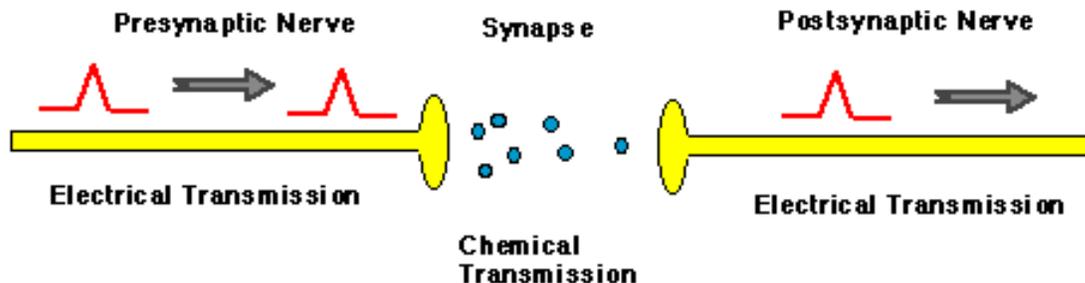


Synapses and Neurotransmitters Notes

Chemical Transmitters called “Neurotransmitters” carry a signal across Synapses (& at Neuromuscular Junctions)

- A point of contact between two neurons is called a synapse
- At the synapse there is a break in electrical transmission (the action potential cannot cross). Instead chemicals called “neurotransmitters” are released that carry the signal to the next nerve.



- There is a delay at synapses, because chemical transmission between neurons is slower than electrical transmission (action potential) within a neuron.
- A neuromuscular junction (NMJ) is a contact between a neuron and a muscle: it is like a synapse in that the action potential stops and the signal is carried by a chemical neurotransmitter released by the neuron.

Neurotransmitters Are Made and Stored in the Pre-synaptic Terminal

- The end of the neuron enlarges into an axon terminal
- Neurotransmitters are produced in the cell body of a neuron and then transported to the ends of the axon terminals in small membrane-enclosed sacs called “synaptic vesicles”.
- At the axon terminus, neurotransmitters are stored in these tiny synaptic vesicles so that they can be released when an action potential reaches the axon terminus
- At a synapse, axon termini of the pre-synaptic neuron contact the dendrites of the post-synaptic neuron. Because the neurotransmitter is only located in the axon termini on one side of a synapse, the impulse can go in only one direction.

Calcium is Required for Neurotransmitter Release

- Neurotransmitter release requires Ca^{2+} ions
- Normally, the concentration of Ca^{2+} in the pre-synaptic neuron is kept very low (by the action of a Ca pump).
- The arrival of an action potential at the axon terminus opens voltage-gated Ca channels, and Ca^{2+} ions rush inside the pre-synaptic neuron
- The intruding Ca^{2+} ions cause some of the neurotransmitter-containing vesicles to fuse to the pre-synaptic membrane, releasing neurotransmitter into the synaptic cleft

Neurotransmitter Diffuses Across the Synaptic Cleft and Binds to a Receptor

- The synaptic cleft is narrow and the neurotransmitter travels across it by simple diffusion
- On the far side of the synaptic cleft, the neurotransmitter binds to a specific receptor protein in the post-synaptic cell membrane
- Not all neurotransmitters fit in all receptors
 - Sort of like a lock and key, or a puzzle
 - If it “fits” the receptor it will bind and the receptor will become “activated”
- Most neurons respond to 3-5 different types of neurotransmitters
- Some diseases are due to defects in the neurotransmitter receptors, e.g. in myasthenia gravis an autoimmune reaction destroys acetylcholine receptors in the neuromuscular junction and causes muscular weakness or paralysis
- Many drugs and toxins block neurotransmitter receptors, including curare, strychnine, atropine, and antihistamines

When Neurotransmitter Binds to a Receptor on the Post-synaptic cell, it Produces an EPSP or an IPSP

- When the transmitter binds to the receptor, ion channels in the post-synaptic cell membrane are opened (ligand-gated channels)
- Once the channels are opened, ions rush into the post-synaptic cell

- If the ions depolarize the post-synaptic cell (e.g., by Na⁺ ions rushing in) they produce an excitatory postsynaptic potential (EPSP)
 - Most neurotransmitters produce EPSPs (e.g., acetylcholine, epinephrine, norepinephrine, and glutamate)
- If the ions hyperpolarize the postsynaptic membrane (e.g., by Cl⁻ ions rushing in) they produce an inhibitory postsynaptic potential (IPSP)
 - The major neurotransmitters producing IPSPs are glycine and GABA (gamma amino-butyrac acid)
- Each neuron may have as many as 10,000 synapses with other neurons, and there are both excitatory and inhibitory neurons coming into most synapses, thus the behavior of the post-synaptic neuron is determined by temporal and spatial **summation** of the EPSPs and IPSPs.
- In summation, if there are enough EPSPs the postsynaptic membrane will be depolarized to the threshold level and an action potential will be produced, then the signal will travel along the second nerve or muscle cell.
- In summation, if there are enough IPSPs to keep the membrane potential of the post-synaptic cell negative (hyperpolarized) and cancel out the EPSPs, then the post-synaptic neuron will NOT generate an action potential, and the signal will stop.

The Neurotransmitter is Broken Down and/or Recycled

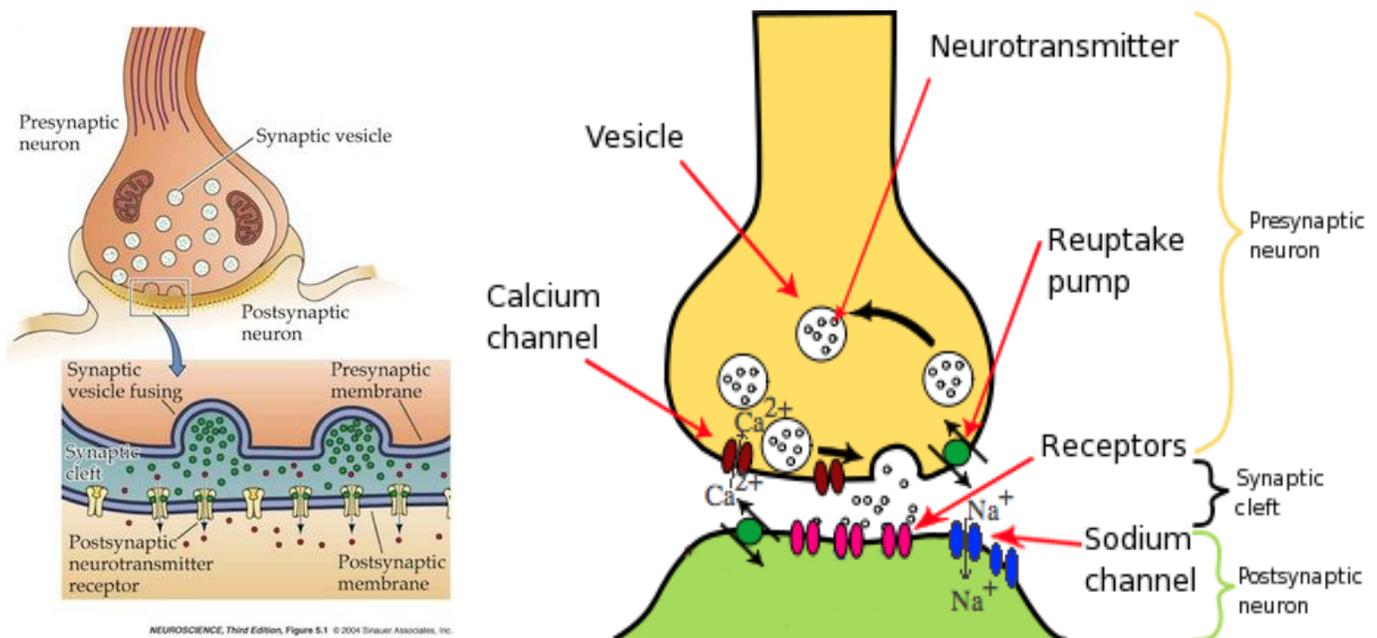
- Once the signal has been delivered the neurotransmitter must be removed from the synaptic cleft so that new signals may be received
- In some cases the neurotransmitter is broken down by an enzyme in the synapse
- In other cases the neurotransmitter is recycled: it is transported back into the pre-synaptic neuron by endocytosis and then stored in vesicles of the axon terminus for reuse. This process is referred to as “reuptake”
- In still other cases these 2 methods are combined
- Some drugs inhibit the enzymes that break down transmitters (e.g., nerve gases, physostigmine)
- Other drugs act by inhibiting “reuptake” (e.g., Prozac, cocaine)

There are Dozens of Neurotransmitters in the Nervous System

- In this class we will deal with only a few class of transmitters:
 - **Acetylcholine**
 - **Amino acids**, such as GABA, glutamate, and glycine.
 - **Biogenic Amines**, such as epinephrine, norepinephrine, dopamine, and serotonin
 - **Neuropeptides**, such as “substance P” and endorphins, and
 - **Gases**, such as NO (nitric oxide) and CO (carbon monoxide)
- There are dozens of other neurotransmitters in the central nervous system (CNS) and new ones are being discovered every year
- A high percentage of pharmaceutical drugs affect the function of neurotransmitters at the synapse or neuromuscular junction

Another way to think about SYNAPSES....

The Synapse, or synaptic cleft, is the gap that separates adjacent neurons or a neuron and a muscle. Transmission of an impulse across a synapse, from pre-synaptic cell to post-synaptic cell, is chemical. In chemical synapses, action potentials are transferred across the synapse by the diffusion of neurotransmitters, as follows:



1. Calcium (Ca^{2+}) gates open. When an action potential reaches the end of an axon, the depolarization of the membrane causes voltage-gated channels to open that allow Ca^{2+} to enter.
2. Synaptic vesicles release a neurotransmitter. The influx of Ca^{2+} into the terminal end of the axon causes synaptic vesicles to merge with the pre-synaptic membrane, releasing a neurotransmitter into the synaptic cleft.
3. The neurotransmitter binds with post-synaptic receptors. The neurotransmitter diffuses across the synaptic cleft and binds with specialized protein receptors on the post-synaptic membrane. Different proteins are receptors for different neurotransmitters.
4. The post-synaptic membrane is excited or inhibited. Depending upon the kind of neurotransmitter and the kind of membrane receptor, there are two possible outcomes for the post-synaptic membrane:
 - If positive ion gates open (allowing more Na^+ and Ca^{2+} to enter than K^+ to exit), the membrane becomes depolarized, which results in an excitatory postsynaptic potential (EPSP). If the threshold potential is exceeded, an action potential is generated.
 - If K^+ or chlorine ion (Cl^-) gates open (allowing K^+ to exit or Cl^- to enter), the membrane becomes more polarized (hyperpolarized), which results in an inhibitory postsynaptic potential (IPSP). As a result, it becomes more difficult to generate an action potential on this membrane.
5. The neurotransmitter is degraded and recycled. After the neurotransmitter binds to the post-synaptic membrane receptors, it is either transported back to and reabsorbed by the secreting neuron ("reuptake") or broken down by enzymes in the synaptic cleft. For example, the common neurotransmitter acetylcholine (ACh) is broken down by acetylcholinesterase (AChE).

Specific examples of Neurotransmitters

Acetylcholine (usually excitatory)

- Acetylcholine was the first neurotransmitter to be discovered
- Acetylcholine has many functions:
 - It is responsible for much of the stimulation of **muscles**, including the muscles of the gastro-intestinal system.
 - Also linked with **learning, emotion and memory**
 - It is also found in sensory neurons and in the autonomic nervous system, and has a part in scheduling **REM (dream) sleep**.
- The plant poisons **curare** and **hemlock** and the nerve gas **sarin** cause paralysis by blocking the acetylcholine receptor sites of muscle cells.
- The well-known poison **botulin** works by preventing the vesicles in the axon ending from releasing acetylcholine, causing paralysis. The botulin derivative **botox** is used by many people to temporarily eliminate wrinkles.
- On a more serious note, there is a link between acetylcholine and **Alzheimer's** disease: There is something on the order of a 90% loss of acetylcholine in the brains of people suffering from Alzheimer's, which is a major cause of senility.

Norepinephrine (excitatory)

- Norepinephrine is strongly associated with bringing our **nervous systems** into "**high alert**."
- It is prevalent in the sympathetic nervous system, and it increases our **heart rate** and our **blood pressure**.
- Our adrenal glands release it into the blood stream, along with its close relative epinephrine (aka adrenalin).
- It is also important for forming **memories**.
- **Stress** tends to deplete our store of adrenalin
- **Exercise** tends to increase it
- Amphetamines ("**speed**") work by causing the release of norepinephrine, as well as other neurotransmitters called dopamine and serotonin

Dopamine (excitatory and inhibitory)

- Another relative of norepinephrine and epinephrine is dopamine
- It can be both **excitatory and inhibitory** depending on the receptor sites
- Dopamine is strongly associated with **reward mechanisms** in the brain.
- Involved **with thought, feeling, motivation, and behavior, movement, attention, decision making**
- Drugs like cocaine, opium, heroin, nicotine, and alcohol increase the levels of dopamine. **If it feels good**, dopamine neurons are probably involved!
- The severe mental illness **schizophrenia** has been shown to involve excessive amounts of dopamine in the frontal lobes, and drugs that block dopamine are used to help schizophrenics.
- On the other hand, too little dopamine in the **motor** areas of the brain are responsible for **Parkinson's disease**, which involves uncontrollable muscle tremors.
- Recently, it has been noted that **low dopamine** may related not only to the unsociability of schizophrenics, but also to **social anxiety**.

GABA (gamma aminobutyric acid) (inhibitory)

- GABA **acts like a brake** to the excitatory neurotransmitters that lead to **anxiety**.
- People with too little GABA tend to suffer from **anxiety disorders**, and drugs like Valium work by **binding** to the GABA receptor sites and thereby enhancing the effects of GABA.
- Lots of other drugs influence GABA receptors, including alcohol and barbiturates.
- If GABA is lacking in certain parts of the brain, **epilepsy** results.

Glutamate (excitatory)

- Glutamate is a relative of GABA.
- It is **the most common neurotransmitter** in the central nervous system - as much as half of all neurons in the brain - and is especially important in regards to **memory and learning**.

- Curiously, glutamate is **actually toxic** to neurons, and an excess will kill them. Sometimes brain damage or a stroke will lead to an excess and end with many more brain cells dying than from the original trauma.
- ALS, more commonly known as **Lou Gehrig's disease**, results from excessive glutamate production.
- Many believe it may also be responsible for quite a variety of diseases of the nervous system, and are looking for ways to minimize its effects.

Serotonin (excitatory and inhibitory)

- Serotonin has been found to be intimately involved in **emotion and mood**.
- Too little serotonin has been shown to lead to **depression, problems with anger control, obsessive-compulsive disorder, and suicide**.
- Too little also leads to an increased **appetite** for carbohydrates (starchy foods) and **trouble sleeping**, which are also associated with depression and other emotional disorders.
- It has also been tied to **migraines, irritable bowel syndrome, and fibromyalgia**.
- Prozac and other recent drugs help people with depression by **preventing** the "reuptake" of serotonin by pre-synaptic neurons, so that there is more left floating around in the synapses.
- Serotonin also plays a role in perception. Hallucinogens such as LSD, mescaline, psilocybin, and ecstasy **work by attaching** to serotonin receptor sites and thereby blocking transmissions in perceptual pathways.

Endorphin (excitatory and inhibitory)

- Endorphin is short for "endogenous morphine."
- **Elevate mood and reduce pain**
- It is structurally very similar to the **opioids** (opium, morphine, heroin, etc.) and has similar functions:
- The opioid drugs **work by attaching** to endorphin's receptor sites.
- It is also the neurotransmitter that allows bears and other animals to **hibernate**. Consider: Heroin slows heart-rate, respiration, and metabolism in general - exactly what you would need to hibernate.