TOURO UNIVERSITY COLLEGE OF OSTEOPATHIC MEDICINE

Pharmacology of the Central Nervous System

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Drugs alter endogenous synaptic neuro-transmission:

Have you ever wondered why so many different types of compounds found in nature alter brain function?

The assignment goal is to provide a framework for medical students to connect the diverse array of drug molecules with central nervous system targets. To do this the basic neuronal structure will be used to describe the drug receptors. For example, we will discuss the drugs that affect the (1) cell body, (2) axon, (3) synaptic vesicle neurotransmitter storage, release, removal and types. The last part of the handout will focus on (4) the pharmacology of specific neurotransmitter pathways. A more detailed description of the molecular components involved in neuronal synaptic neurotransmission is reviewed elsewhere (1)

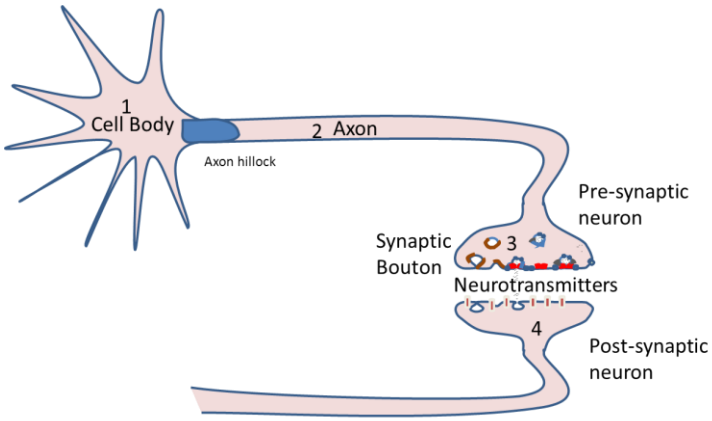


Figure 1

Presynaptic Neuron:

Neurons are cells that receive, integrate, and transmit information. They are composed of 4 functional components; cell body, axon, synaptic bouton or active zone, and dendrites (Fig 1).

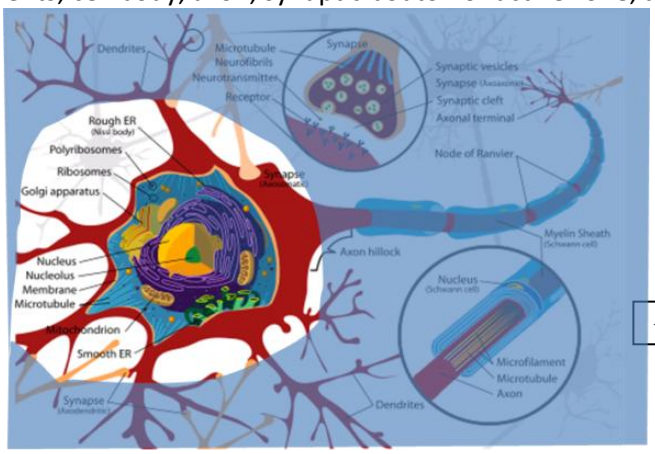


Figure 2

www.chemistry.ucsc.edu

(1) Cell Body:

The cell body contains the nucleus, many mitochondria, and other major cytoplasmic organelles responsible for the synthesis, processing, and transport of most neuronal proteins (Fig 2). Drugs that directly affect neurotransmitter synthesis are less clinically relevant due to the relative lack of specificity of action--alterations in upstream events can produce many distal consequences. The therapeutically useful drugs of this type include; *Metyrosine* (inhibitor of catecholamine synthesis) and *levodopa* (once in the CNS serves as a precursor for dopamine). See table 1 for how they are used clinically. Think about the cost risk benefit ratio of using these drugs.

Table 1 Drug involved in NT synthesis

Drug	Neuronal Target/Mechanism of Action	Pathology	Clinical Use
***Met-* tyrosine**	Catecholamine neurons—Inhibits tyrosine hydroxylase. Prevents synthesis of norepinephrine and dopamine.	NE release ↑HR (β_1-R) and ↑BP (α_1 R)	Pheochromocytoma (Treat Hypertension)
levodopa	Dopaminergic neurons—serves as a dopamine precursor allowing the ↑ synthesis of dopamine	Loss of dopaminergic neurons in substantia nigra	Treat Parkinson's Disease

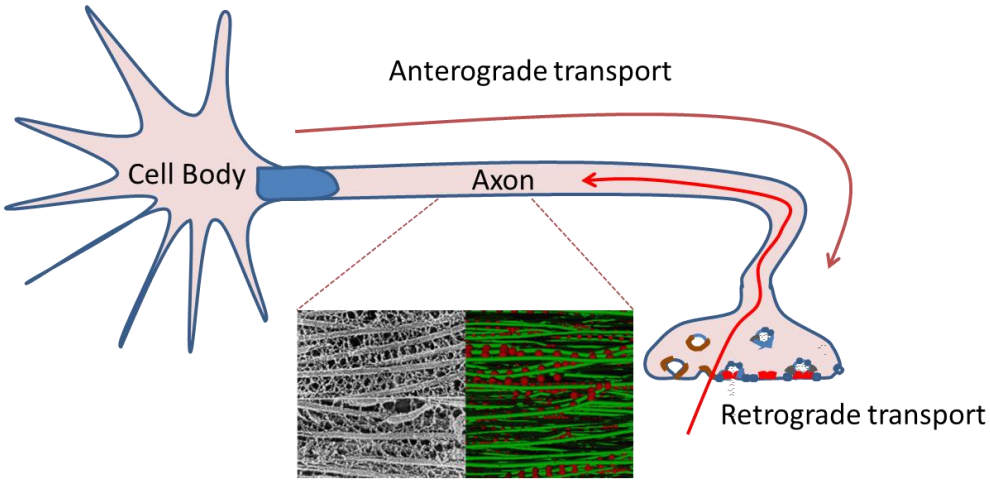
Can you imagine another mechanism to alter gene expression in neurons besides direct effects? What will happen when the brain is exposed continually to the presence of a drug that alters signal transduction cascades?

Remember these questions when drug tolerance, dependence, and addiction are discussed.

(2) The axon

Figure 3

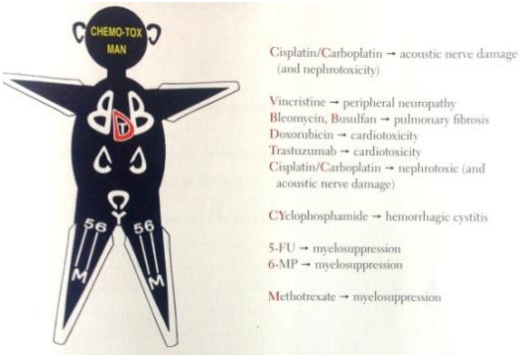
Next we will focus on drugs targets in the axon. The axon serves



two major functions.

Left: Image of an axonal microtubule cytoskeleton (source: Chen et al. Projection domains of MAP2 and tau determine spacings between microtubules in dendrites and axons. Nature. Vol. 360. 12 December, 1992) Right: Simulated microtubule network.

a) The first is to mediate active transport of proteins along a microtubule cytoskeleton to the synapse (anterograde transport) and molecules from the synapse to the cell body (retrograde transport) (2). Much interest has been generated to develop drugs targeting neuronal CNS microtubules because of the genetic connections between neurodegenerative diseases (Alzheimer's, Parkinson's disease, and Amyotrophic lateral sclerosis) and dysfunction in the cytoskeleton (3).



The indirect drug-effects are very important in neuron function. For example, neuronal microtubule function can be affected by anti-neoplastic drugs that target mitotic spindle microtubules. Peripheral neuropathy is observed in patients treated with *vincristine* (table 2)--long peripheral axons that require protein transport over long distances are especially vulnerable. Notice the V highlighting peripheral nerve innervation on the arms and legs of the 1st Aid's USMLE Step 1 Chemo-Tox Man.

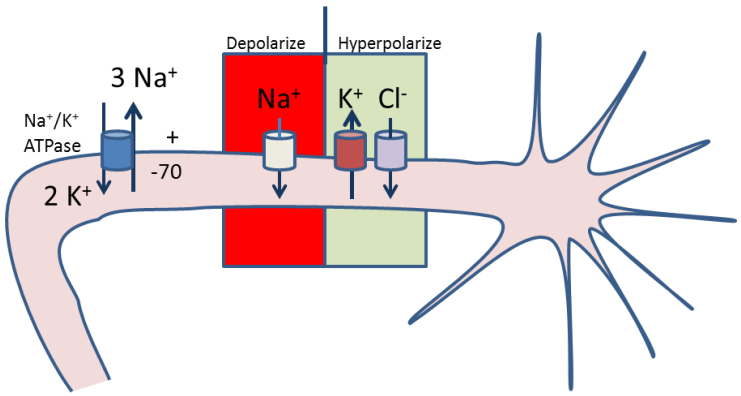
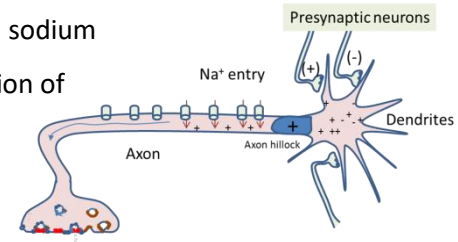


Figure 4

b) The second major axonal function is to conduct electrical impulses via a sequential opening of voltage gated sodium channels (see Fig. 4). Neurons like all excitable cells have a negative intracellular membrane potential with a larger concentration of extracellular Na^+ ions and intracellular K^+ ions creating a potential for ion flow. This potential is produced by the plasma membrane Na^+/K^+- ATPase (inhibited by the cardiac glycoside--*digoxin*) that transports 2-K^+-ions in and 3-Na^+-ions out of the neuron (Fig. 4, table 2). Neurons become depolarized when Na^+ flows into the neuron and hyperpolarized when either K^+ flows out or Cl^- flows into the neuron. This concept is exactly analogous to what occurs in cardiac myocytes and is why *digoxin* affects both cardiac and neuronal function.



Note: The initiation of the opening of voltage gated sodium channels starts in the **dendritic** branches**.** This portion of the neuron receives and summates positive (influx of Na^+ or Ca^{++} ions) and negative (influx of Cl^- or efflux of K^+ ions) inputs from other presynaptic neurons. When the accumulation of enough positive charge occurs at the axonal hillock, a specialized structure located at the top of the axon, action potential threshold is achieved and voltage gated Na^+ channels open allowing the influx of Na^+. Sequential opening of Na^+ channels propagates a depolarizing signal down the axon (4).

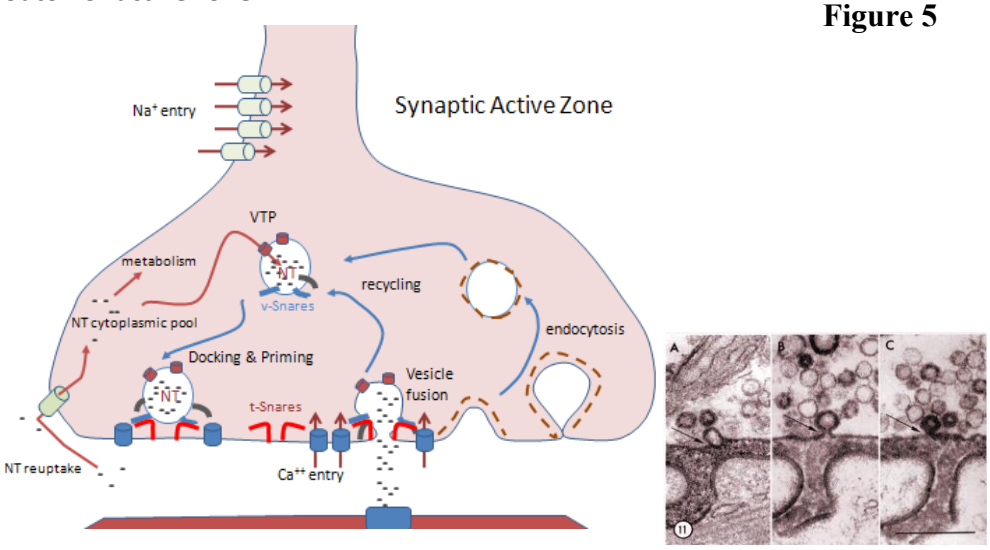
Table 2: Drugs that alter axonal function

Drug Class	Examples	Molecular Target	Pathology	Clinical Use
Cardiac Glycosides	Digoxin	Inhibits Na^+/K^+ ATPase (depolarizes neurons & myocytes)	Congestive heart failure & SV Tachyarrhythmias	↑cardiac contractility and vagal nerve firing
Local Anesthetics	Lidocaine	Axonal Na^+ Channels blocked	Nociceptive neuron firing	Pain management, regional anesthesia, treat ventricular arrhythmias
Anti-seizure drugs	Phenytoin	↑Axonal Na^+ Channels inactivation	Synchronous firing of neuronal arrays	Treat Seizure Disorders
Microtubule inhibitors	Vincristine, paclitaxel	Microtubule polymerization altered	Neuronal toxicity → disruption of microtubule function	Cancer chemotherapy

This process provides several targets for drug action. For example, preventing pain sensory neuronal firing by injecting a Na^+ -channel-blocker (e.g. *lidocaine*—previously covered in the antiarrhythmic lecture) into tissue around nerves is the basis for local anesthesia. Similarly, drugs that increase the inactivation of sodium channels are used to treat epileptic seizures produced by rapid-repetitive firing of CNS neurons. See table 2 for other examples of drugs that affect axonal function.

(3) Synaptic bouton or active zone

Figure 5



3a) NT vesicular storage and release

In 2013 the Nobel Prize was won by James Rothman, Randy Schekman, and Thomas Sudhof for the discovery of the machinery regulating vesicle traffic-- illustrated above.

The synaptic terminal is a highly organized structure that stores and releases chemical signals upon membrane depolarization. The synaptic vesicle (SV) is the primary component of this process. The unique features of the SV include a specific neurotransmitter transporter (VTP) that fills the SVs with a set number or "quantal amount" of NTs, and membrane proteins that are responsible for docking, priming, and fusion (e.g. v-snares and t-snares, synaptotagmin) of the SV with the plasma membrane (reviewed in detail 1 and described briefly below).

A V-snare is a vesicle protein (e.g. synaptobrevin) that binds to t-snares (target proteins; SNAP-25 and syntaxin) located at the active zone plasma membrane. The electrical signal is converted into a chemical signal when membrane depolarization opens voltage-gated-Ca^{++} channels and the subsequent influx of Ca^{++} produces a conformational change in SV proteins, resulting in fusion of docked vesicles with the plasma membrane Once fused, the intracellular contents of the vesicle are released into the synaptic cleft (Fig. 5 and electron micrograph). After fusion with the plasma membranes the synaptic vesicles are either recycled directly or reprocessed after endocytosis back into synaptic vesicles.

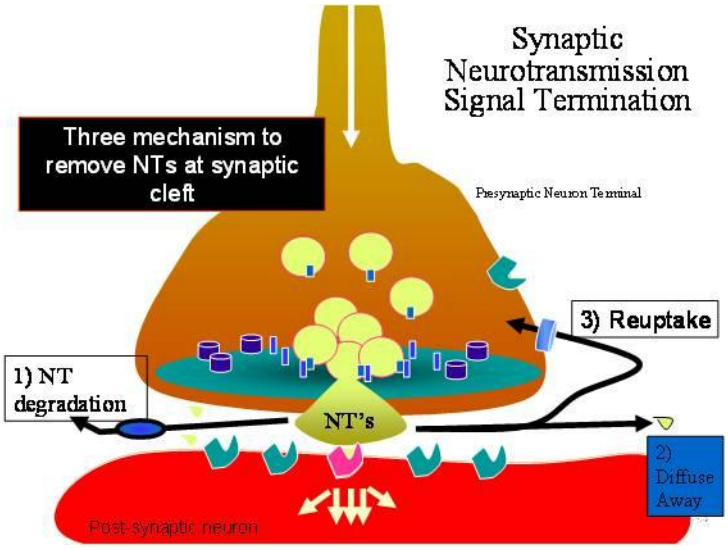
The importance of these steps described is illustrated by the many animal toxins that are produced to kill or immobilize their prey or competitors. Some toxins have clinical value. For example, a recombinant form of the neurotoxic product of Clostridium Botulinum, *botulinum toxin* (Botox), is used to treat spastic muscle conditions and, in Hollywood, to prevent glabellar lines, normal to all humans, from forming. It's mechanism of action (high yield board item) is to cleave the docking and fusion proteins, V and T snares preventing the vesicles from fusing with the plasma membranes. This inhibition occurs for several weeks or until new proteins are made and transported down axon.

Table 3: Toxins involved in neurotransmission

Toxin	Mechanism/protein target	Source	Clinical use
Tetrodotoxin (TTX)	Na^+ channel blocked	Puffer fish 	Experimental only, Fugu-sashimi
Batrachotoxin (BTX)		Colombian frog 	
Omega cono toxin (⍵-CTX)	Ca^{++} channel blocked	Pacific cone snail 	Experimental--spastic disorders
Botulinum Toxin	Cleaves synaptic docking proteins (many V and T snares)	*C. botulinum* 	Treatment of spastic disorders, hyperhidrosis, and cosmetic
Tetanus Toxin	Cleaves the V-snare protein--synaptobrevin	*C tetanus* 	none

3b) Removal of NT:

Figure 6



The other significant role of the presynaptic terminal is to remove the released NTs. In order for a NT to be a signal it has to be present only when needed and for a short time. The removal of NTs from the synaptic cleft provides several targets for valuable pharmacologic agents used to treat uni-polar depression, insomnia, ADHD, Parkinson's disease, and to increase cognition in patients with Alzheimer's disease (table 4).

There are 3 main methods to remove the NTs after they have been released.

1) Enzymatically degraded:

   The NTs can be broken down by enzymes located in the synaptic cleft. For example, acetylcholinesterase, responsible for the breakdown of acetylcholine, is located in the synaptic cleft of cholinergic neurons. This process was covered during the autonomic pharmacology section.

2) Diffuse away:

   Diffusion away from the synapse—in this case the NT can be taken up by supporting glial cells or produce effects on adjacent nerves.

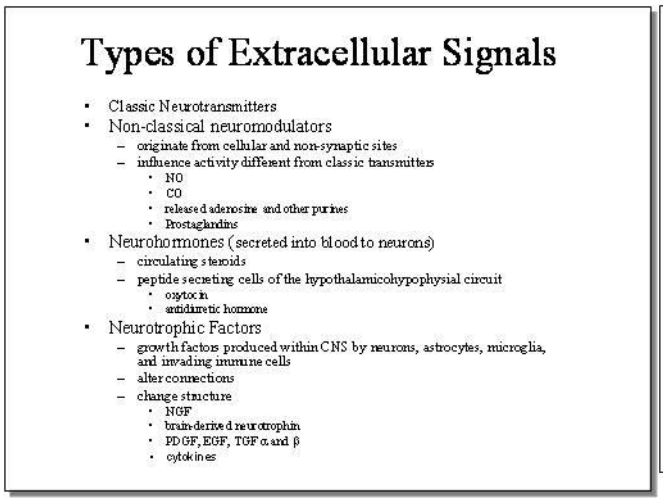
3) Reuptake:

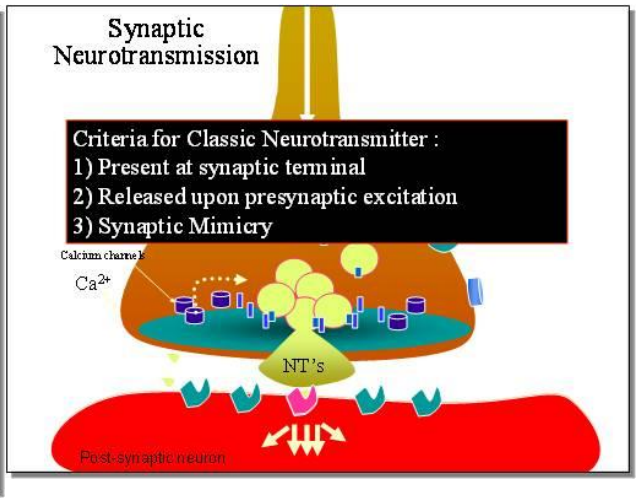
   The NTs can be taken back up into the presynaptic neuron where they are either repackaged into synaptic vesicles or degraded by metabolic enzymes. This is the common mechanism for most NTs. Clinical relevance for these molecules as targets is shown in table 4.

Table 4: Drugs that alter NT reuptake or degradations

Drug	Molecular Target/Mechanism of action	Clinical Use
Amphetamine	Catecholaminergic neurons—↑ extrasynaptic release of catecholamines (norepinephrine and dopamine) through NT transporter	Treat ADHD, stimulant, appetite suppressant
Tricyclic Antidepressants (TCAs)	Noradrenergic, serotonergic neurons—↓. Reuptake of Norepinephrine and serotonin. ↑ **amount** in the synaptic cleft.	Treat Depression
Cocaine	Noradrenergic, dopaminergic neurons—↓ reuptake of dopamine and norepinephrine. ↑ **amount** in the synaptic cleft.	also sodium channel blocker
Selective Serotonin reuptake Inhibitors (SSRIs)	Serotonergic neurons—↓ reuptake of serotonin. ↑ **amount** in the synaptic cleft.	Treat Depression
Non-specific MAO inhibitors	Catecholaminergic neurons—↓degradation of serotonin, dopamine, and norepinephrine. ↑ **amount** of transmitters available for release.	Treat Depression
Specific MAO B inhibitors	Dopaminergic neurons—↓ dopamine degradation. ↑ **amount** of transmitters available for release.	Parkinson's
AChE inhibitor	Cholinergic neurons—dec Ach degradation	Alzheimer's dementia

Can you identify something in common regarding drugs used to treat depression?





3c) Types of Neurotransmitters

NTs are endogenous molecules synthesized and released by pre-synaptic neurons. When released they travel across the synaptic cleft where they bind to specific post-synaptic receptors. Many different types of molecules can serve as NTs. For example, amino acids, biogenic amines, neuropeptides, purines, fatty acids, gases, neurotrophic factors, and chemokines (see slide above) have all been shown to be neurotransmitters.

Commonly a neuron releases only one type of classic neurotransmitter, such as acetylcholine, dopamine, norepinephrine, serotonin, glutamate, GABA (γ-amino butyric acid) or histamine. Neurons are often defined by which one of the classic NTs they release; cholinergic, dopaminergic, noradrenergic, etc. Many neurons are also able to synthesize and co-release two or perhaps more non-classical-neurotransmitter types. For example, most synaptic vesicles contain large amounts of ATP and adenosine that are released along with the classic neurotransmitter. These co-transmitters modulate both pre- and post-synaptic effects of the classic neurotransmitters. The co-release of monoamines (dopamine or norepinephrine) along with types of peptide neurotransmitter has also been documented. The ability to release classic and atypical neurotransmitters adds to the information available to the post-synaptic neuron.

Table 5 summarizes the important NTs, their neuronal distribution, function, and clinical relevance.

Table 5: Common neurotransmitter function and related diseases

Type	NT	projections	General Function	Disease
Biogenic amine	Acetylcholine	projections from brainstem, nucleus basalis Meynert, medial septal and diagonal band nuclei widely distributed to cortex	cognition (nucleus basalis Meynert), reward (projections to ventral tegmental area), motor control (projections to striatum), PNS: muscle contraction, ANS	Alzheimer's dementia, Drug addiction, Parkinson's Disease,
	Dopamine	Projections throughout cortex, important connections shown in general function	Meso-limbic (higher order thought, decision processing), Nigrostriatal (fine motor control), Medulla (area postrema) Tuberoinfundibular (lactation-prolactin release)	Schizophrenia, Drug Addiction, Parkinson's Disease, Nausea and vomiting Hyperprolactinemia,
	5-HT (serotonin)	projections from raphe to almost every region of the cortex and brain stem.	CNS: regulates sleep, arousal, attention, processing of sensory information. Important role in emotion and mood regulation. Vasculature of CNS, Medulla (area postrema), PNS: myenteric neurons	Depression, anxiety, psychosis (?), Migraine headaches, Nausea and vomiting, Appetite
	Nor-epinephrine	projections from cell bodies in the pons (e.g. Locus Ceruleus) and brain stem to all levels	CNS: regulates sleep, arousal, attention, response to stimuli, optimization of task performance, exploratory behavior, anxiety. Important role in emotion and mood regulation.	Depression, anxiety, attention deficit disorder, insomnia, drug withdrawal symptoms
Amino Acid and derivatives	GABA (γ-amino butyric acid)	Principle inhibitory interneurons throughout the CNS and spinal cord	Provide inhibitory balance to excitatory (glutaminergic) neurons or the "off signal". Reduces all brain activity when activated.	Under excitation produces anxiety, insomnia, seizures. Spinal chord--muscle spasms
	Glycine	Spinal interneurons, midbrain + projections	Similar to GABA--provides inhibitory influence to CNS	Strychnine antagonist to glycine receptors produces seizures in rats
	Glutamate	Primary excitatory neurons used to for all levels of communication throughout the brain and spinal chord. Hippocampus	principle excitatory communication throughout brain ("the on signal"). Hippocampus, Nucleus Accumbens	Seizure (over excitation), excito-neurotoxicity, Memory acquisition, Drug Addiction
	Histamine	projections throughout CNS from Tuberomamillary nucleus + projections	arousal, attention, learning and memory	insomnia
Peptides	Endogenous Opioid Peptides	Cell bodies at all levels; long and short	reward (Ventral tegmental projections to nucleus accumbens), nociception, PNS: gut motility	Drug Addiction, Nociceptive Pathways (pain sensation)
Fatty acids	endogenous cannabinoids	atypical--released in response to neural activity	unclear--may act as a retrograde messenger (?). General function--stimulates appetite, reduces nausea and vomiting	obesity
Nucleosides	ATP, adenosine	atypical--stored and released in synaptic vesicles along with classic NTs	inhibitory neuromodulatory tone on CNS--reduce anxiety	
Gases	NO, CO	atypical	NO regulates neural plasticity,	

4) Post-Synaptic Response

Neurotransmitter receptor motifs

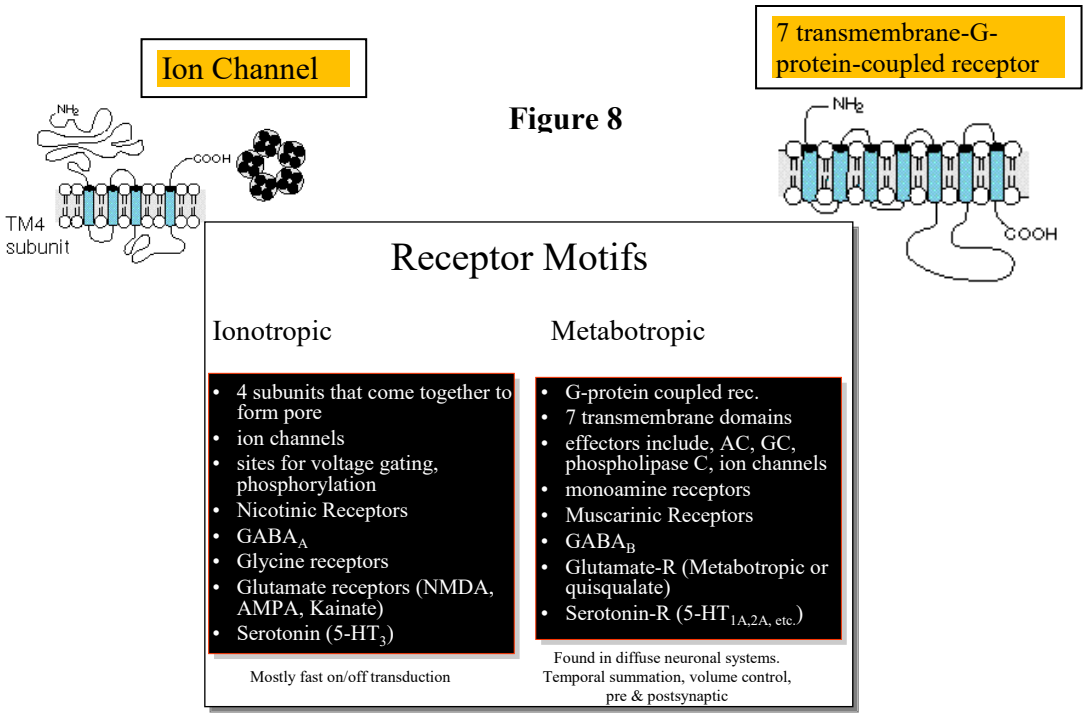
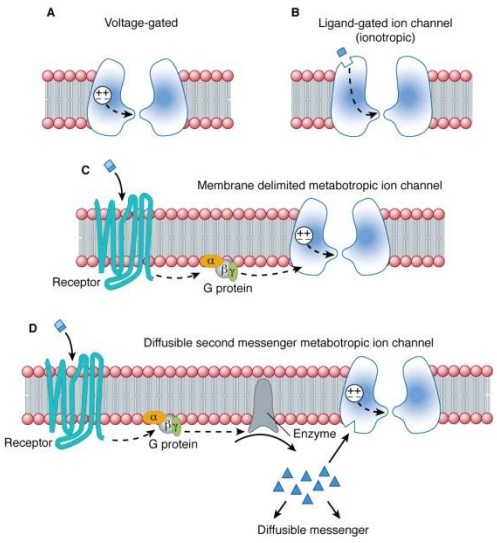


Figure 8

The released neurotransmitters produce two general effects on the post-synaptic cell when they activate their respective receptors. The first-immediate-response is an alteration in membrane potential. The second-delayed-long lasting-effect often includes changes in gene-expression.

Post-synaptic neurons have two principle receptor motifs. Many classic NTs (acetylcholine, GABA, glycine, glutamate, and serotonin) can activate both ionotropic (ion channels) receptors and metabotropic (G-protein-linked transmembrane) receptors (see figures 8 and 9). In general, ion channel effects are fast while G-protein-coupled effects are slower in onset and longer lasting.

Figure 9

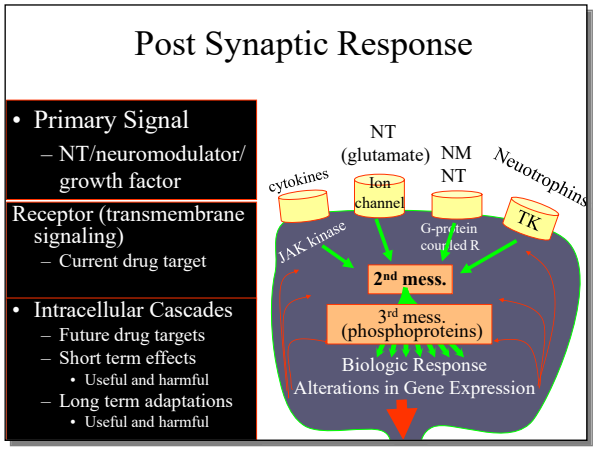


The post synaptic effects of these receptors can be similar or can occur in opposite directions. Most neurons have a mixture of receptor types. The ion channels produce the most depolarizing or hyperpolarizing response. The

metabotropic receptors in general modulate the post-synaptic effect of the ion-channels either directly via g-protein subunits or changes in ion channel function via second messenger cascade-induced phosphorylation of ion channels. The combination of receptor types allows for increased temporal summation of inputs and further increases the complexity of information processed by a neuron. The other major consequence is that many distinct responses can be achieved when the same neurotransmitter activates various receptor types located in distinct brain regions. For example, serotonin (5-HT3) ion channels located in the medullary-emetic-center *(high yield board item)* are important for producing emesis and serotonin (5-HT1) types located on the vasculature are involved in migraine headache pathophysiology.

Long-term adaptations:

Figure 10



Activation of post synaptic receptors is the first event. The second and long lasting response is produced by the intracellular cascades altering protein kinase activity, enzyme function, and changes in gene expression. Short and long term use of drugs can be both useful and harmful. For example, short-term drug therapies are important in reducing pain (opioid agonist) and treating anxiety (GABA receptor activators). Long-term use of these medications produces an adaptive compensatory response in neurotransmitter synthesis, receptor number, signaling pathway proteins, and even the cytoarchitecture of neuronal connections. These adaptive changes are the basis for tolerance, dependence, and withdrawal symptoms observed with chronic drug use. For example, long-term use of sedative-hypnotic drugs (e.g. diazepam) to treat anxiety can result in the down-regulation of GABA-inhibitory-receptors. In these situations prompt cessation of drug use can lead to seizures resulting from unopposed Glutaminergic activity. A similar mechanism occurs during long-term ethanol consumption.

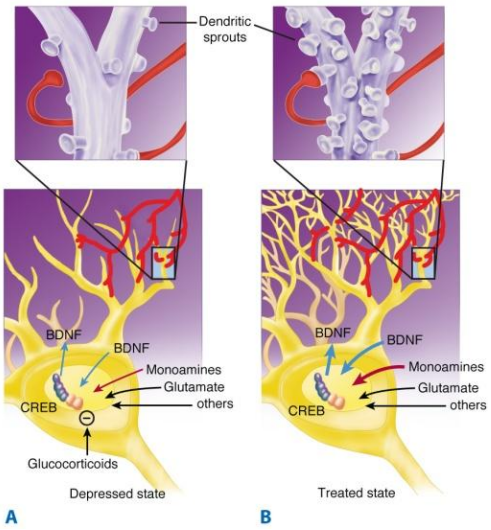


Figure 11

Normally, the adaptive response is what clinicians and patients are trying to avoid. However, patients with depression have to be treated with drugs, which increase norepinephrine and serotonin in the synaptic cleft, for over a month before benefits are realized. In this case neural adaptations produced by release of neurotrophic factors and changes in gene expression create beneficial influences on neuronal cytoarchitecture, such as increased dendritic arborization and sprouting (Fig 11, see page 510 of Katzung). The exact compensatory mechanisms that are produced by anti-depressant drugs is an area of active research.

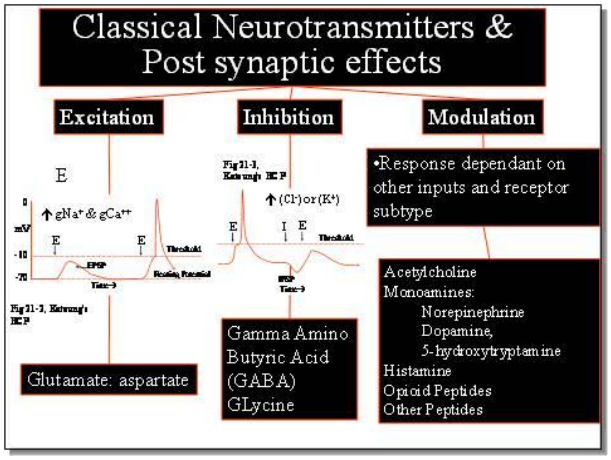
The next section focuses on the individual NT systems and the relevant pharmacology as it relates to disease states.

Table 6: NT, receptors, and clinical pharmacology

Transmitter	Receptor (g-prot. or ion flow) excitatory (↑) or inhibitor (↓)	Location	Relevant Clinical Pharm.	Disease Treated by agonist or antagonist
Acetylcholine	M1 (Gq) ↑			
	M2 (Gi) ↓	Substantia nigra	antagonist	Parkinson's Disease
	N (↑ cations) ↑	Cortex	AchE i	Alzheimer's dementia
		NMJ	antagonist	Muscle Relaxation
		Nucleus accumbens?	Partial agonist	Smoking cessation
Dopamine	D1 (Gs)	Connections throughout		
	D2 (Gi) ↓	Meso limbic connections	Antagonist	Schizophrenia
		Nigrostriatal connections	Agonist	Parkinson's Disease
		Tuberoinfundibular	Agonist	Hyperprolactinemia
		Medulla (area postrema)	Antagonist	Nausea and vomiting
GABA	GABA-a (↑ cl-.) ↓	CNS and spinal cord	Increased activity	Anxiety, insomnia, seizures
	GABA-b (Gi) ↓	Spinal cord	agonist	Muscle spasm
Glutamate	NMDA (↑cations) ↑	Hippocampus		Impaired Memory
		Throughout CNS	antagonist	Excitotoxicity (Alzheimer's)
		Nucleus Accumbens?	antagonist	Addiction
	AMPA (↑ cation) ↑			
	Kainite			
	Quisqualate (Gq) ↑			
Glycine	↑ Cl- (inhibitory)	Spinal interneurons, midbrain + projections	Antagonist (strychnine)	Rat infestations
5-HT (serotonin)	5-HT1Aand B (Gi) ↓	Basal ganglia, CNS, brains stem	agonist	Migraine headaches
	5-HT2A (Gq) ↑	cortex	antagonist	Depression, anxiety, psychosis (?)
	5-HT3 (↑cations) ↑	Medulla (area postrema)	antagonist	Nausea and vomiting
	5-HT4 (Gs)↑	myenteric neurons	agonist	Gastric acid reflux (?)
Nor-epinephrine	⍰1 (Gq) ↑	Cell bodies in the pons		
	⍰2 (Gi) ↓	and brain stem project	agonist	Drug withdrawal symptoms
	⍰1 (GS) ↑	to all levels	Reuptake inhibitors and	Depression
	⍰2 (Gs) ↓		MOA inhibitors	
Histamine	H1 (Gq) ↑	Tuberomamillary	antagonist	insomnia
	H2 (Gs) ↑	nucleus + projections		
	H3 ↓			
Opioid Peptides	Mu (Gi, ↓ Ca++) ↓	Cell bodies at all levels;	Agonist	Pain management
	Kappa Gi, ↓ Ca++) ↓	long and short	agonist	Pain management
	Delta (Gi, ↑ K+) ↓	Projections		
tachykinins	NK1 (Gq) ↑	Primary sensory neurons	antagonist	Nausea and vomiting
endocannabinoids	CB1(Gi, ↓ Ca++) ↓	Widely distributed	antagonist	obesity

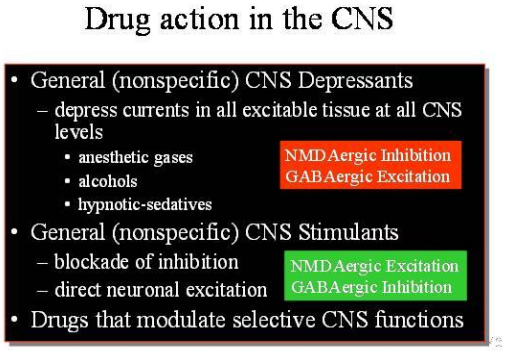
Specific Neurotransmitter Pathways

The two most wide spread CNS neurotransmitters are glutamate and GABA. Glutaminergic neurons are the principle excitatory communication neurons between brain regions and to the periphery. GABAergic neurons are the main inhibitory influence in the CNS. In simple terms, activating Glutaminergic neurotransmission is analogous to turning on the light.



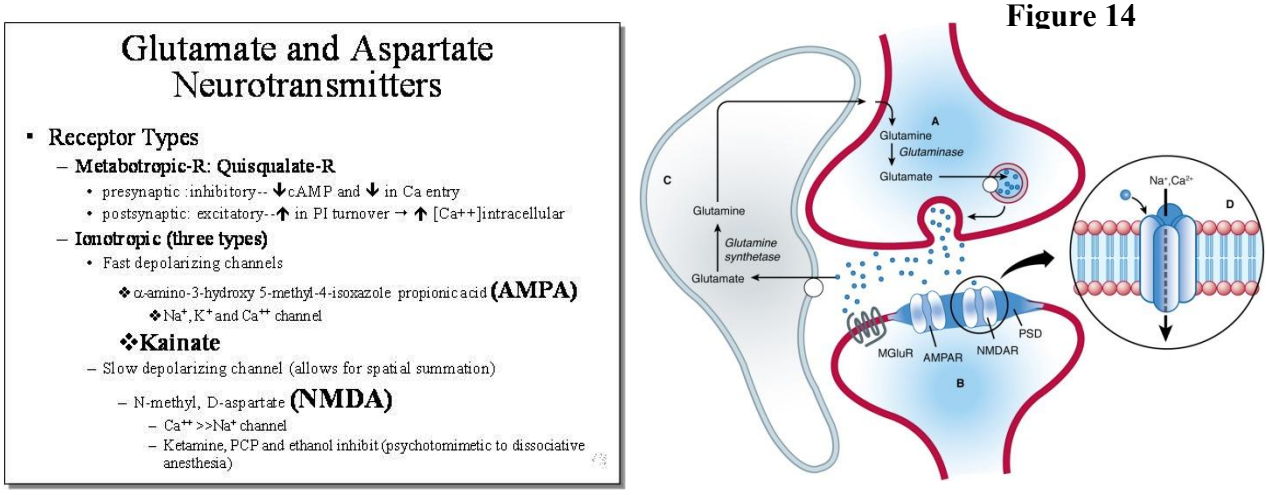
Activating GABAergic neurotransmission provides the dimmer switch. The rest of the NTs provide the colors and textures required to paint a picture of the world.

Clinical pearl: Excess or unopposed Glutaminergic activity results in seizures and excitotoxicity. Excitotoxicity (neuronal cell death) is produced by extended influx of calcium inside neuron, which stimulates apoptotic pathways. Patients with status epilepticus (defined as unremitting seizure activity) are susceptible to permanent excitotoxic-brain-damage. Cell death can be prevented in these patients by administering IV drugs that increase GABA-inhibitory activity.



Excitatory neurotransmitters (Glutamate and aspartate)

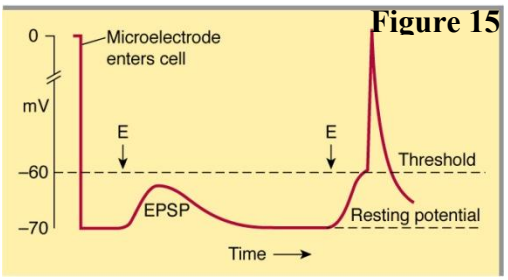
Figure 14



Glutaminergic neurons (Figure 14) are usually long relay neurons that can stimulate virtually all other neuronal types. Synaptic release of glutamate is central to memory acquisition (synaptic plasticity), drug addiction, brain damage (excitotoxicity), and anxiety as well as seizure activity--when over active. There are three types of glutamate receptors named for the agonists used first to identify them. The two ionotropic forms, AMPA and NMDA, when bound by glutamate produce neural excitation by allowing the influx of Na^+ and Ca^{++}. The metabotropic or quisqualate receptor increases the intracellular concentration of Ca^{++}.

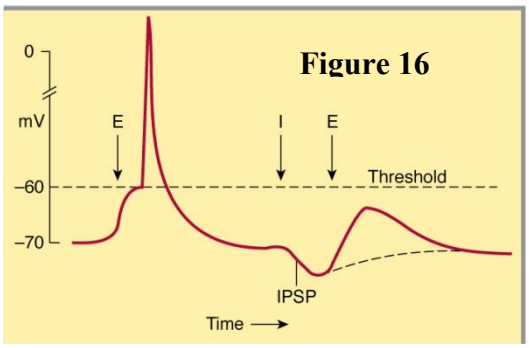
An electrophysiologic measurement of post-synaptic response to glutamate is shown in figure 15. The excitatory post-synaptic potential (EPSP) occurs when the stored glutamate from a single synaptic vesicle is released. The post-synaptic depolarization occurs upon opening of post-synaptic NMDA or AMPA Glutaminergic-cation channels. The resulting influx of cations moves the membrane potential to a more depolarized state. Action potential is reached when enough glutamate is released, either from a single neuron or several neurons to increase the post-synaptic membrane potential above threshold.

Figure 15



The clinical pharmacology for drugs that affect Glutaminergic receptors is limited. Currently, the NMDA receptor antagonist, *ketamine* and *felbamate* are used. *Ketamine* is used as a general anesthetic agent and illicitly to produce hallucinations. It produces a type of anesthesia called dissociative anesthesia because it disconnects the pain sensation from a cortical response. Felbamate has multiple CNS targets and is used to treat epilepsy.

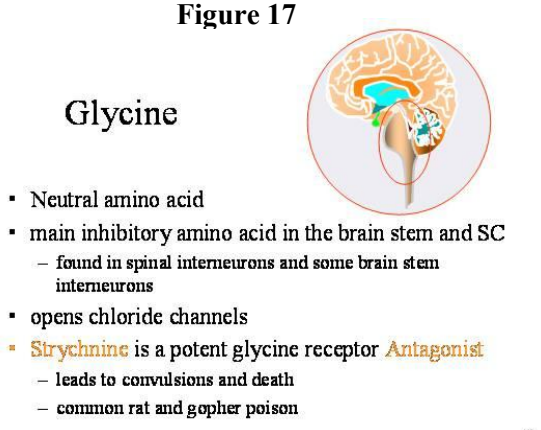
Inhibitory neurotransmitters (Glycine and GABA)



The neurotransmitters **glycine** and **GABA** produce a hyperpolarizing response in post-synaptic membranes by opening Cl^- channels, allowing the influx of the negative ion into the neuron, which is driven by its electrochemical gradient. The increased intracellular negative charge reduces the membrane potential and the ability of the neuron to reach action potential threshold. Illustration of this type of inhibitory influence is shown in figure 16. This figure represents an electrophysiologic recording of a post-synaptic neuron. The IPSP (inhibitory post-synaptic potential) is produced when the released GABA activates the opening of chloride channels allowing Cl^- to flow into the post-synaptic neuron. Increasing efflux of positive K^+ ions (this is common mechanism for metabotropic receptor) is the other mechanism to produce hyperpolarization.

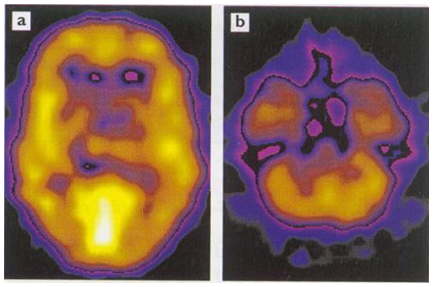
The discussion of glycine-activated chloride channels will not be the focus of this exercise due to the limited clinical value. The main clinical feature of glycine-chloride channels is that *strychnine*, a rat poison, produces its effects by antagonizing these channels. See figure 17 for details regarding glycine.

Figure 17



Gamma Amino Butyric Acid (GABA)

Figure 18



Perhaps the most important targets for therapeutic intervention are the receptors activated by the NT, **GABA**. For example, anxiolytic drugs (sedatives), sleep aides (hypnotics), anti-seizure medications, general anesthetics, ethanol, as well as some muscle relaxants produce their beneficial therapeutic effect by increasing the activity of GABA-receptors. The wide spread distribution of GABA activity is found throughout the CNS and spinal cord. The orange in the PET scan illustrates the abundance of GABA activity in the brain (fig. 18).

Like many classic NTs GABA binds to metabotropic (GABA-B) and ionotropic (GABA-A) receptors *(Fig. 19).* GABA-B agonist (e.g. *baclofen*) is used as antispastic drugs (Spasmolytics) because they activate spinal inhibitory interneurons, which results in a reduction in motoneuron-induced skeletal muscle contraction. This will be discussed in detail during your "muscle relaxant lecture".

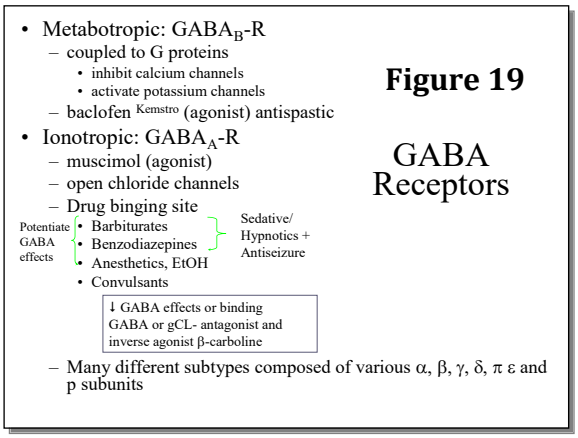


Figure 19

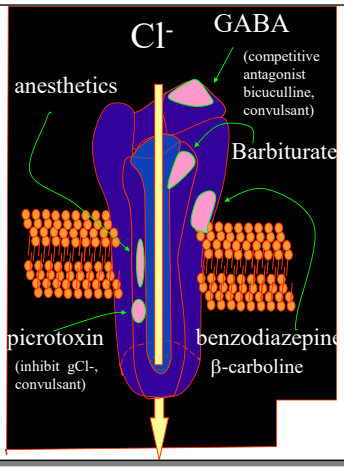
GABA Receptors

GABA-A chloride channels *(Fig. 20)* is the target for the potent CNS depressant agents, including, general anesthetics, barbiturates, benzodiazepines and ethanol. A Dose-dependent increase in GABA-A channel activity produces a gradient of effects ranging from decreased anxiety → sedation → sleep → general anesthesia →coma and death.

Figure 20

GABA-A Receptor

Molecular site of action for benzodiazepines, barbiturates and some general anesthetics



For example, the common sedative-hypnotic drugs, barbiturates and benzodiazepines, allosterically regulate the binding of GABA to the GABA-A receptor. This is a different mechanism of action as it relates to most agonists. In this case barbiturates and benzodiazepines bind to a distinct site on the channel separate from the GABA binding site.

When bound by these drugs a conformational change in the protein increases channel opening after GABA is bound to its receptor pocket. The importance of this will be discussed in detail during the sedative hypnotic lecture. The effects of both of these classes of drugs on chloride channel opening are shown it figure 21. The board relevant mnemonic is to pronounce barbiturates as barbi-durate-s—the durate is to remind you of duration.

Benzodiazepines vs. Barbiturates Basic and Clinical Pharmacology, 7th Ed., p. 361, Katzung,

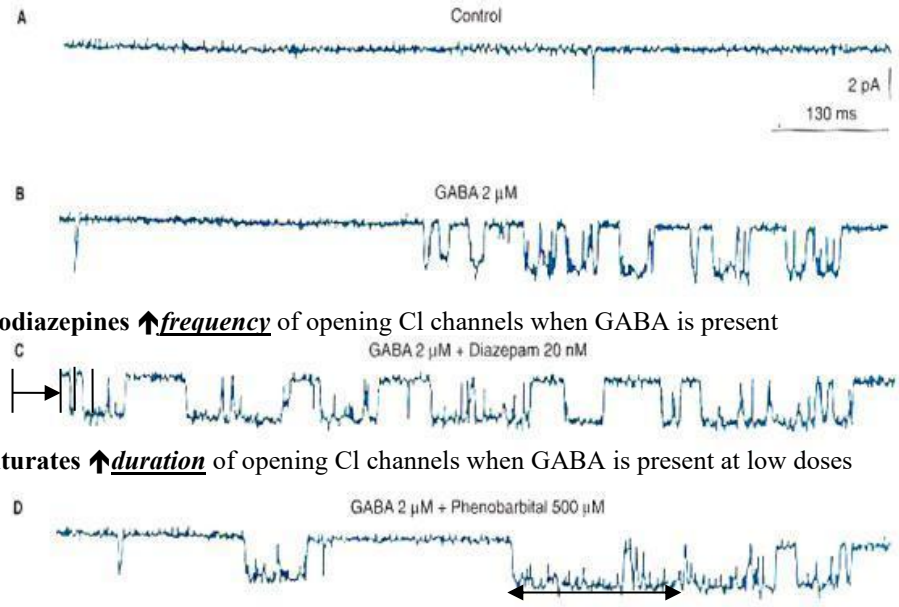


Figure 21

Some examples of each class of drug is shown below

Benzodiazepines

- Anxiolytics
  - **Alprazolam** Xanax
  - **Chlordiazepoxide** Librium
  - **Diazepam** Valium
- Hypnotics
  - **Triazolam** Halcion
  - **Zaleplon** Sonata

  Zolpidem Ambien
- Anesthesia compliment

  Midazolam Versed

Barbiturates

Hypnotics/Anxiolytics

Amobarbital Amytal

Phenobarbital *

Secobarbital Seconal

Technically not benzodiazepines but they allosterically regulate the GABA-a channel similar to benzodiazepines

Modulatory Neurotransmitter Pathways

Neurotransmitters that modulate synaptic transmission

Modulatory effects on virtually every brain circuit
- Dampen or facilitate neuronal communication
- regulate plasticity

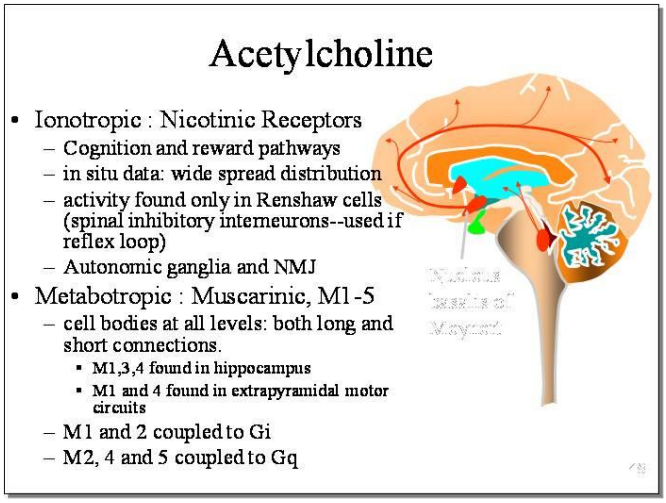
- Acetylcholine
- Catecholamines
  - Dopamine
  - Norepinephrine
  - Epinephrine
- Serotonin
- Histamine

Modulation of Glutaminergic activity is also produced by catecholaminergic, cholinergic, and histaminergic neurons. The cell bodies of modulatory neurons are localized in specific clusters (nuclei) that send projections to other brain areas. Below is a brief overview of each NTs role in brain function.

Figure 22

Acetylcholine:

Figure 22 illustrates the wide spread neuronal projections from brainstem, nucleus basalis Meynert, medial septal and diagonal band nuclei to all areas of the cortex. Both metabotropic and ionotropic type acetylcholine receptor are present in the CNS as they are in the periphery. The clinically relevant pharmacology for drugs that affect cholinergic receptors includes the following:

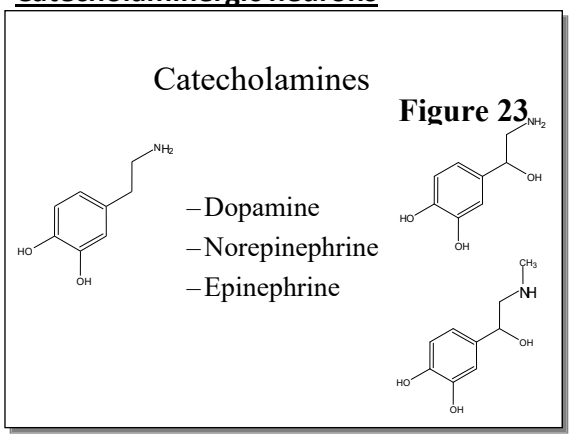


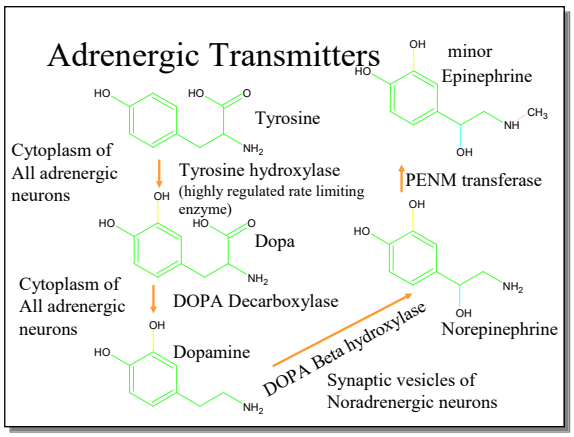
- Parkinson's: cholinergic neurons oppose the function of depleted dopaminergic neuronal activity. This is why antimuscarinic-drugs are used in conjunction with others to treat the symptoms of Parkinson's disease . Note: Parkinson's disease is a

neurodegenerative disease in which dopaminergic connections in the striatum are lost over time (fig. 29)

- Alzheimer's patients lose cholinergic neurons especially ones projecting from the nucleus basalis Meynert (long acting cholinesterase inhibitors help increase cognition. Note: they won't help you to study more effectively ☹)
- Motion Sickness (scopolamine, muscarinic antagonist)
- Many antidepressants and anti-psychotics have non-specific inhibitory effects
- Activation of the nicotinic receptor is central to addiction. More on this in the drugs of abuse lecture.

Catecholaminergic neurons





Catecholamines include dopamine, norepinephrine and epinephrine. Epinephrine is mainly found in peripheral neurons and is not prevalent in the CNS. Remember that a molecule with two hydroxyls on a benzene ring is a catechol (fig. 23).

Biosynthesis:

The biosynthetic pathway is shown above. Tyrosine hydroxylase is the rate limiting enzyme for the biosynthesis of all catecholamines. This is the enzyme inhibited by metyrosine (the drug used to reduce the symptoms of catecholamine excess produced by adrenal tumors). Both dopaminergic neurons and noradrenergic neurons have the ability to produce dopamine from the precursor dopa. Noradrenergic neurons have the additional enzyme DOPA beta hydroxylase that converts dopamine into norepinephrine.

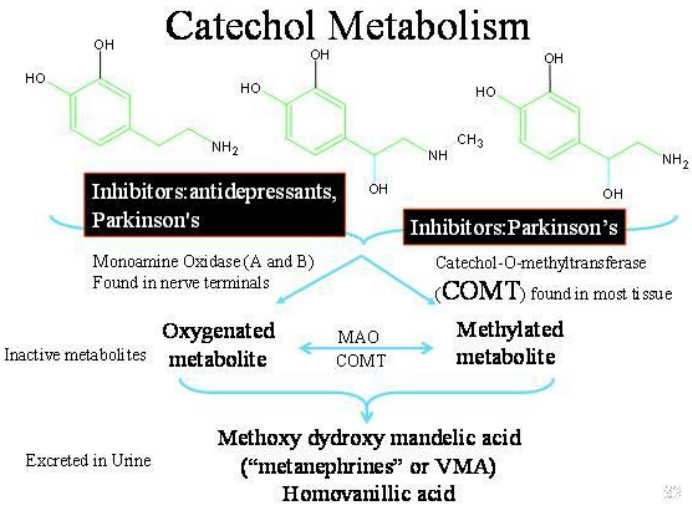


Figure 25 **Figure 24**

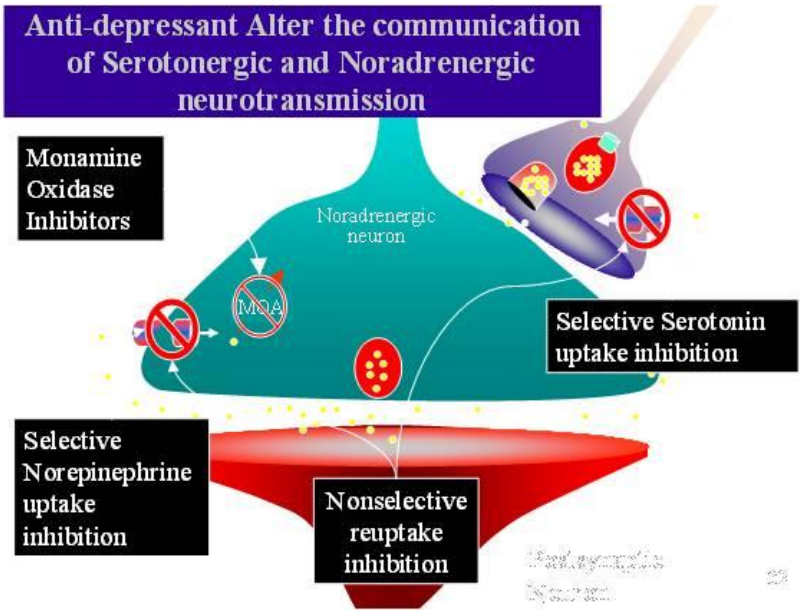
Metabolism:

Catecholamine can be metabolized by a variety of enzyme combinations. The two principle types of metabolism are via oxidations by monoamine oxidases or methylation by catecholamine methyl transferase (fig 24). The products produced are called metanephrines.

The two subtypes of Monamine Oxidase (MAO) are A and B. MAO-A is found in predominantly in noradrenergic neurons. This isotype is relatively nonspecific. MAO-A metabolizes epinephrine, norepinephrine, tyramine and serotonin. MAO-B is found mainly in neurons that synthesize and store serotonin or histamine. MAO-B selectivity degrades dopamine and tyramine. Non-specific inhibitors of MAO-A and B, like *phenelzine* and *tranylcypromine*, are used to treat unipolar depression. Presumably, continuous long-term increases in these NTs result in post-synaptic adaptations and neuronal remodeling that are beneficial in patients with depression (see figs 13 and 25). Nonselective inhibitors are associated with many potentially lethal drug-drug interactions. For example, tyramine a compound found in many types of aged or fermented food, can cause a hypertensive crisis when metabolism is prevented in patients using *phenelzine*. Selective MAO-B inhibitors, like *selegiline*, are used to treat patients with Parkinson's disease to increase synaptic dopamine levels.

Catechol-O-methyl transferase is a second mechanism used to breakdown catecholamines. Inhibitors of this enzyme are useful in preventing the breakdown of dopamine in patients with Parkinson's disease (see fig. 29 for description).

Clinical Pearl

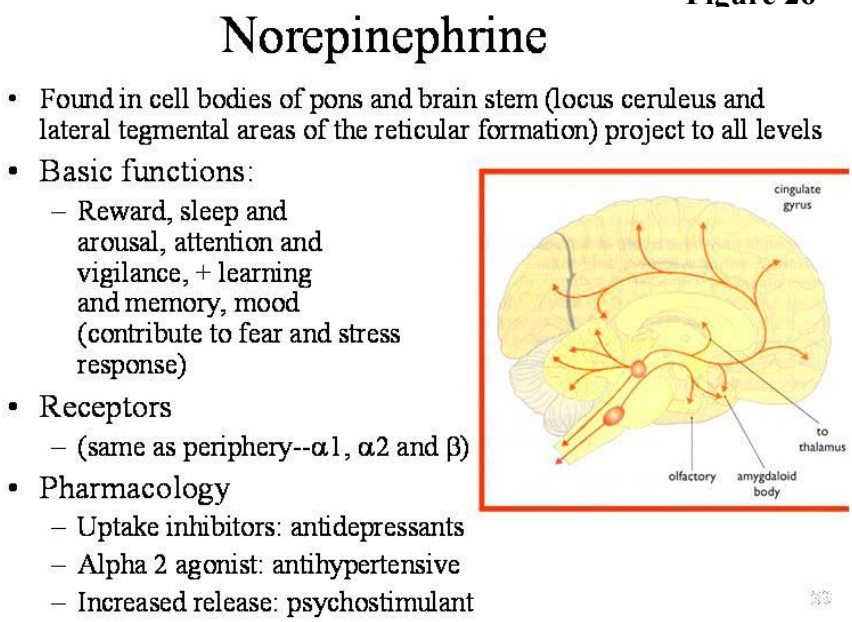


Unipolar depression;

Treating depression involves increasing norepinephrine and serotonin at the synapse. Drugs such as MAO inhibitors that prevent the breakdown are useful. Tricyclic antidepressants block both serotonin and norepinephrine uptake. SSRIs selectively block serotonin uptake. The side effect profile of SSRIs because they are specific to serotonin is much less than MAO inhibitors (too many drug interactions) and TCA. This is the principle reason for their popularity.

Noradrenergic Neuron Distribution and function

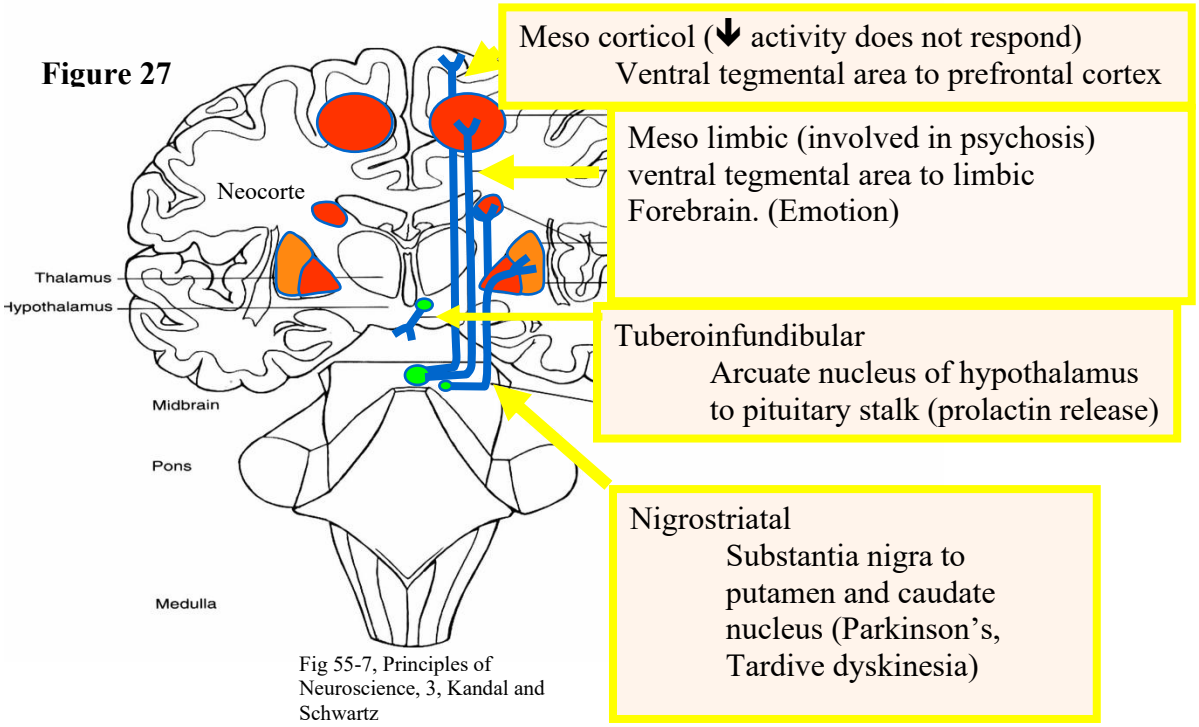
Figure 26



The cell bodies of noradrenergic neurons are localized in the brain stem and basal ganglia and that send projections throughout the brain (fig. 26). This distribution pattern helps explain the wide ranging effects of activating or inhibiting these neurons. See figure 26 for basic functions and relevant pharmacology.

Disease states associated with norepinephrine include unipolar depression, attention-deficit-hyperactivity syndrome, and play a symptomatic role in many other disease states, including withdrawal symptoms produced by the cessation of opioids and ethanol. Drugs that increase the amount of synaptic norepinephrine are used as appetite suppressants and to produce CNS stimulation.

Dopaminergic neurons



Dopaminergic pathways have been well mapped using modern molecular techniques. The four main connections are shown above and listed below.

- Nigrostriatal pathway is central to Parkinson's
- Meso-systems are involved in schizophrenia:
- Tuberoinfundibular pathway regulates lactation: Dopamine ↓ lactation.
- Dopamine receptors in the medullary-area-postrema are involved in vomiting

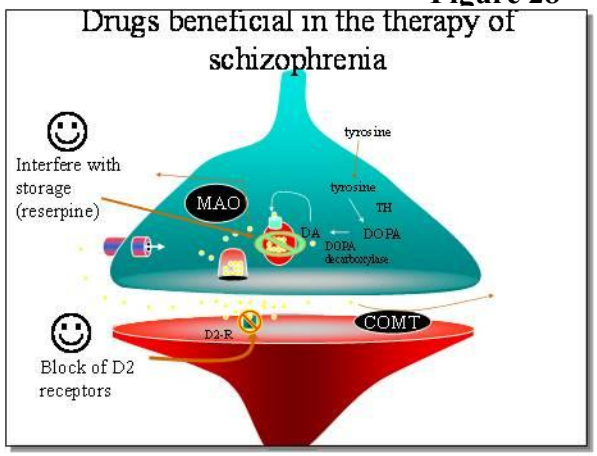
Drugs that alter dopamine-signaling affect all three systems simultaneously. For example, typical antipsychotic drugs are antagonist at dopamine type-2 receptors. The use of these drugs is sometimes associated with the unwanted side effects of bradykinesia and hyperprolactinemia. Conversely, dopamine agonist used to treat patients with Parkinson's disease may produce psychosis, vomiting, and inhibit lactation. Dopamine secretion via the tuberoinfundibular tract (hypothalamus to pituitary) is responsible for suppression of prolactin (promotes lactation) secretion in the pituitary. Therefore, drugs used to suppress hyperprolactinemia are dopamine agonist. Alternatively, blocking the communication between

the hypothalamic neurons and pituitary cells leads to an increase in prolactin production and secretion.

Specific disease states involving dopaminergic neurotransmission:

Schizophrenia (dopamine hypothesis)

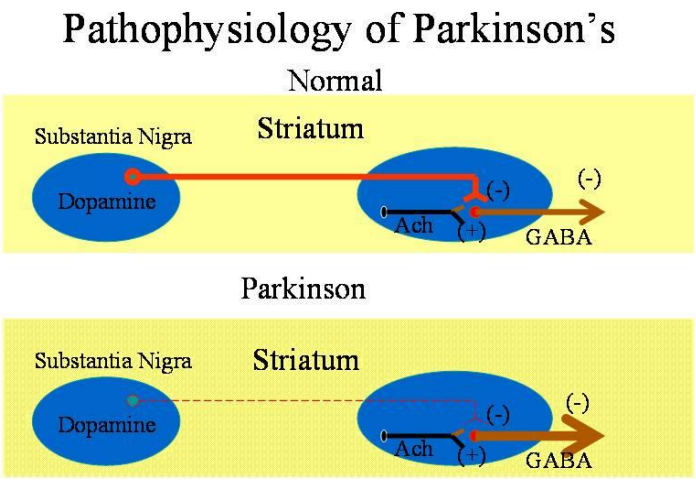
Figure 28



The dopamine hypothesis for schizophrenia stems from two principle observations: 1) All drugs beneficial in the treatment of schizophrenia have in part some dopamine type-2- receptor-antagonism as a component of their mechanism of action. 2) Drugs that increase the synaptic levels of dopamine can produce symptoms of schizophrenia.

Parkinson's disease and Parkinsonism:

Figure 29



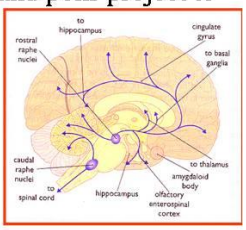
Parkinson's disease involves selective destruction of dopaminergic connections between the substantia nigra and the striatum. Therefore, drugs that increase dopamine synthesis (levodopa) or prevent breakdown (MAO inhibitors) reduce the symptoms in patients with Parkinson's disease. Cholinergic neurons oppose the effects of dopaminergic neurons in the striatum (see cholinergic section). Blocking striatal post-synaptic muscarinic receptor is an additional therapy in the management of this disease.

Serotonergic Neurons

Figure 30

5-hydroxytryptamine or Serotonin

- Located cell body of midbrain and pons project to all levels
- Receptors: 5-HT (14 so far)
  - Metabotropic
    - 1A-F: ↓ cAMP, ↑ gK^+ (inhibitory)
    - 2A-C: ↑ PI turnover, ↓ gK^+(excitatory)
    - 4-7: ↑ cAMP
  - Ionotropic (excitatory)
    - 3: ↑ cation conductance
- Role in:
  - Mood, sleep/arousal and appetite



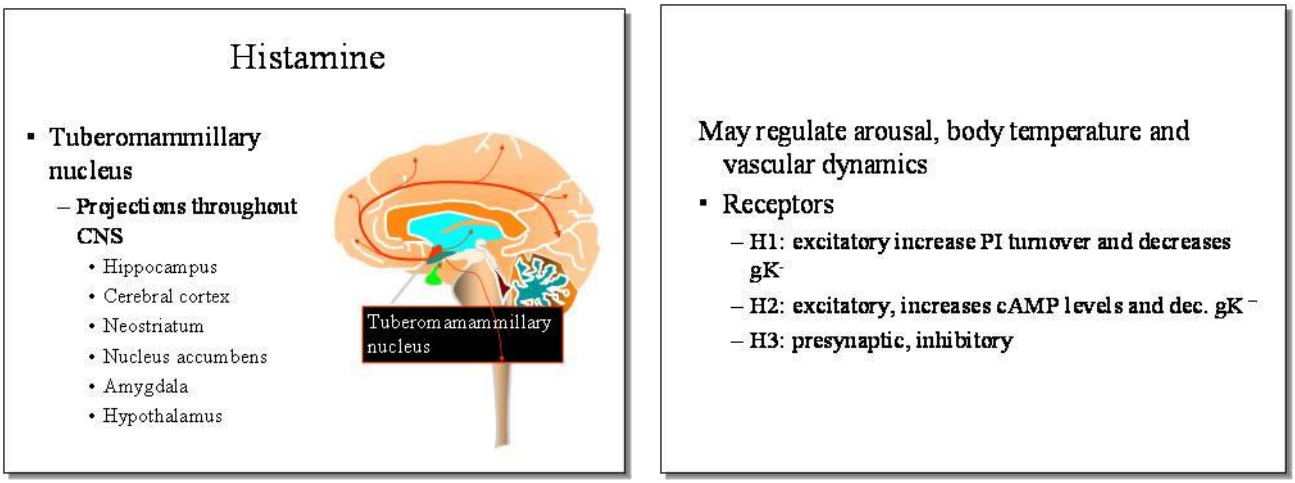
Serotonergic neurons are perhaps one of the most interesting neuronal types in the CNS. These neurons originate in the midbrain and pons and control many homeostatic processes, including appetite, sexual arousal, sleep and mood.

Drugs that alter these neurons include

- LSD is an partial agonist
- Serotonin uptake inhibitors are antidepressants and to treat general anxiety disorders
- Drug-induced vesicular release used as an appetite suppressant (Fenfluramine)
- Migraine headaches (5-HT2 antagonist and 5-HT1D agonist)
- Centrally acting antiemetics (5-HT3 antagonist)
- MDMA (Ecstasy) inhibits 5-HT2 receptors
- Only FDA approved drug to treat acquired, generalized hypoactive sexual desire disorder (HSDD) in premenopausal women. Flibanserin which is a 5-HT1A agonist and a 5-HT2A antagonist.
  http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm458734.htm

Figure 31

Histaminergic



Histaminergic neurons are found in the tuber mammillary nucleus and send projections throughout the CNS. Histamine increases CNS arousal and wakefulness (role in sleep wake cycle), by binding to post-synaptic histamine receptors (shown above) (5). Other roles include regulation of appetite, drinking and anti-nociception.

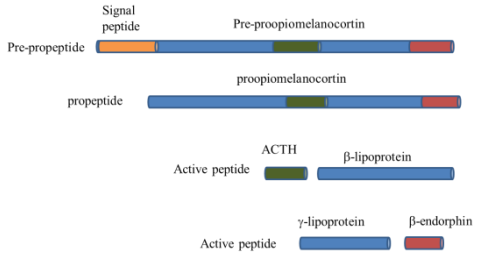
Clinical pearl: Anti-histamines that have CNS penetration (diphenhydramine, trazodone, etc) produces sedation and can be used as sleep aides.

Central Neurotransmission

- **Dale Hypothesis (in 1935)**
  - **a given neuron releases the same transmitter substance at each of its synaptic terminals**
- **Dale Hypothesis (revised)**
  - **a given neuron will release the same SETS of transmitters from a given neuron**
    - Neuropetides and purines released with classical small-molecule NTs

It was once thought that a neuron could only synthesize and release one type of neurotransmitter. This was the Dale Hypothesis. It is now known that a neuron usually releases more than one type of neurotransmitter along with the classic neurotransmitters. They can be stored in the same vesicle like adenosine or they can be stored in large dense core vesicles that are released upon different cues like the endogenous opioids.

Endogenous Opioid Peptides



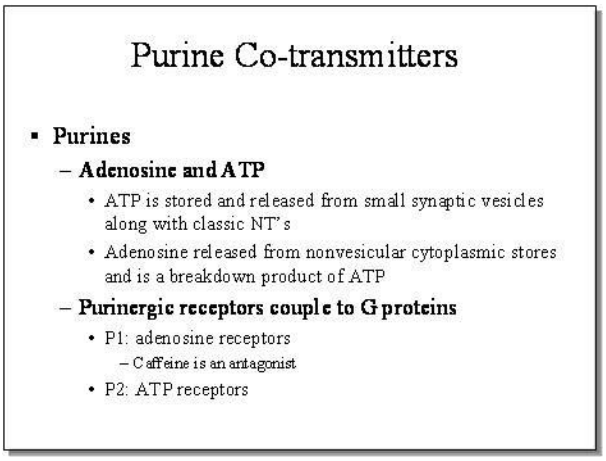
Peptide Neurotransmitters

- **Neuropeptides**
  - Modulate neurotransmission
  - Generally metabotropic G protein coupled events
  - Synthesized as large precursor peptides which are cleaved into several small signaling peptides
  - Packaged in large dense core vesicles
    - Release of content requires Ca++ (lower levels and longer duration than small synaptic vesicles containing classical NTs
  - Some Released in same neurons as classic small-molecule NTs others released into blood
  - May diffuse long distances

Examples of Peptides in Nervous System

- **Gut-Brain peptides**
  - E.g. Insulin, glucagon, Neuropeptide Y, VIP, Gastrin, Substance P, etc.
- **Pituitary hormones**
- **Hypothalamic Releasing Factors**
- **Opioid Peptides**
  - B-endorphin, Dynorphin, Leu-enkephalin, Met-enkephalin
- **Others**
  - E.g. Angiotensin, Bradykinin, etc.

Peptide NTs provide important modulatory roles in pain perception, appetite, reward, anxiety and peripheral regulation. Endogenous opioids will be covered in the opioid lecture. They provide a classic example of a peptide neurotransmitter that is produced as a large precursor peptide and then subsequently cleaved into smaller signaling peptides with a variety of functions. Peptides, like the endogenous opioids, are stored in large dense core vesicles that require long duration increases of intracellular calcium to be released.



Small molecule transmitters, like adenosine and ATP, are found in the same synaptic vesicles as classic NTs. The role of these small molecules is to provide subtle modulatory influences. A clinically useful illustration of this occurs when a triple-nonfat-latte is consumed. The caffeine in the coffee bean stimulates brain activity—how? Caffeine is an adenosine receptor antagonist that can block the inhibitory effects of adenosine receptor activation.

More to come…

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