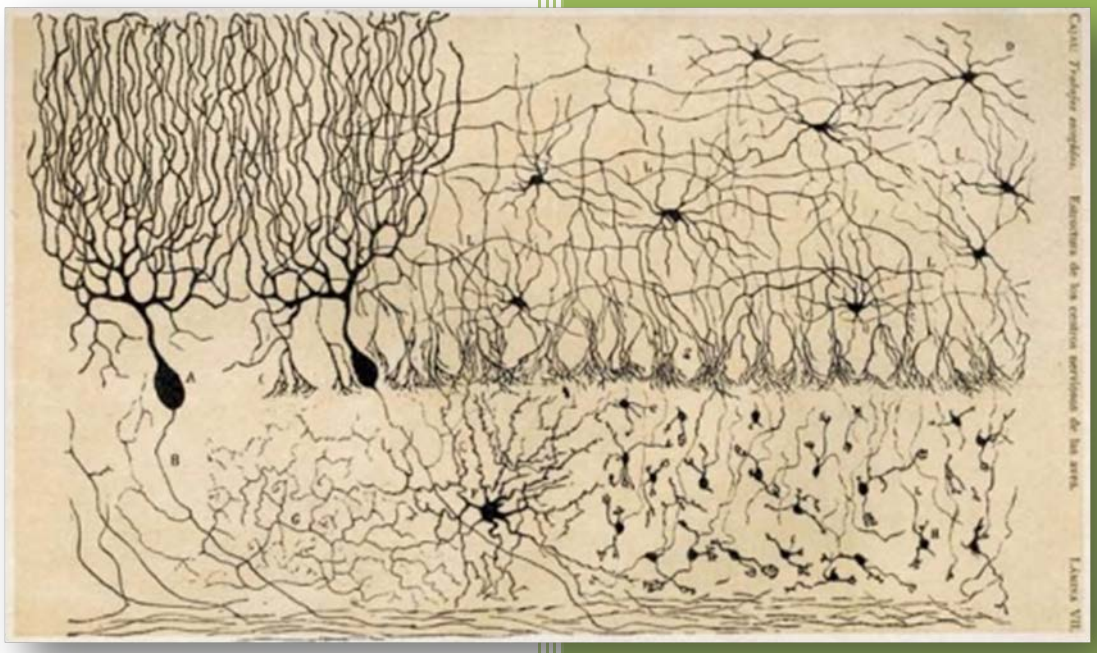
Neurosciences: Neuronal and synaptic transmission



One of the earliest illustrations of neurons as drawn by Santiago Ramon y Cajal based on what he observed through his beloved Zeiss microscope.
From: Ramon y Cajal, S. *Histologie du système nerveux de l'homme et des vertébrés*. Paris: 1911. English translation: *Histology of the Nervous System of Man and Vertebrates* (trans. Swanson, N. & Swanson, L. W.), Oxford University Press, 1995.

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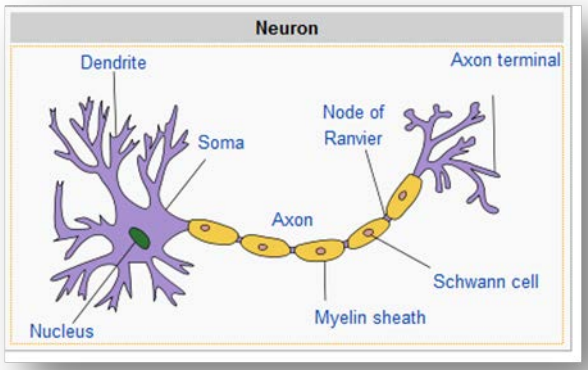
PSY1101 B,C,D

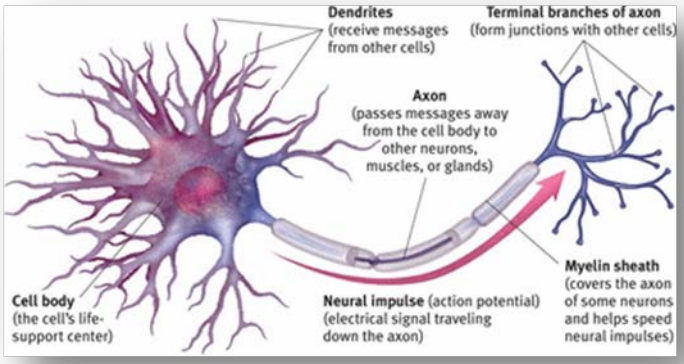
Introduction to Experimental Psychology

Introduction to Experimental Psychology

Biology of the Mind (Neurosciences): Neuronal-Synaptic Transmission

Structure of Neuron





- *DENDRITES*: short branches projecting from cell body. Within the dendrites are embedded highly specialized receptors (see section on terminal endings below)
- *receive* messages from other neurons
- *CELL BODY (soma):* contains the nucleus of the cell and other basic elements necessary for the survival of the cell.
- *AXON*: a long, slender tube which carries information from the cell body to synaptic terminals. It is analogous to a wire or a cable.
    - The axons of longer neurons are surrounded by a *myelin sheath*. This causes them to appear white. Axons of shorter neurons are not surrounded by a myelin sheath. They thus appear to be grey.
    - The myelin sheath is made up of a lipid (fat) material that may surround long axons. They serve to (1) protect the axon (2) insulate the axon … this thus preventing axonal "cross-talk" (3) speed up transmission
- *TERMINAL ENDING (bouton endings):* As the name indicates, this is the terminal ending of the axon. At this ending, there is a swelling (the "bouton"). This is caused by the storage of neurotransmitter substance here. A physical gap (called the "synaptic gap" or simply the "synapse") separates the terminal ending and the dendrites of the next neuron. When (and if) the neurotransmitters are released, they must travel across this gap. Embedded in the walls of the dendrites of the postsynaptic neuron are highly specialized receptors that can "recognize" the chemical code of the neurotransmitters. The neurotransmitters can then attach themselves (or "bind") to the receptor site. The neurotransmitter may excite or may inhibit the activity of the second neuron (more about this later)

Different Types of Neurons

- *Sensory Neurons*: transmit impulses received by sensory receptors to CNS. These are also called *afferents*.
- *Motor Neurons*: carry outgoing signals from CNS to muscles & glands. These are also called *efferents*.
- *Interneurons*: Sometimes, receive signals from sensory neurons and send impulses to other motor neurons. Much more often, the interneuron is far removed from either sensory or motor neurons. One interneuron communicates with another. This is the route to memory, learning, and complex behaviour.

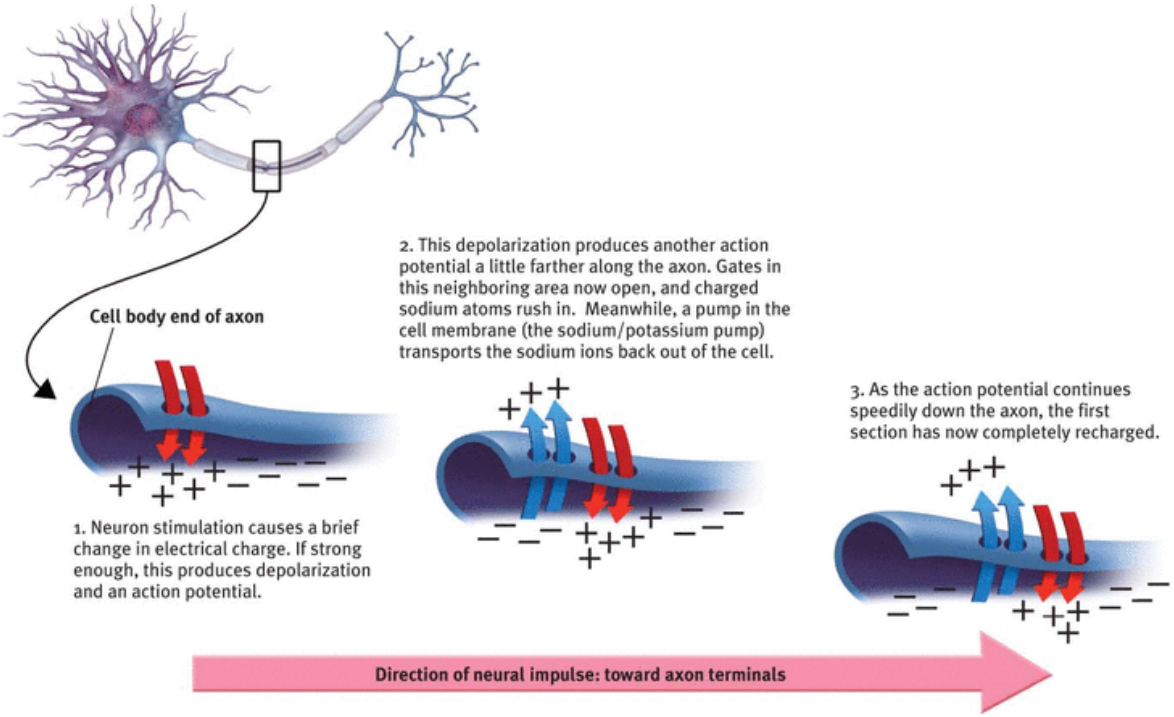
Neuronal Transmission

Resting Potential

- The neuron, like other cells, carries an electrical charge. Unlike other cells, the charge of the neuron can change.
- This allows one neuron to communicate with another (or perhaps with a muscle).
- An inactive neuron contains an excess of *negatively* charged ions *inside* the cell membrane
- The charge inside the neuron is about -70 mVolt (mV), but this does vary depending on the species studied (see Figure below on Action Potentials.)
- This charge is called the *resting potential* of the neuron. Thus, the resting potential represents the electrical charge of a neuron when it is inactive.

Excitation of the Neuron (*Depolarization*)

- Inside the neuron there is a surplus of negatively charged molecules ("ions"). This is mainly because of the buildup of chloride. Outside of the neuron, there is a buildup of positively

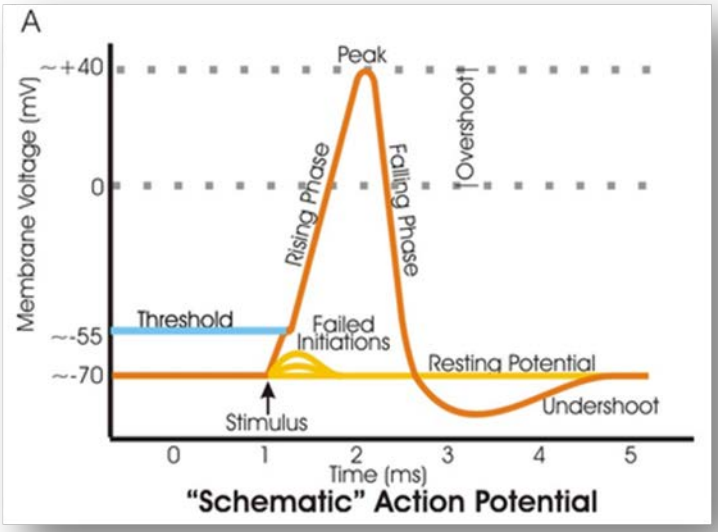


charged ions (largely sodium, but also potassium).

- The sodium-chloride balance is critical for the proper functioning of the neuron. Where does the sodium-chloride come from? The salt balance within the body.
- Sodium (and potassium) cannot easily pass through the cell wall (the membrane) of the neuron. Sodium is a relatively large molecule. Moreover, other molecules easily bind to the sodium molecule making it even larger.
- When the dendrite is stimulated by another neuron through the release of an excitatory neurotransmitter (or artificially by electrical stimulation), the cell membrane's "channels" (or "gates") open, allowing *positively* charged ions to flow in (point 1 in the figure above).
- This change in the charge of the neuron (less negativity or more positivity) is called *depolarization.*

Action Potential

- The flow of the positively charged ions into the nerve cell causes the cell's resting electrical potential (or charge) to change. The cell is now less negatively charged (it is now "depolarized"). In the Figure on the right, an electrode stimulates the nerve cell at time 0. Within 1 ms, we see the effect. The stimulation causes the cell's electrical potential to change (i.e., to depolarize). The extent of change is dependent on the intensity of stimulation. If it is a small stimulation (low intensity stimulation), the change in the electrical potential of the nerve cell might now be -65 mV (see yellow lines, "failed initiations" in the Figure). If the intensity of the stimulation increases, the electrical potential of the cell may now change to -60 mV (also in yellow).



- Again, the reason the inner cellular environment is now less negatively charged is because of the flow of positively charged ions into the cell.
- When the flow of positively charged ions reaches a certain critical threshold (the "*threshold of excitation"),* the neuron "fires". In the Figure on the right, the "threshold" is about -54 mV. Once the change in electrical potential reaches this -54 mV threshold, a dramatic change is observed.
- This is called the *action potential.* Now, the channels)or gates) of the neuron wall open completely and so many positively charged ions rush into the cell (the raising phase of the action potential in the illustration) that the electrical potential initially is at 0 mV (the net charge of negatively and positively charged ions are balanced) but then the neuron becomes "hyperpolarized". There is now a net positive charge in the nerve cell. The action potential also "propagates" the entire length of the axon. The action potential (the rushing in of the sodium and other positively charged molecules) continues inevitably down the entire length of the axon. Again, this is called *propagation* of the action potential. (point 2 and 3 in Figure above)

- If the level of excitation is not enough (the critical threshold is not reached), the electrical charge of the neuron will return to its resting potential ("failed initiations" in the Figure) and the charge will not propagate the entire length of the axon.
- The likelihood of reaching the critical threshold is increased by either having a single (or a few) neurons release a great deal of excitatory neurotransmitters (explained later) or perhaps many neurons release only a small quantity of excitatory neurotransmitters but more or less at the same time and the effects of one excitation summates with the consequent excitation). Thus, the effects of the excitation of several neurons can summate together.
- Once the action potential is initiated, it will travel down the length of the axon. It may then subsequently influence the firing of another neuron.

All-or-None Law

- The action potential will be *propagated* the entire length of the axon or, if the threshold of excitation is not reached, it will not be propagated at all. It is *all-or-none*.
- The amplitude of the action potential is also constant (again, no variation here). In the Figure, the change in the electrical potential in now +40 mV. This amplitude will not vary as the charge moves down the length of the axon. This is inevitable (no variation here). This is also part of the the *all-or-none law*. We either get the action potential or we do not. Increasing the intensity of stimulation will not cause the action potential to get larger.
- This has important consequences for coding in the nervous system.
- For example, we cannot code the intensity of the stimulus by the size (or amplitude) of the action potential. Its amplitude cannot vary. If I whisper in your ear and you hear the sound, it is because of an action potential in your auditory neurons. If I now shout, the action potential will be exactly the same amplitude. It will not be larger! However, you can certainly distinguish a whisper from a shout. How? Intensity could be coded by how often the neuron fires or perhaps by how many neurons carry the message.
- The all-or-none law ensures that once the action potential is initiated, it will travel the length of the axon and its amplitude will not vary. There is little room for "freedom" or "flexibility" in the well-protected world of the axon. The response (the action potential) cannot easily be altered (unless there is a fault with the chemical or nutritional balance).
- Once the action potential reaches the end of the axon (at the terminal ending), it will cause a release of neurotransmitters that may travel across the gap (the "synapse") between the pre- and post-synaptic neurons.
- The all-or-none law will NOT apply to synaptic communication. Learning will involve changing how the nervous system responds (we'll see this when we study learning and memory). Thus, in very advanced brains (those seen especially in mammals, primates and humans), many more synapses will form to make exceedingly complex connections in grey matter.

Propagation of Action Potential

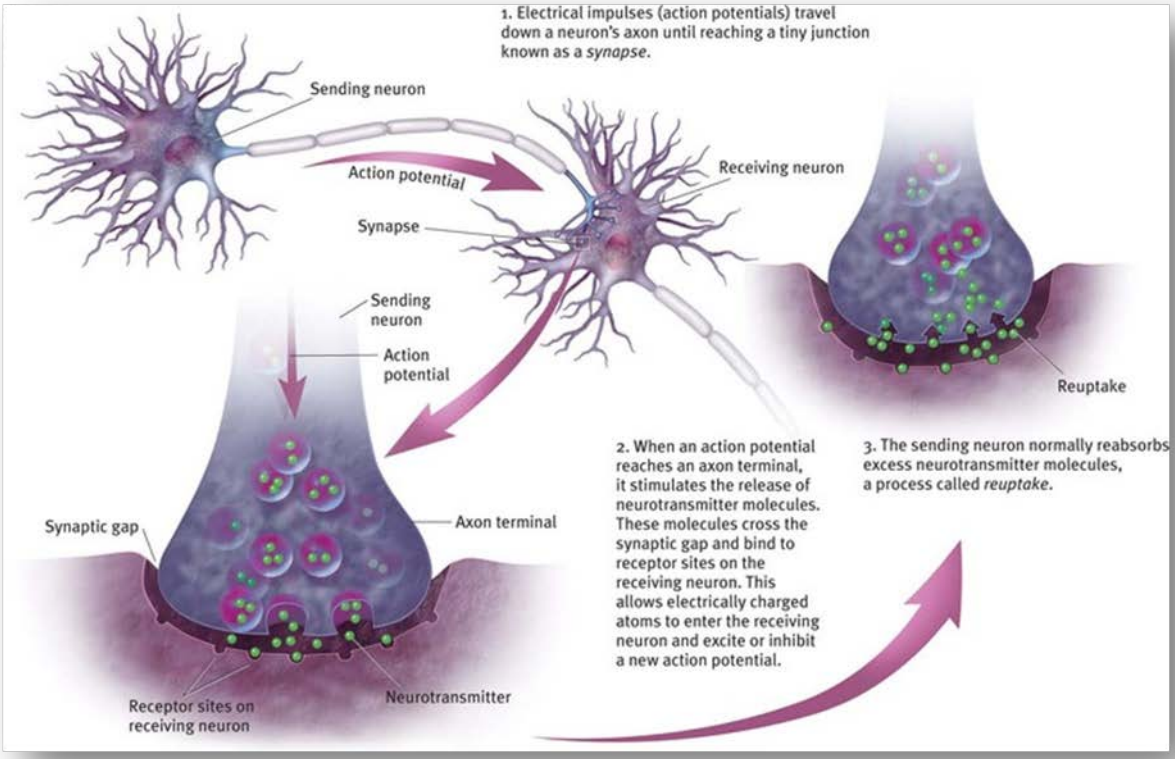
- Action potentials will travel down the length of the axon.
- This involves a slow, tedious process. The membrane gates initially open upon excitation. This depolarization causes the neighbouring membrane gates to also open, and then this neighbour's gates also open and so forth until the action potential slowly reaches the end of the axon at the terminal ending.
- Long axons are mylineated (they have a myelin sheath).

- The myelin sheath is not continuous. Because the myelin is made of lipid material, the charged molecules cannot penetrate into the axon. At places, the bare axon is exposed. These places are called the nodes (or more correctly, the nodes of Ranvier, named after the French neuroanatomist)
- This allows the action potential to "jump" from node to node.
- Thus, transmission is much faster in mylineated axons. Because long axons tend to be myelinated, while short axons are not, transmission is much faster in long axons.

Release of Neurotransmitter

- Under influence of action potential, neurotransmitters are released into the synaptic gap.
- Neurotransmitters may travel across this gap to the post-synaptic neuron.
- Keep in mind that this gap is the "real" extra-cellular (outside the cell) environment outside of the well-protected neuron. Nature protects the neuron. The neurotransmitters are not nearly as well protected in the synaptic gaps. The neurotransmitters are subject to attack by poisons (toxic agents). They might not be released. They might not reach the post-synaptic site.
- Embedded in the dendrites of the post-synaptic neuron (or perhaps a muscle), specialized receptors can "recognize" the chemical code of the neurotransmitter (similar to a lock and key mechanism).
- The neurotransmitter binds to the post-synaptic receptor. Other chemicals in the synaptic gap cannot bind to the post-synaptic receptor site because their chemical code fails to match the "correct" code (but as we shall see later, certain "drugs" may have a chemical code that is quite similar to that of the neurotransmitter and thus these drugs may well bind with the receptor site). It is at the receptor site that the neurotransmitter has an effect on the post-synaptic neuron. It may have an excitatory or an inhibitory effect (see next section).

- The neurotransmitter will have a long-term effect unless its actions are terminated. Enzymes break down the neurotransmitter so that its effect is not continuous. The molecule is "broken apart". Often the more basic elements of the neurotransmitter are then recycled back into the



pre-synaptic neuron to be used again. This is the reuptake process step 3 in the figure above).

- Each and every one of these steps can be altered. "Drugs" that are similar in chemical structure to a true neurotransmitter may also bind with the receptor site. They may block the site. When the true neurotransmitter arrives, it will find the receptor site already occupied. As an example, a neurotransmitter called acetylcholine (ACh) causes muscles to contract. A drug may have a chemical structure similar to Ach and binds with the receptor site on the muscles. Thus, even though the neurotransmitter has been released and should cause muscles to contract, they will not. Your lungs contract because of muscles. This drug will thus prevent the animal from inspiring (breathing in) and it will die a very painful death. This is how the nerve gases of World War I (and more recently in Iraq and Syria) operate. Drugs can also mimic the effect of a neurotransmitter. Thus certain drugs may cause you to hyperventilate (you breathe too rapidly). The reuptake process may be ineffective. Perhaps the enzymes are in short supply. Perhaps drugs "attack" the enzymes. Thus, the effect of the neurotransmitter will be prolonged. And, the reuptake mechanism will be delayed. This will leave a short-supply of neurotransmitters in the pre-synaptic site.
- The cozy protected environment of the axon is thus not the rule at the synapse. While transmission in the axon was highly inflexible, obeying an all-or-none law, this is not the case at the level of the synapse. If we wish to design a nervous system in which flexibility of behaviour

(altering past behaviour), learning, memory and complexity are desired, the synapse is the place to do it. It should come as no surprise that in evolution, complex behaviour comes about as a result of expansion of the grey matter, where tiny, unmyelinated neurons are tightly packed, forming billions and trillions of synapses, and permitting exceedingly complex inter-neuronal communication. Unfortunately, these exceedingly complex interactions are also exceedingly complex to understand. The end result is that we, in fact, poorly understand the functioning of the higher centres (the grey matter of the cortex) of the brain, even in very simple animals (those that are not well-cortically endowed). This should however be good news for students… lots of information yet to be discovered.

Actions of Neurotransmitters

- Recall the all-or-none law of the action potential. No flexibility here. This is not the case with the neurotransmitters.
- Neurotransmitters are either excitatory or inhibitory. Thus, it is possible either to increase or to decrease the likelihood that a post-synaptic neuron will fire.
- An *excitatory* neurotransmitter will increase the likelihood that the post-synaptic cell will fire. An excitatory neurotransmitter *depolarizes* the neuron. The resting potential becomes less negatively charged than normal.
- An *inhibitory* neurotransmitter will decrease the likelihood that the post-synaptic cell will fire. An inhibitory neurotransmitter hyperpolarizes the neuron. The resting potential becomes more negatively charged than normal. Perhaps rather than having a resting potential at -70 mV, it is now -94 mV. Thus, in order to now reach the threshold of firing for the action potential, the level of excitation must be much higher than usual.
- Why is it necessary to have both excitatory and inhibitory neurotransmitters? Imagine trying to walk. Certain muscles in your leg must be excited (an excited muscle contracts). Others, however, must not contract. If all muscles were contracted, you could not walk (incidentally, this lack of motor "coordination" is often a problem in various dystrophies and in Parkinson's-like diseases). Another example, this time from cognitive psychology and the study of consciousness: Your sensory receptors are constantly bombarded with incoming stimuli. You are however only conscious of a very, very small number of these sensory inputs. Your brain cannot possibly process all this input because of its limited capacity (even though you have a massive amount of grey matter). Only the most relevant of sensory input should reach the very busy cortex and you might become conscious of this. The vast majority of sensory input is irrelevant, thus processing of what in the end is irrelevant, needs to be inhibited and you will never be conscious that this input had actually stimulated the receptor. Another example: A good deal of the frontal regions of your brain is involved with the inhibition of inappropriate action. This is the essence of the saying: reason over passion… the need to inhibit the passions.

Drug Interaction

As already mentioned, drugs can wreak havoc on neurotransmitters. There are at least 6 ways that this is possible (again, please note the very large flexibility in synaptic transmission):

- Block release of neurotransmitter
- Block storage of neurotransmitter in pre-synaptic neuron
- Cause release of excessive amount of neurotransmitter

- Stimulate or block receptor on post-synaptic membrane
- May attack enzymes that break down neurotransmitter
- Block reuptake of neurotransmitter

Neurotransmitters

Adding to the complexity and flexibility of synaptic transmission is the fact that there are many different types of neurotransmitters having different chemical structures. Several neurotransmitters have now been identified (although we will mercifully only mention a few) and it is thought that considerably more remain to be discovered (any budding biochemists?) All neurotransmitters need to be synthesized from simpler elements, typically extracted from the circulating blood. We shall return to the neurotransmitters when we discuss how psychoactive drugs can alter the "mind". Here is a short list of known neurotransmitters:

Acetylcholine (ACh)

- ACh is generally excitatory on membranes of skeletal-muscle fibers. It causes muscles to contract.
- Muscle paralysis can be caused by, for example:
    - Botulin (or more properly, botulinum toxin). Botulin blocks ACh release. Pure botulin is amongst the most toxic and lethal substances known 100-200 ng (billionths of a gram) can kill a human adult weighing 100 kg. Botox, an extremely low dosage of botulin, causes muscle paralysis preventing "wrinkling" of the skin.
    - Nerve gas may block receptor site, or interfere with reuptake. Many insecticides work in this manner.
- Muscle convulsions can be caused by venom in many animals
    - Example: Black widow spider venom (stimulates release of ACh)
- In CNS, role in memory –
    - ACh is depleted in Alzheimer's disease.

Norepinephrine (NE) in the U.S., but *Noradrenaline (NA)* in many other countries

- Synthesized from epinephrine (or adrenaline), a hormone released by the adrenal gland (and the entire world calls it the adrenal gland).
- Important role in alertness and mood.
- Cocaine and amphetamines prolong action of NE -- stimulant effects.
- Lithium -- speeds up breakdown of NE -- depressed mood.

Gamma-Aminobutyric Acid (GABA)

- Major *inhibitory* neurotransmitter of the brain.
- Sedative, sleep and anti-anxiety medications.
    - Benzodiazepines (For example, valium acts by stimulating GABA receptors)

Dopamine (DA)

- Predominantly inhibitory.

- Implicated in movement in the periphery. In the brain, attention, decision-making and learning. Might be involved in ADHD.
- Insufficient quantity of DA: Parkinson's disease leading to tremors & paralysis
- Too much DA: psychosis.
- A side effect of Parkinson's treatment is psychotic symptoms.

Serotonin (5-HT)

- plays a role in sleep (dreaming?), perhaps control of eating, mood, and pain regulation.
- Drugs that mimic 5-HT may result in bizarre hallucinations. Psychedelic drugs such as LSD, and mescaline have a chemical structure that is remarkably similar to 5-HT. They may thus block the receptor site.
- Certain drugs cause an over-release of 5HT (example MDMA – "Ecstasy"… increase energy. It may cause 5-HT to be completed depleted resulting in withdrawal-like symptoms).

Endorphins

- So-called "natural opiates" of the brain
- Chemical structure similar to opiates (heroin, morphine)
- Inhibit sensation of pain. This explains how pain can be reduced through "natural" means.
- Increase mood and pleasure