**
3. **Kappa-type opioid receptor**
   Actions: **agonist**

Indication

Codeine can be used as an analgesic to relieve mild/moderate pain

-**Dental extraction**

Side Effects
Pentazocine weakly antagonizes the analgesic effects of morphine and meperidine;

-**Hallucinations**
-**Psychotomimetic effects**
-**Cardiovascular effects**

Withdrawal

Will cause withdrawal in opioid dependent person

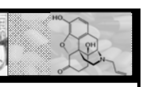
Note: Necrosis and sepsis

Severe injection site necrosis and sepsis has occurred (sometime requiring amputation of limb) with multiple injection of pentazocine lactate

References:
Pain-Killing Drug Approved By F.D.A., New York Times, June 27, 1967, pg. 41.
"TALWIN (pentazocine lactate) injection, solution". National Institute of Health. http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=8926. Retrieved 2009-02-01.

Naloxone
antagonist

- High affinity for μ-opioid in the CNS
- Antagonist action for κ- and δ Rec.



1. **Mu-type opioid receptor**
   Actions: antagonist
2. **Delta-type opioid receptor**
   Actions: antagonist
3. **Kappa-type opioid receptor**
   Actions: antagonist

Naloxone is an opiate antagonist and prevents or reverses the effects of opioids including respiratory depression, sedation and hypotension.

Also, it can reverse the psychotomimetic and dysphoric effects of agonist-antagonists such as pentazocine.

Naloxone is an essentially pure narcotic antagonist, i.e., it does not possess the "agonistic" or morphine-like properties characteristic of other narcotic antagonists;
naloxone does not produce respiratory depression, psychotomimetic effects or pupillary constriction.

In the absence of narcotics or agonistic effects of other narcotic antagonists, it exhibits essentially no pharmacologic activity.

Side Effects

-**Change in mood**
-**Trembling**
-**Change in heart rhythm**
-**Block the action of pain-lowering endorphins**

Note: out-of-body experience killer

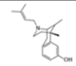
Naloxone can be used to successfully treat depersonalization disorder.

Depersonalization disorder (DPD) is a dissociative disorder in which the sufferer is affected by persistent or recurrent feelings of depersonalization. Diagnostic criteria include persistent or recurrent experiences of feeling detached from one's mental processes or body.

References:
^ "Journal of Emergency Nursing".
Simpson K, et al. (2008 Dec).
^ Sauro, Marie D; Greenberg, Roger P. (Feb 2005),
http://www.jyi.org/news/nb.php?id=429

Pentazocine
Partial agonist

Two enantiomers:
(-) Κ-Rec agonist and μ-Rec. antagonist
(+) δ-Rec agonist



Indication

Codeine can be used as an analgesic to relieve mild/moderate pain

-Dental extraction

Side Effects

-Hallucinations
-Psychotomimetic effects
-Cardiovascular effects

Withdrawal

Will cause withdrawal in opioid dependent person

Note: Necrosis and sepsis

Severe injection site necrosis and sepsis has occurred (sometime requiring amputation of limb) with multiple injection of pentazocine lactate

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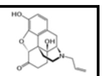
Naloxone
antagonist

- High affinity for μ-opioid in the CNS (competitive antagonist).
- Antagonist action for κ- and δ Rec.



Indication

Naloxone is a drug used to counter the effects of opioid overdose

-Naloxone is specifically used to counteract life-threatening depression of the central nervous system and respiratory system

-Treatment of Congenital insensitivity to pain with anhidrosis (CIPA) is an extremely rare inherited disorder of the nervous system which prevents the sensation of pain, heat, and cold

Side Effects

-Change in mood
-Trembling
-Change in heart rhythm
-Block the action of pain-lowering endorphins

Note: out-of-body experience killer

Naloxone can be used to successfully treat depersonalization disorder.

Depersonalization disorder (DPD) is a dissociative disorder in which the sufferer is affected by persistent or recurrent feelings of depersonalization. Diagnostic criteria include persistent or recurrent experiences of feeling detached from one's mental processes or body.

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^ "Journal of Emergency Nursing". Simpson K, et al. (2008 Dec).
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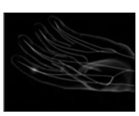
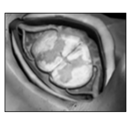
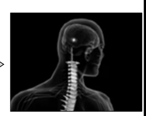
Opioids Induce Analgesia by Reducing the Amount of Information



1) Signaling via opioid receptors on peripheral nerve endings, **reduce the release of inflammatory mediators** (e.g., substance P and excitatory amino acids) by reducing Ca2+ conductance.



2) A-delta and C primary sensory afferents express μOR, δOR and κOR on their pre-synaptic central termination sites in the dorsal horn. Activation of these receptors **decreases the Ca2+-dependent release of excitatory transmitters**.



3) Secondary neurons within the dorsal horn also express μOR which when activated hyperpolarize the cell effectively **decreasing firing rate**.

Effects on PAIN MODULATION

Opioid analgesics are the ONLY clinically available drugs used that can modulate the subjective component to pain. This is due to their ability to activate mOR and **suppress neuronal firing in limbic brain regions**. (eg. patients report that, although they can still sense pain, they are no longer bothered by it).

Opioids: effects and side effects

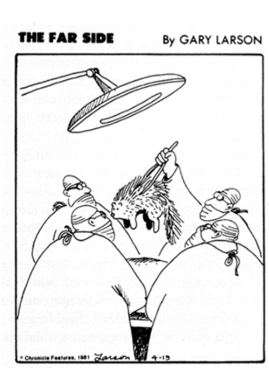
Overdose

Nervous system – At higher doses, sedation takes over and you become drowsy. An excessive dose can produce stupor and coma, and possible death.

Heart, blood and circulation – slows down your circulation and heart rate. also increases the size of certain blood vessels (making you feel warm).
Lungs – suppresses your cough reflex and slows down your breathing, causing hyperventilation. This can put you at risk of lung disease. An overdose of can cause respiratory failure and death.

Stomach – It depresses bowel activity, which can result in constipation. can make you feel sick, and first-time users often vomit.

Sexual organs – can cause irregular periods in women. In both men and women, it can make you lose interest in sex, and it affects your sexual performance.



"Well, I guess that explains the abdominal pains."

Dr. Saverio Gentile, Ph.D.
Department of Molecular Pharmacology & Therapeutics
Loyola University Chicago
Stricht School of Medicine
sagentile@lumc.edu
Tel: 708-216-3263

#20 - LOCAL ANESTHETICS

1. GENERAL PROPERTIES:

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

A. Physicochemical Characteristics.

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

B. Pharmacodynamics.

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

C. Pharmacokinetics.

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

D. Pharmacology and Toxicity.

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

2. EVALUATION OF SPECIFIC DRUGS.

A. Esters.

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

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

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

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

B. Amides.

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

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

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

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

3. CLINCIAL USES.

A. Topical Anesthesia
B. Infiltration Anesthesia
C. Intravenous Regional Anesthesia
D. Peripheral Nerve Block: a block of a peripheral nerve or plexus occurs when local anesthetic is deposited within the nerve sheath. The block onset will proceed from proximal to distal because the proximal nerve fibers are organized on the exterior of the nerve (mantle fibers), and the distal nerve fibers are located on the interior of the nerve (core fibers). The first sign of a successful nerve block is often loss of coordination in proximal muscle groups due to blockade of A gamma fibers.
E. Spinal Anesthesia: a block of spinal nerves (autonomic, sensory and motor) in the subarachnoid space occurs when local anesthetic is injected into the CSF from L_{2-3} caudad (to avoid hitting the spinal cord which ends at L_{1-2}.) Drugs can be prepared so that they are hyperbaric (more dense than CSF) so they can rise and produce blockade at levels higher than the site of injection. Since a band of drug is placed in the CSF when injected, all nerves caudad to the site are automatically blocked.
F. Epidural Anesthesia: a block of spinal nerves (autonomic, sensory and motor) in the epidural space occurs when drug is deposited there. The block can be done at any level of the cord from the cervical region to the sacrum and drug moves equally caudad and cephalad from the injection level. The resultant block is segmental, so, it is possible to produce a band of anesthesia with retained ability to move the legs.
G. Anti-arrhythmics

Table 1. Properties of some ester and amide local anesthetics.

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

#20 - LOCAL ANESTHETICS

Date: Wednesday, September 12, 2012

Reading Assignment: **Basic and Clinical Pharmacology – 11th ed.**
B.G. Katzung, Chapter 26
Pharmacology, Examination & Board Review, 8th ed.
Katzung & Trevor, Chapter 26

KEY CONCEPTS AND LEARNING OBJECTIVES

1. To understand how local anesthetics block nerve conduction.

2. To understand how the physiochemical properties of local anesthetics influence the pharmacodynamics and pharmacokinetics of these drugs.

3. To understand what undesirable side effects may occur with the use of local anesthetics and why these side effects happen.

4. To become familiar with prototype local anesthetics, the unique characteristics and the common clinical use for each of these drugs.

5. To understand the common uses of the local anesthetics with particular emphasis on spinal and epidural anesthesia, as well as peripheral nerve blocks.

6. Important Drugs (* prototypes):

   a. *Esters: Procaine, Cocaine, Tetracaine, Benzocaine*
   b. *Amides: Lidocaine, Mepivacaine, Bupivacaine, L-Bupivacaine, Ropivacaine*

#21 - GENERAL ANESTHETICS

I. PRINCIPLES OF ANESTHESIA:

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

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

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

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

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

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

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

II. INHALATIONAL ANESTHETICS:

A. Pharmacology of Inhalational Anesthetics.

1. Mechanism of Action.

Almost all general anesthetics act at the $GABA_A$ receptor-chloride channel and facilitate the GABA mediated neuronal inhibition at these receptor sites. Nevertheless, the exact mechanism of inhaled anesthetics remains unclear.

2. Safety, Dosage and Potency.

Anesthetics have an unusually narrow margin of safety with therapeutic indices of only 2 to 4.

A measure of potency of inhalational agents is MAC; the minimum alveolar concentration of an anesthetic, at 1 atmosphere, that prevents movement to a standard noxious stimulus (skin incision in humans) in 50% of humans or animals tested (refer to Table 25-1, Katzung). MAC is frequently multiplied by a factor of 1.3 to achieve "nearly" 100 percent clinical efficacy (i.e., ED_{95}). Inhalational anesthetics used in combination appear to have an additive effect. Several factors change MAC. These include body temperature, age and other drugs (e.g., opioids and benzodiazepines). Factors that do not influence MAC include sex, species, state of oxygenation, acid-base changes, and arterial blood pressure. MAC is also used as an equipotent dose model for comparing non-anesthetic effects of these agents.

B. Pharmacokinetics of Inhalational Anesthetics.

1. Uptake and Distribution.

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

a. Concentration of the Anesthetic Agent in Inspired Gas and Alveolar Uptake of Anesthetic Gases.

Gases diffuse from areas of high partial pressure (or tension) to areas of low partial pressure. Thus, the tension of anesthetic in the alveolus provides the driving force to establish a therapeutically effective brain tension.

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

b. Transfer of Anesthetic Gases from Alveoli to Brain.

In the absence of ventilation-perfusion disturbances, four major factors determine how rapidly anesthetics pass from the inspired gases to brain. These are (i) the solubility of the anesthetic in blood, (ii) rate and depth of ventilation, (iii) the rate of blood flow through the lungs, and (iv) the partial pressure of the anesthetic in arterial and mixed venous blood.

Solubility of the Anesthetic in Blood. This is usually expressed as the blood/gas partition coefficient, or λ which represents the ratio of anesthetic concentration in blood to anesthetic concentration in a gas phase when the two are in partial pressure equilibrium (refer to Table 25-1, Katzung). The more soluble an anesthetic is in blood, the more of it must be dissolved in blood to raise its partial pressure there appreciably. Thus, the blood tension of soluble agents rises slowly. Because the potential reservoir for relatively insoluble gases is small and can be filled more quickly, their tension in blood also rises quickly (Figure 25-3, Katzung).

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

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

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

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

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

Tissue Blood Flow. Tissues with high rates of blood flow (e.g., the brain) will exhibit rapid rises in concentration of anesthetic and, therefore, are able to take up significant amounts of the agent during the early stages of anesthesia. Because blood flow to adipose tissue is very limited, anesthetic gases will be delivered to, and taken up by, fatty tissues very slowly. Consequently, these tissues contain a significant amount of anesthetic agent only after some time has elapsed.

Partial Pressure of Gas in Arterial Blood and Tissues. As the tissues take up an anesthetic agent, the partial pressure of the gas in tissues increases towards that of the arterial blood. The rate at which gas diffuses from arterial blood to tissues varies with the partial-pressure difference between them and tissue concentration changes rapidly in the early minutes of anesthesia; however, as the tissue tension comes closer to the arterial tension, the tissue uptake of gas slows.

2. Elimination of Inhalational Anesthetics.

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

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

C. Clinical Pharmacology of Individual Agents.

1. Volatile anesthetics

a. Halothane

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

CNS. Halothane has a mild analgesic effect, but often requires the addition of another analgesic agent such as N_20 or a narcotic in a balanced technique to achieve the anesthetic state at more modest concentrations.

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

Respiration. Halothane depresses respiratory minute volume at all levels of anesthesia, leading to a dose-dependent decreased tidal volume. This results in the characteristic pattern of short, rapid breaths. Halothane is far less irritating to the respiratory tract than isoflurane. It does not increase secretions from the tracheobronchial tree, does not induce bronchospasm in light planes of anesthesia and is an effective bronchodilator. It is, therefore, a desirable agent for asthmatic patients.

Muscle. At clinical levels of anesthesia, halothane alone does not produce significant neuromuscular blockade. Relaxation is produced by CNS-mediated depression of muscle activity. Halothane-induced muscle relaxation will potentiate the effects of a skeletal muscle relaxant such as vecuronium.

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

b. Isoflurane

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

Respiration. Isoflurane is a potent ventilatory depressant.

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

Muscle. Isoflurane potentates the action of neuromuscular blockers.

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

c. Sevoflurane

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

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

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

Muscle. Sevoflurane potentates the action of neuromuscular blockers, decreasing the doses needed of these drugs.

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

d. Desflurane

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

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

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

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

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

2. Gaseous Anesthetics: Nitrous oxide.

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

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

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

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

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

III. INTRAVENOUS ANESTHETICS AGENTS:

A. Ultrashort-Acting Barbiturates.

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

1. Pharmacokinetic Properties.

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

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

2. Pharmacologic Properties.

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

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

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

Muscle. Relaxation of skeletal muscle is transient with little effect on uterine contractions, but thiopental crosses the placenta can depress the fetus.

Evaluation. Most of the complications associated with the use of thiopental are minor and can be avoided or minimized by judicious use of the drug. The advantages of thiopental are rapid, pleasant induction of anesthesia and fast recovery, with little postanesthetic excitement. Methohexital, opposite to thiopental, reduces seizure threshold and is useful only in elctroconvulsive therapy for depression or epileptic cerebral mapping.

B. Other Hypnotics.

1. Ketamine

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

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

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

2. Etomidate

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

3. Propofol

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

C. Opioid Analgesics.

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

#21 - GENERAL ANESTHETICS

Date: Thursday, September 13, 2012

Reading Assignment: **Basic and Clinical Pharmacology, 11th ed.,**
B.G. Katzung, Chapter 25
Pharmacology, Examination & Board Review, 8th ed.,
Katzung & Trevor, Chapter 25

KEY CONCEPTS AND LEARNING OBJECTIVES

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

2. To develop a working understanding of the pharmacokinetics for inhalational anesthetics.

3. To understand the various stages of anesthesia.

4. To understand how the blood:gas coefficient influences the onset of action (and termination of anesthesia) for inhaled anesthetics.

5. To understand how the ventilation rate and pulmonary blood flow influence the onset of action for inhalation anesthetics.

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

7. To understand minimum alveolar concentration (MAC) and what information it provides about a volatile anesthetic.

8. To understand the pharmacokinetic properties of the ultrashort-acting hypnotics and how these properties make this class of drugs popular general anesthetic agents.

10. To understand the advantages and disadvantages for clinically used inhaled and intravenously administered general anesthetics (listed below). When they should be used and when they are contraindicated.

    a. Halogenated Hydrocarbons: Isoflurane, Sevoflurane, Desflurane
    b. Inert Gas: Nitrous Oxide
    c. Ultrashort-Acting Barbiturates: Thiopental, Methohexital
    d. Sedative-Hypnotics: Ketamine, Etomidate, Propofol
    e. Opioids: Morphine, Fentanyl
    f. Benzodiazepines: Midazolam

Final Copy Received: 8/18/09

#22 - Complementary and Alternative Medicine: Acupuncture

Aaron J. Michelfelder, M.D., FAAFP, FAAMA
Vice-Chair and Predoctoral Director, Family Medicine
Associate Professor of Family Medicine, and Bioethics & Health Policy
Board Certified Medical Acupuncturist

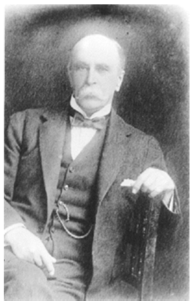
Objectives

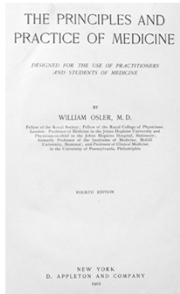
- By the end of this presentation, you should ...
  - Know the National Institutes of Health guidelines on the use of acupuncture (JAMA 1998; 280:1518-24).
  - Identify the endogenous opioid peptides and major neurotransmitters implicated in acupuncture analgesia.
  - Understand the neurochemical effects of low frequency/high intensity and high frequency/low intensity electroacupuncture.
  - Understand the inherent thermoelectrical properties of acupuncture needles

Presentation Outline

- Acupuncture in the United States
- Meridian Theory
- Cortical Effects
- Neural-Hormonal Effects
- Clinical Evidence
- WHO Uses for Acupuncture

Osler was an acupuncturist?




THE PRINCIPLES AND PRACTICE OF MEDICINE

DESIGNED FOR THE USE OF PRACTITIONERS AND STUDENTS OF MEDICINE

BY

WILLIAM OSLER, M. D.

Fellow of the Royal Society; Fellow of the Royal College of Physicians, London; Professor of Medicine in the Johns Hopkins University and Physician-in-chief to the Johns Hopkins Hospital, Baltimore; formerly Professor of the Institutes of Medicine, McGill University, Montreal; and Professor of Clinical Medicine in the University of Pennsylvania, Philadelphia

FOURTH EDITION

NEW YORK
D. APPLETON AND COMPANY
1901

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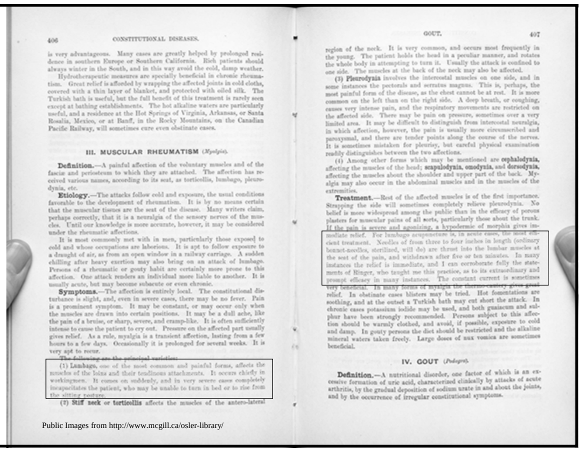
406 CONSTITUTIONAL DISEASES.

is very advantageous. Many cases are greatly helped by prolonged residence in southern Europe or Southern California. Rich patients should always winter in the South, and in this way avoid the cold, damp weather.

Hydrotherapeutic measures are specially beneficial in chronic rheumatism. Great relief is afforded by wrapping the affected joints in cold cloths, covered with a thin layer of blanket, and protected with oiled silk. The Turkish bath is useful, but the full benefit of this treatment is rarely seen except at bathing establishments. The hot alkaline waters are particularly useful, and a residence at the Hot Springs of Virginia, Arkansas, or Santa Rosalia, Mexico, or at Banff, in the Rocky Mountains, on the Canadian Pacific Railway, will sometimes cure even obstinate cases.

III. MUSCULAR RHEUMATISM (*Myalgia*).

Definition.—A painful affection of the voluntary muscles and of the fasciæ and periosteum to which they are attached. The affection has received various names, according to its seat, as torticollis, lumbago, pleurodynia, etc.

Etiology.—The attacks follow cold and exposure, the usual conditions favorable to the development of rheumatism. It is by no means certain that the muscular tissues are the seat of the disease. Many writers claim, perhaps correctly, that it is a neuralgia of the sensory nerves of the muscles. Until our knowledge is more accurate, however, it may be considered under the rheumatic affections.

It is most commonly met with in men, particularly those exposed to cold and whose occupations are laborious. It is apt to follow exposure to a draught of air, as from an open window in a railway carriage. A sudden chilling after heavy exertion may also bring on an attack of lumbago. Persons of a rheumatic or gouty habit are certainly more prone to this affection. One attack renders an individual more liable to another. It is usually acute, but may become subacute or even chronic.

Symptoms.—The affection is entirely local. The constitutional disturbance is slight, and, even in severe cases, there may be no fever. Pain is a prominent symptom. It may be constant, or may occur only when the muscles are drawn into certain positions. It may be a dull ache, like the pain of a bruise, or sharp, severe, and cramp-like. It is often sufficiently intense to cause the patient to cry out. Pressure on the affected part usually gives relief. As a rule, myalgia is a transient affection, lasting from a few hours to a few days. Occasionally it is prolonged for several weeks. It is very apt to recur.

The following are the principal varieties:

(1) **Lumbago**, one of the most common and painful forms, affects the muscles of the loins and their tendinous attachments. It occurs chiefly in workingmen. It comes on suddenly, and in very severe cases completely incapacitates the patient, who may be unable to turn in bed or to rise from the sitting posture.

(2) **Stiff neck or torticollis** affects the muscles of the antero-lateral

GOUT. 407

IV. GOUT (*Podagra*).

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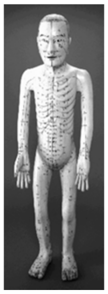
Now, Let Me Tell You About My Appendectomy in Peking...

by James Reston

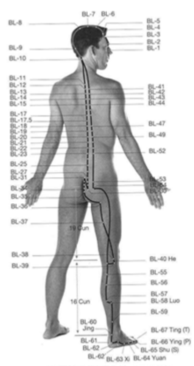
New York Times, Monday July 26, 1971

Basic Acupuncture Principles



- Based on 12 Meridians or Channels
- In Between Muscle Cleavage Planes
- Fascia is Electrically Active

Principal Meridians



Acupuncture Physiology

- The needle is working through multiple vectors in the body's physiology:
  - Functioning electrically on the body surface
  - Electro-ionically in interstitial milieu
  - Nerve and neurohumoral functions as per Pomeranz's studies
  - Perineural conduction along myelin sheaths
  - Blood input via effects of neurohumoral, cellular, and blood chemistry changes
  - Immunologically via humoral and cellular changes

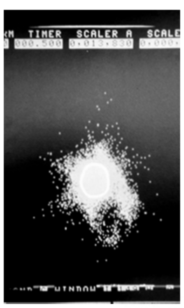
Electrical Propagation

- Zang 1960
  - Needle at LI-4 and LI-11
  - Stimulated LI-4
  - Measured Galvanic Change at LI-11
  - Electrical Current Follows Direction of Meridian.

THE ACUPOINTS

- TECHNETIUM 99 studies in France showed linear flow when injected in real points at 6 cm per minute by Dewars et al.
- “Dummy” points did not show linear flow of Tc99.
- Stimulation of the injected points with a needle, electricity, or helium-neon laser increased the migration rate not corresponding to vascular or lymphatic channels.

Tc99 Studies



From Giovonardi *et al.* 1988 - http://agopuntura.org/html/mandorla/rivista/numeri/Marzo_1998/TC99M.htm Accessed 8/24/07

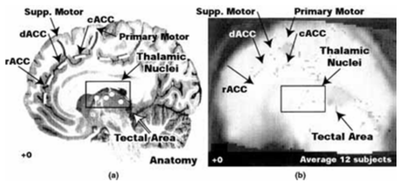
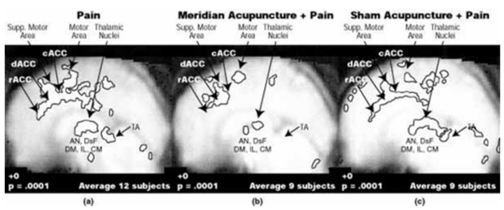


Figure 1. A typical anatomical image and corresponding functional magnetic resonance imaging (fMRI) data of the mid-sagittal view obtained by pain stimulation. Locations of the various pain-related brain areas are also shown: (a) An anatomical image showing the anterior cingulate cortex (ACC) (dACC [dorsal], rACC [rostral], and cACC [caudal]), the supplementary and primary motor areas, and the thalamic nuclei overlaid on a mid-sagittal view of an anatomical image of a human brain. (b) Averaged fMRI data obtained by pain stimulation overlaid on a mid-sagittal view image (average of 12 subjects).

Zang-Hee Cho et al. fMRI Neurophysiological Evidence Of Acupuncture Mechanisms.2002. http://www.medicalacupuncture.org/aama_marf/journal/vol14_1/article1.html - Accessed 8/24/07



Zang-Hee Cho et al. fMRI Neurophysiological Evidence Of Acupuncture Mechanisms.2002. http://www.medicalacupuncture.org/aama_marf/journal/vol14_1/article1.html - Accessed 8/24/07

Patient

Mr. N is a 64 y/o male with chronic low back pain for years due to osteoarthritis of the spine. He presents for acupuncture therapy.

The acupuncture method chosen for him is Percutaneous Electrical Nerve Stimulation (PENS)

- After 1 treatment, he states his pain decreased by 80% for 20 minutes
- After 2nd treatment, his pain decreased 90% for 3 days
- After 3rd treatment, his pain decreased to 0/10 for 2 weeks

Electroacupuncture

The Endogenous Opioid Peptide Families Implicated in Acupuncture Analgesia

- Beta-endorphin
- Enkephalin
  - Met-enkephalin
  - Leu-enkephalin
- Dynorphin

Major neurotransmitters implicated in acupuncture analgesia

- Serotonin
- Norepinephrine
- Substance P
- Gama-aminobutyric acid (GABA)
- Dopamine
- ACTH

NEUROHUMORAL EFFECTS OF ELECTRO-ACUPUNCTURE

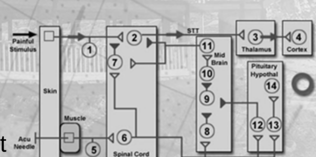
This Set of Slides Adapted from the American Academy of Medical Acupuncture and are Used With Permission

PHYSIOLOGY OF NERVE FIBERS

- Various afferent nerve fibers are involved in transmitting pain impulses
  - Large myelinated nerves
    - A- Beta (skin) carry touch
    - Type I (muscle) carry proprioception
  - Small myelinated nerves carry pain
    - A-delta (skin)
    - Type II and III (muscle)
  - Type II, III, IV and C carry nonpainful messages

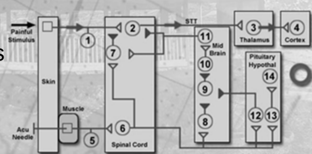
REVIEW OF TRANSMISSION OF A PAINFUL STIMULUS

- An injury to the skin activates the sensory receptors (squares) of small afferent A-delta and C-fibers (#1)
- These synapse onto the Spinothalamic Tract in the spinal cord (#2)



REVIEW OF TRANSMISSION OF A PAINFUL STIMULUS

- The Spinothalamic Tract cell projects its axon to the Thalamus (#3)
- Here it synapses with a cell that sends impulses to activate the primary sensory cortex (#4)
- White triangles are excitatory synapses, Dark are inhibitory



Electroacupuncture

- PENS
  - Local needles in the back
  - Distant Needles in the ankles, head, wrists
  - Low Frequency/High Intensity PENS for 15 min
  - High Frequency/Low Intensity PENS for 15 min

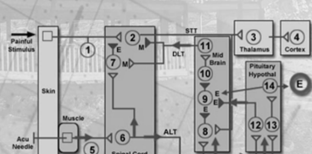
PENS

- Low Frequency/High Intensity
  - 2 to 15 Hz as strong as patient can tolerate
- High Frequency Low/ Intensity
  - 30 to 200 Hz just to where patient can barely feel it

EFFECT OF LOW FREQUENCY/HIGH INTENSITY ELECTRO-ACUPUNCTURE STIMULATION

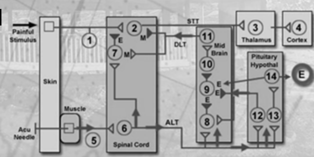
EFFECT OF LOW FREQUENCY/ HIGH INTENSITY ELECTRO-ACUPUNCTURE STIMULATION

- Acupuncture needle activates a Type II or III small afferent nerve (#5) from a sensory receptor in the muscle



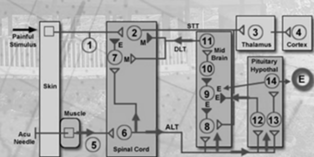
EFFECT OF LOW FREQUENCY/ HIGH INTENSITY ELECTRO-ACUPUNCTURE STIMULATION

- This cell synapses in spinal cord onto an Anterolateral Tract cell (#6) which projects to:
  - spinal cord
  - midbrain
  - pituitary-hypothalamus complex



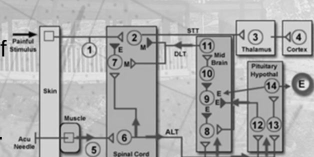
EFFECT OF LOW FREQUENCY/ HIGH INTENSITY ELECTRO-ACUPUNCTURE STIMULATION

- In the spinal cord, Cell 6 sends a segmental branch to cell 7 (endorphinergic cell)
- This releases either enkephalin or dynorphin (but not B-endorphin)



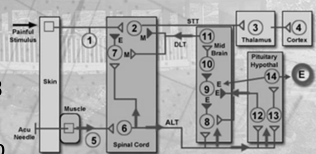
EFFECT OF LOW FREQUENCY/ HIGH INTENSITY ELECTRO-ACUPUNCTURE STIMULATION

- This, in turn, causes presynaptic inhibition of Cell 1, thus prevents transmission of the painful message 1 to 2.



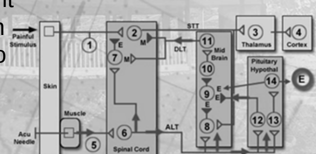
ADDITIONAL EFFECTS

- Cell 6 also ascends Anterolateral Tract of the spinal cord to the midbrain
- Excites cells in Periaqueductal Grey (8 & 9)
- Releases enkephalin to disinhibit Cell 10



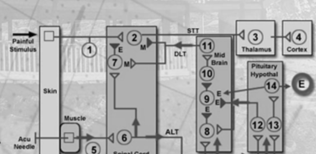
ADDITIONAL EFFECTS

- This activates the raphe nucleus in the medulla (#11) causing it to send impulses down the dorsolateral tract to release monoamines (M) such as serotonin and norepinephrine onto spinal cord cells



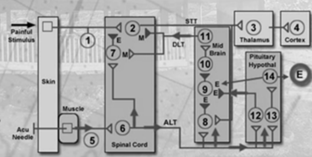
ADDITIONAL EFFECTS

- Cell 2 is thereby inhibited by postsynaptic inhibition, while Cell 1 is presynaptically inhibited through Cell 7



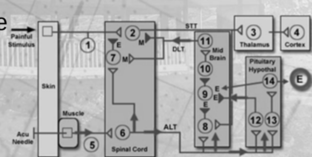
EFFECT ON PITUITARY-HYPOTHALAMUS COMPLEX

- Probably Cell 12 in the arcuate nucleus activates the raphe through ß-endorphin
- Cell 13 in the hypothalamus releases B-endorphin from the pituitary



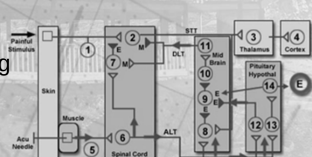
EFFECT ON PITUITARY-HYPOTHALAMUS COMPLEX

- In the pituitary ß-endorphin and ACTH are co-released on an equimolar basis into the circulation
- ACTH travels to the adrenal cortex, cortisol is released into blood. May explain anti-inflammatory effects



EFFECT OF PITUITARY-HYPOTHALAMUS COMPLEX

- This slide shows the three centers activated by low frequency/high intensity electro-acupuncture (EA) using the endorphin mechanisms in them
- Low frequency stimulation is thus inhibited by naloxone.



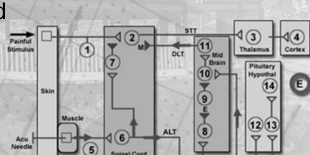
PENS

- Low Frequency/High Intensity
  - 2 to 15 Hz as strong as patient can tolerate
- High Frequency Low/ Intensity
  - 30 to 200 Hz just to where patient can barely feel it

EFFECT OF HIGH FREQUENCY/ LOW INTENSITY EA STIMULATION

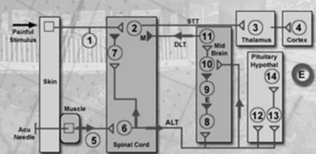
EFFECT OF HIGH FREQUENCY/ LOW INTENSITY EA STIMULATION

- HF/LI EA stimulates only the spinal cord and midbrain, but bypasses endorphin synapses there
- Thus not blocked by naloxone, but sensitive to manipulations of monoamines



EFFECT OF HIGH FREQUENCY/ LOW INTENSITY EA STIMULATION

- High frequency EA has a strong spinal segmental effect, not antagonized by naloxone
  - suggests Cell 7 uses non-endorphinergic transmitters such as GABA



ELECTRO-ACUPUNCTURE SUMMARY

- EA activates nerve fibers in the muscle, which send impulses to the spinal cord to activate three centers to cause analgesia
  - the spinal site
    - enkephalin and dynorphin to block incoming messages with low frequency stimulation
    - other transmitters such as GABA at high frequencies
  - the midbrain
  - the pituitary

SUMMARY EA EFFECTS

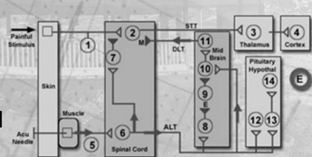
- The midbrain uses enkephalin to activate the raphe descending system
  - this inhibits spinal cord pain transmission by a synergistic effect of the monoamines serotonin and norepinephrine
  - also a circuit bypasses the endorphinergic links at high frequency stimulation

SUMMARY EA EFFECTS

- The Pituitary
  - releases ß-endorphin into the blood and CSF to cause analgesia at a distance
  - the Hypothalamus sends long axons to the midbrain which, along with ß-endorphin, activate the descending analgesia system, activated only at low frequency stimulation

SIGNIFICANCE OF 3-LEVELS

- When needles placed close of pain site, they maximize segmental circuits operating at Cell 7 within the spinal cord, while also bringing in Cells 11 and 14 of the other 2 centers.



SIGNIFICANCE 3-LEVELS

- When needles are placed in **distal** points away from the painful region, they activate the midbrain and hypothalamic-pituitary complex without benefit of segmental effects
- Clinically, the two kinds of needling are often used together, to enhance one another.

THE ANALGESIA PRODUCED BY THE 2 APPROACHES IS QUITE DIFFERENT

- The **low frequency** stimulation produces analgesia of slower onset and long duration, with a 20 minute stimulation effecting 30-120 minutes of analgesia
  - The effects are cumulative in repeat sessions
  - may be due to observed increase in m-RNA for endorphins seen for 48 hours after stimulation
- The **high frequency** stimulation is rapid but short duration and no cumulative effects

PENS

- Low Frequency/High Intensity
  - 2 to 15 Hz as strong as patient can tolerate
  - Spinal Cord – Enkephalin, Dynorphin B
  - Midbrain – enkephalin, Serotonin, Norepinephrine
  - Pituitary/Hypothal – B-endorphin, ACTH
  - Effect blocked by Naloxone
  - Analgesia slow onset/long duration
  - Cumulative Effects
- High Frequency Low/ Intensity
  - 30 to 200 Hz just to where patient can barely feel it
  - Spinal Cord/Midbrain only– GABA
  - Effect NOT blocked by Naloxone
  - Analgesia fast onset/short duration
  - Non-cumulative effects

ACUPUNCTURE NEEDLES PHYSICAL PROPERTIES

- ACUPUNCTURE NEEDLES are ideal instruments due to their physical properties.
- COMPOSITION: stainless steel shaft with a spiraled handle of copper, bronze, or alloy
- THERMOCOUPLE EFFECT OF KELVIN-THOMAS describes a gradient along the length of a homogenous conductor with a temperature gradient produced by the ends of the conductor at different temperatures.

THE BENEDICK'S EFFECT

- The current along a uniform conductor is rein-forced by the electro-magnetic effect between the second (spiraled) metal of the handle in contact with the first metal of the shaft.
  - Typical needle is 1 to 8 cm long, 0.3-0.4mm in diameter or 28 to 26 gauge
  - Electrical potential is 3 microvolts, the tip at body temperature and the handle at T°

NEEDLE IN DISPERSION

- This gradient reaches equilibrium in 10-15 minutes.
- Dispersion is used in conditions defined as a problem of excess, such as acute strain or sprain.
- The needle inserted, allow reaction to take place, often produces local erythema of skin, reaches equilibrium as erythema clears.

NEEDLE IN TONIFICATION

- Manipulation of the needle manually.
- The potential changes to 10-15 microvolts.
- Reaches equilibrium in 60 to 90 minutes.
- Indicated in “deficiency states,” chronic or dysfunction states.
- Requires heat, manual manipulation or electrical stimulation in an anatomically logical circuit.

NEEDLE IN TONIFICATION

- Provokes a wave of depolarization/repolarization that propagates itself from one needle to the next along the course of least resistance, the lamellar flow around the muscles, the deep aspect of the acupuncture meridians.

INTO THE MEDICAL MAINSTREAM

- FDA 1996 - Classified acupuncture needle as Class 2b medical device
- National Institute of Health 1997 Consensus Conference showed “clear evidence” of acupuncture efficacy in various clinical conditions and deemed appropriate as “part of comprehensive care for others.” Chairman Dr. David J. Ramsay states, “It’s time to take it seriously.”

NIH CONSENSUS DEVELOPMENT REPORT

- While there have been many studies of its potential usefulness, many of these studies provide equivocal results because of design, sample size, and other factors. The issue is further complicated by inherent difficulties in the use of appropriate controls, such as placebos and sham acupuncture groups.
- However, promising results have emerged, for example, showing efficacy of acupuncture in adult postoperative and chemotherapy nausea and vomiting and in postoperative dental pain.

(JAMA/Vol 280, 1998)

NIH CONSENSUS DEVELOPMENT REPORT

- There are other situations such as addiction, stroke rehabilitation, headache, menstrual cramps, tennis elbow, fibromyalgia, myofascial pain, osteoarthritis, low back pain, carpal tunnel syndrome, and asthma, in which acupuncture may be useful as an adjunct treatment or an acceptable alternative or be included in a comprehensive management program.
- Further research is likely to uncover additional areas where acupuncture interventions will be useful.

(JAMA/Vol 280, 1998)

What should you know?

- For USMLE 1:
  - Pain Pathway
  - Endogenous Opioids and Neurotransmitters in Analgesia
  - PENS/TENS Theory
- For P&T Test
  - Differences between LF and HF stimulation
  - NIH Consensus Panel Recommended Uses for Acupuncture
  - Thermocouple Effect of Kelvin-Thomas
  - Benedick's Effect

MEDICAL LITERATURE SHOWS ACUPUNCTURE'S EFFECTS ON NEARLY EVERY BIOPHYSICAL SYSTEM

PULMONARY

- Attenuation of exercise-induced asthma (Lancet)
- Diminishes bronchoconstriction in clinical asthma attacks (Annals of Allergy)

OBSTETRICS

- Relief of pain of labor and delivery (Anesthesiology)
- Aided in induction of labor (Obstetrics and Gynecology)
- Controlled morning sickness (Obstetrics and Gynecology, 11/92)

GENITO-URINARY

- Treatment for infertility (Gynecology and Endocrinology 9/92 and a German publication)
- Treatment of renal colic. Acupuncture demonstrated more rapid response than Avaforton with no side effects (Journal of Urology 1/92)

GASTROINTESTINAL

- Relieves GI tract spasm which failed medication (Lancet)
- Arrested cholestatic crisis (personal communication Dr. Frank with Dr. Chan Gunn)
- Decrease in peri-operative nausea and vomiting (British Medical Journal, Anesthesiology News)

CARDIOVASCULAR

- Reversal of cardiac arrest in experimental animals (Journal of Surgical Research)

WOUND HEALING

- Acceleration of wound healing demonstrated with electro-acupuncture (Archives of Physical Medicine and Rehabilitation)
- Accelerated skin ulcer healing (Southern Medical Journal)
- Augmentation of bone repair (Science)

SPORTS MEDICINE

- Increased maximum performance capacity over controls (International Journal of Sports Medicine 8/92)
- Substance P and Prostaglandin E have been shown to be increased in patients with unsuccessful acupuncture anesthesia (Pomeranz)

DRUG DETOXIFICATION

- Dramatic enhancement of drug detoxification programs for over twenty years (Lincoln Hospital programs of Dr. Michael Smith)

Evidence

- Fibromyalgia
  - RCCT – single blind, 50 patients – Significant improvement in pain, fatigue, anxiety[1]
  - Cochrane Review 2005 – 8 studies, 130 patients – “Strong Evidence for Acupuncture”[2]
  - RCCT – single blind, 114 patients – “Needle insertion led to analgesia and improvement in somatic symptoms”[3]

Evidence

- Chronic Neck Pain
  - Cochrane 2006 – 10 trials, 661 participants
    - “Moderate Evidence” acupuncture more effective than inactive, sham treatments immediately post treatment and at short-term follow-up”[4]

Evidence

- Knee Pain/OA
  - 2004 – RCCT, 570 patients – "Acupuncture provides improvement in function and pain relief as an adjunctive therapy for OA of the knee when compared to credible sham acupuncture and education control groups"[5]
  - 2002 – RCCT, 294 patients – "After 8 weeks, pain and joint function are improved more with acupuncture than with minimal or no acupuncture."[6]

Evidence

- Low Back Pain
  - 2004 Cochrane Review of Dry-Needling– 35 RCTs, 2861 patients – "Acupuncture is more effective for pain relief and functional improvement than no treatment or sham treatment immediately after treatment and in the short-term only."[7]
  - 2005 Meta-Analysis, 33 RCTs on all types of acupuncture – "Acupuncture effectively relieves chronic low back pain."[8]

Common Conditions For Acupuncture Treatment

WORLD HEALTH ORGANIZATION INDICIATIONS FOR ACUPUNCTURE

Respiratory Tract
Acute sinusitis
Acute rhinitis
Common cold
Acute tonsillitis

Bronchopulmonary Disorders
Acute bronchitis
Bronchial asthma

WORLD HEALTH ORGANIZATION INDICIATIONS FOR ACUPUNCTURE

Disorders of the Eye
Acute conjunctivitis
Central retinitis
Myopia (in children)
Cataract (without complications)

Disorders of the Mouth Cavity
Toothache
Pain after tooth extraction
Gingivitis
Acute and chronic pharyngitis

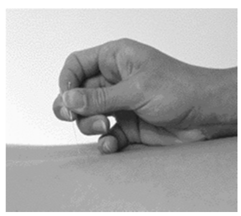
WORLD HEALTH ORGANIZATION INDICIATIONS FOR ACUPUNCTURE

Gastrointestinal Disorders
Spasm of the esophagus and cardia
Hiccups
Gastroparesis
Acute and chronic gastritis
Gastric hyperacidity
Chronic duodenal ulcer
Acute and chronic colitis
Acute bacterial dysentery
Constipation
Diarrhea
Paralytic ileus

Neurologic and Orthopedic Disorders
Headache
Migraine
Trigeminal neuralgia
Facial paralysis
Paralysis after apoplectic fit
Peripheral neuropathy
Paralysis caused by poliomyelitis
Meniere's syndrome
Neurogenic bladder dysfunction
Nocturnal enuresis
Intercostal neuralgia
Periarthritis humeroscapularis
Tennis elbow
Sciatica, lumbar pain
Rheumatoid arthritis

Other Conditions for Acupuncture

- RSD/Complex Regional Pain Syndrome
  - Better if Early in Course of Disease
- Depression
- Anxiety
- Insomnia



Loyola University Medical Center Acupuncturists

Youngran Chung, M.D. - Peds Pulmonology
Mariadas Chinthagada, M.D. – Anesthesia
Haemi Choi, M.D. – Family Medicine
Chuck Dumont, M.D. - Peds GI
Mary Pat Fitzgerald, M.D. - Urogynecology
Kit Lee, M.D. – Family Medicine
Aaron Michelfelder, M.D. - Family Medicine

Resources

- National Center for Complementary and Alternative Medicine www.nccam.nih.gov
- American Academy of Medical Acupuncture www.medicalacupuncture.com

References

- 1. Martin, Sletten, Williams, Berger. Improvement in Fibromyalgia Symptoms With Acupuncture: Results of a Randomized Controlled Tria. *Mayo Clin Proc*. 2006;81(6):749-757.
- 2. Holdcraft, Assefi, Buchwald. Complementary and alternative medicine in fibromyalgia and related syndromes. *Cochrane Database of Abstracts of Reviews of Effectiveness 2006 (updated 2005),*Volume 3, Article # 20031645.
- 3. Harris, Tian, Williams, Tian, Cupps, Petzke, Groner, Biswas, Gracely, Clauw. Treatment of Fibromyalgia with Formula Acupuncture: Investigation of Needle Placement, Needle Stimulation, and Treatment Frequency. The Journal of Alternative and Complementary Medicine. 2005;11(4):663-671.
- 4. Trinh, Graham, Gross, Goldsmith, Wang, Cameron, Kay. Acupuncture for Neck Disorders. *Cochrane Database of Systematic Reviews 2006 (updated 2006),* Volume 3, Article #00075320-100000000-03808.

References

- 5. Berman, Lao, Langenberg, Lee, Gilpin, Hochberg. Effectiveness of Acupuncture as Adjunctive Therapy in Osteoarthritis of the Knee. *Ann Intern Med*. 2004;141:901-910.
- 6. Brinkhaus, Linde, Streng, Wagenpfeil, Hummelsberger, Walther, Melchart, Willich. Acupuncture in patients with osteoarthritis of the knee: a randomised trial. The Lancet. 2005;366:137-143.
- 7. Furlan, van Tulder, Cherkin, Tsukayama, Lao, Koes, Berman. Acupuncture and Dry-needling for Low Back Pain. *The Cochrane Database of Systematic Reviews 2006 (updated 2004).* Volume 3.
- 8. Manheimer, White, Berman, Forys, Ernst. Meta-Analysis: Acupuncture for Low Back Pain. *Ann Intern Med*. 2005;142:651-663.

#24- #25- Non Steroidal Anti-inflammatory Drugs (NSAIDs) I & II

Date: September 17th, 2012 – 9:30am- 11:30am

Relevant reading:
Pharmacology: Examination & Board Review. AJ Trevor, 7th Edition, Chapter 36 p307-311
Basic and Clinical Pharmacology- B.G. Katzung, 11th Edition, Chapter 36 621-629 (Optional)

KEY CONCEPTS AND LEARNING OBJECTIVES

1. NSAIDs are used in the treatment of:
   a) Inflammation,
   b) Fever
   c) Pain.

2. The mechanism of action of **all** NSAIDs involves the inhibition of **cyclooxygenase** (COX) enzymes and the consequent inhibition of **prostaglandin** synthesis.

3. Prostaglandins are lipid mediators that act in an autocrine/paracrine fashion to promote inflammation, pain and fever, as well as control a variety of housekeeping functions (e.g. cytoprotection of the stomach).

4. Understand the molecular differences between COX-1 and COX-2: COX-1 is expressed constitutively and is primarily involved in the regulation of housekeeping functions, whereas COX-2 is primarily inducibly expressed in a variety of cell types in response to inflammatory stimuli.

5. Understand the physiological roles of prostaglandins in both inflammatory processes and general housekeeping functions.

6. Recognize and understand the principal differences between the three distinct classes of NSAIDs:
   a) Aspirin and Salicylates
   b) Traditional NSAIDs
   c) Specific COX-2 inhibitors

7. Understand that aspirin has a unique mechanism of action compared to the other NSAIDs. Whereas the salicylates, traditional NSAIDs and selective COX-2 inhibitors simply act as reversible competitive antagonists of COX activity, aspirin irreversibly inhibits COX enzyme activity by covalently modifying an amino acid in the active site that inhibits access to the arachidonic acid substrate.

8. Understand the mechanism underlying the use of low-dose Aspirin in the prevention of cardiovascular disease.

9. Understand the pharmacokinetics of aspirin and the adverse effects associated with aspirin use, including salicylate intoxication.

10. Be able to describe some of the key **general** features of the Traditional NSAIDs and COX-2 inhibitors

11. Be able to describe the **common** adverse effects of all classes of NSAIDs

12. Understand the contraindications for **all** classes of NSAIDs

13. Recognize specific classes of drugs that are known to interact with the NSAIDs.

14. Understand the properties, indications and adverse effects of the non-NSAID analgesic acetaminophen.

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.

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

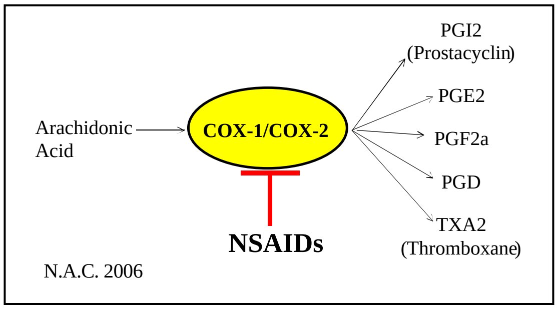
1. All NSAIDs work by inhibiting the activity of cyclooxygenase enzymes.

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.

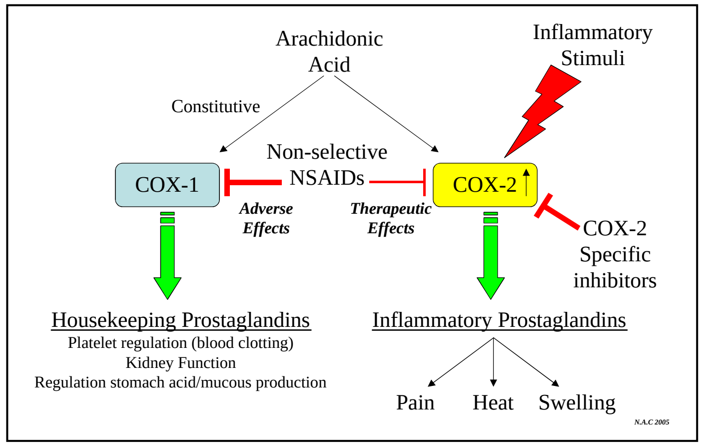
A3. Cyclooxygenase enzymes: Expression and Function

	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

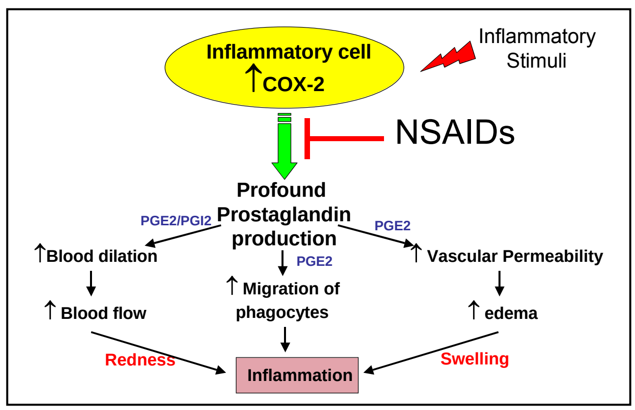
- COX-2 is specifically upregulated in inflammatory cells

- 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

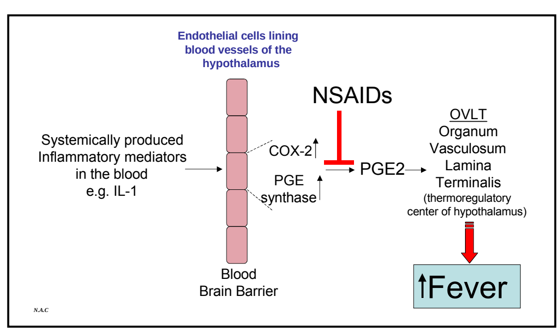
- prostaglandin production by COX-2 in inflammatory cells affects primary afferent neurons by lowering their threshold to painful stimuli

- 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

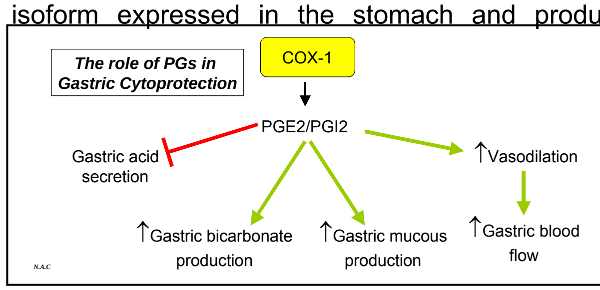
- systemically produced inflammatory mediators (e.g. IL-1/TNF-□) induce the expression of COX-2 in the endothelial cells lining the hypothalamus causing the production of PGE2, which then acts on the **Organum Vasculosum Lamina Terminalis** (OVLT: the thermoregulatory center of the hypothalamus) to cause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



A4.2 Homeostatic functions of prostaglandins- __associated with adverse NSAID effects__

<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

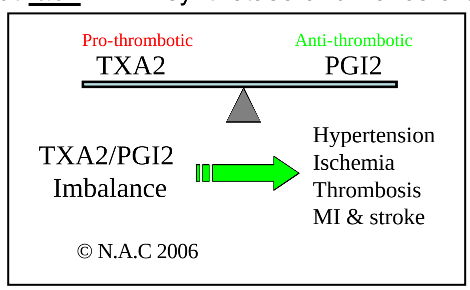
- **<u>Inhibition of COX-1 in the stomach is the cause of significant adverse effects of both Aspirin and the traditional NSAIDs</u>**

<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.

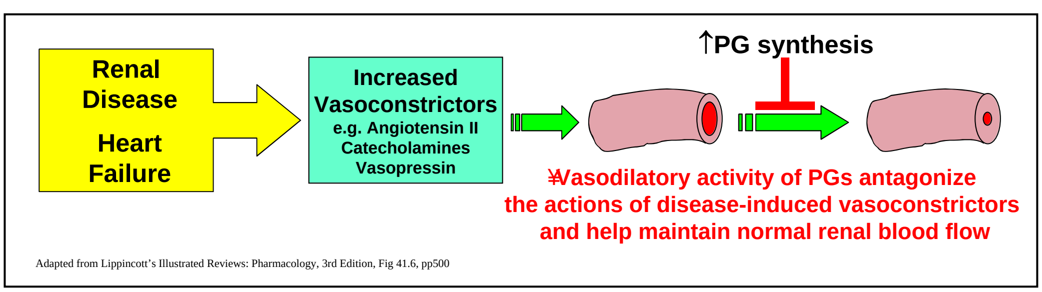


- The balance between the production of TXA2 & PGI2 regulates systemic blood pressure and thrombogenesis.

<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.

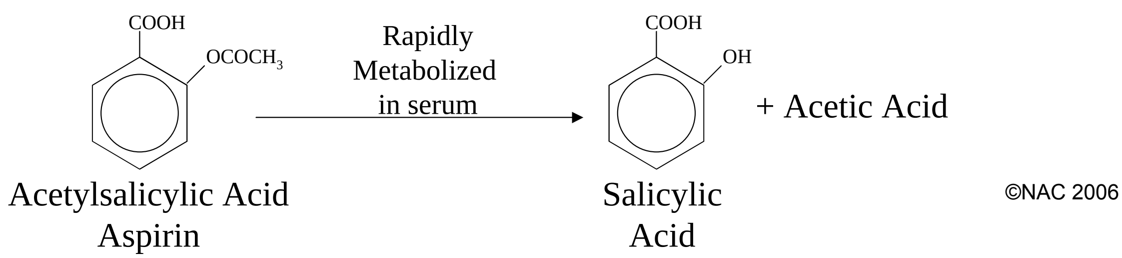
There are three distinct classes of NSAIDs:

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

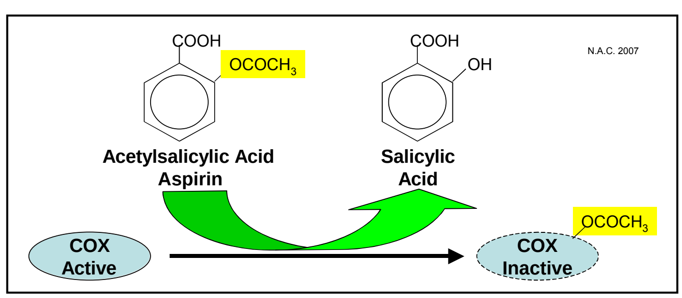
B2.1 Aspirin- the prototypical NSAID

- 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

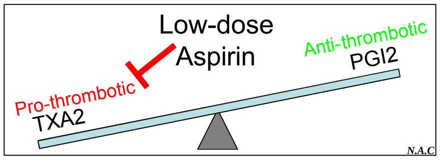
B2.6 Mechanism of action of low-dose aspirin in the treatment of CVD

- 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 >15 hrs

- 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)

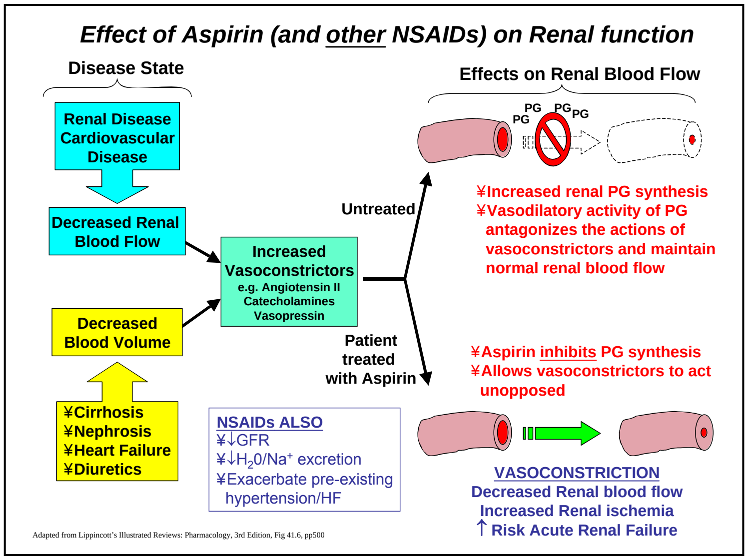
- **NSAID treatment can aggravate and promote development of gastric & duodenal ulcers**

- 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) Increased Bleeding

- By blocking TXA2 production aspirin prolongs the bleeding time
- Aspirin is therefore **contraindicated** in hemophilia patients and individuals about to undergo surgery

(iv) 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

(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

- ~15% 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 protein uria
- 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
- 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®)

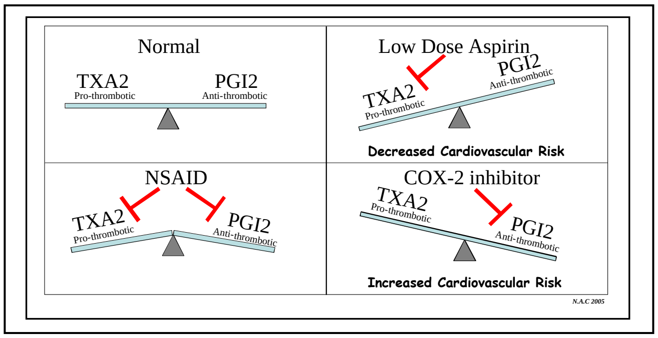
- Selectively inhibits **COX-2** not COX-1
- Anti-inflammatory, anti-pyretic and analgesic properties similar to traditional NSAIDs
- Associated with **fewer GI side effects** (does not inhibit COX-1 in the stomach)
- No effect on platelet aggregation as does not inhibit COX-1
- Similar renal toxicities 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.

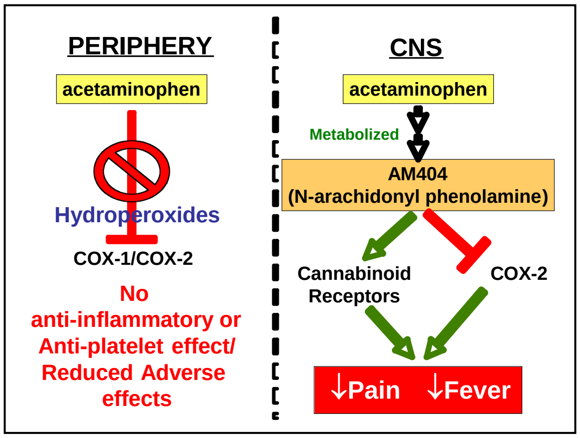
(vi) The COX-2 inhibitor celecoxib is indicated for patients at highest risk of GI bleeds

(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: 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

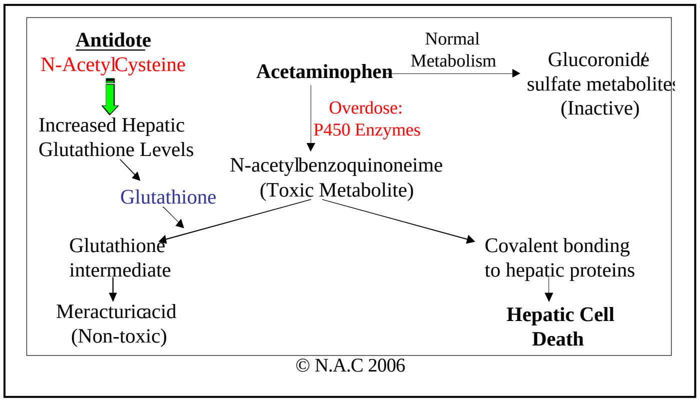
a) At normal doses (4g/day) Acetaminophen is essentially free of adverse effects

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) Liver
    e) Anti-platelet effects/increased bleeding
    f) Hypersensitivity
    h) CNS
    i) Skin
    j) Photosensitivity
    k) 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_2O 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.