NEUROSCIENCE

LECTURE 01: Organization of the Nervous System

Nervous system- the master controlling and communicating system of the body functions:

1. Sensory receptors to monitor changes occurring inside & outside body stimuli- changes sensory input- gathered information

2. Processes and interprets the sensory input integration- nervous system makes decisions about what should be done

3. Effects a response by activating muscles or glands (effectors) via motor output Regulating and Maintaining Homeostasis nervous system - fast-acting control via electrical impulses endocrine system- slow-acting control via hormones release into the blood

Structural Classification

2 subdivisions: Central Nervous System and Peripheral Nervous System

1. Central Nervous System (CNS) consists of: brain spinal cord

functions: integrating center.....interpret incoming sensory information

commandcenter.....issue instructions based on past experience & current conditions

2. Peripheral Nervous System (PNS) consists of: nerves 2 types: cranial nerves- carry impulses to and from the brain spinal nerves- carry impulses to and from the spinal cord ganglia- groups of nerve cell bodies

function: communication lines, linking all parts of the body

Functional Classification

only deals with peripheral nervous system (PNS)

Sensory (Afferent) Division- nerve fibers that carry impulses to the CNS from sensory receptors located throughout body

sensoryfibers types:

1. somatic sensory fibers- delivering impulses from the skin, skeletal muscles, & joints

2. visceral sensory fibers- transmitting impulses from the visceral organs

Motor (Efferent) Division- nerve fibers that carry impulses from the CNS to effector organs ossicles and glands, bringing about a motor response

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2 types:

1. Somatic nervous system: conscious control of skeletal muscles voluntary control skeletal muscles

2. Autonomic nervous system (ANS)- regulates activities that are automatic, involuntary, cardiac muscle, smooth muscle, glands

2 nerve types that target same organ but yield opp. effects

exception: targeted only by sympathetic: some glands, most blood vessels, most structures of the skin

2 types:

1. sympathetic-" fight or flight" f'ns during extreme situations ex: increase heart rate rapid breathing cold, sweaty skin dilated pupils

2. parasympathetic- "resting & digesting" most active when body at rest causing normal digestion, voiding feces& urine goal: conserving energy

If brain or spinal cord are sectioned, we find that two major areas of brain tissue may be defined on the basis of their color in fixed, unstained tissue. In living tissue gray matter is actually pink due to blood in the many capillaries coursing through this tissue.

1. **gray matter** - neuron perikarya (cell bodies), glial cells, axons, dendrites, synapses

2. **white matter** - axons + myelin sheaths and glial cells. No neuron perikarya, no synapses

Nervous Tissue: Structure and function

2 types of cells:

1. neuroglia- supporting cells
   not able to conduct impulses
   can undergo cell division
   most brain tumors are gliomas- formed by glial cells
2. neurons

   nerve cells that transmit impulses

   functional unit of nervous system

A. Neuroglia not able to conduct impulse

   glia (glial cells) f'n: support, insulation, & protection

   ~90% cells in brain are glial cells

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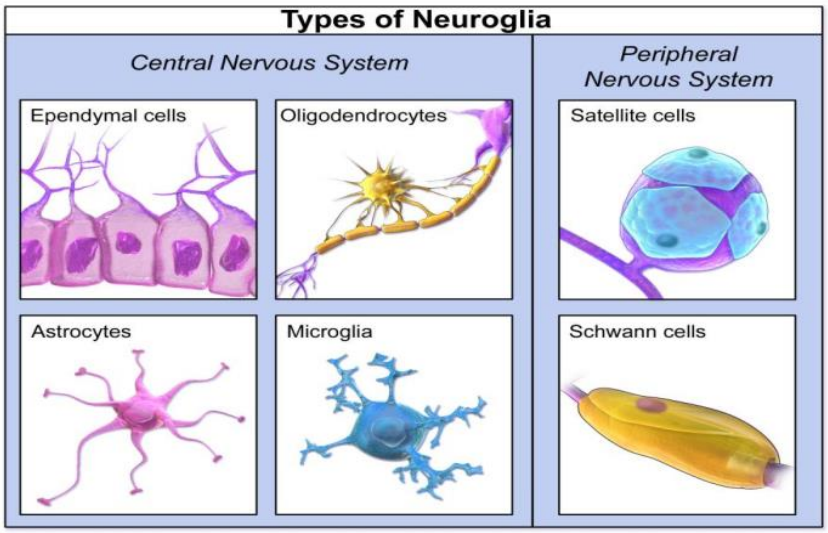
CNS: 4 types: astrocytes,microglia, ependymal, oligodendrocytes

PNS: 2 types schwann cells, satellite cells

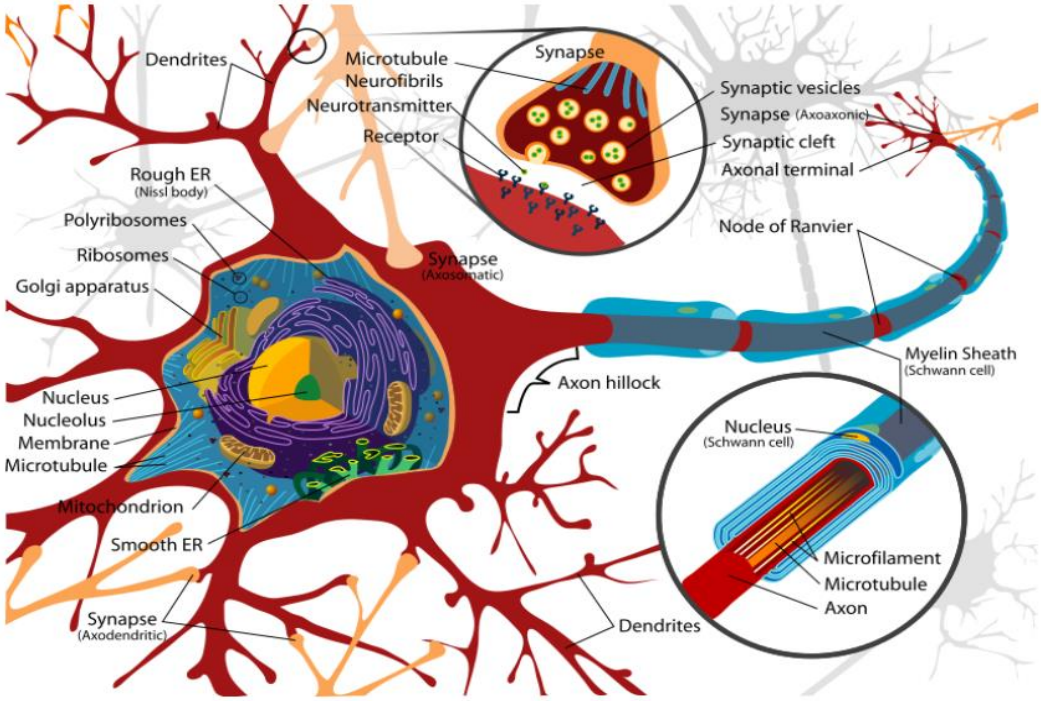


Location	Name	Description
CNS	Astrocytes	Most abundant type of macroglial cell in the CNS, Have numerous projections that anchor neurons to their blood supply They regulate the external chemical environment of neurons by removing excess ions Predominant "building-blocks" of the blood–brain barrier. Regulate vasoconstriction and vasodilation Astrocytes signal each other using calcium. In general, there are two types of astrocytes, protoplasmic and fibrous, similar in function but distinct in morphology and distribution. Protoplasmic astrocytes have short, thick, highly branched processes and are typically found in gray matter. Fibrous astrocytes have long, thin, less branched processes and are more commonly found in white matter. It has recently been shown that astrocyte activity is linked to blood flow in the brain, and that this is what is actually being measured infMRI. They also have been involved in neuronal circuits playing an inhibitory role after sensing changes in extracellular calcium.

CNS	Oligodendrocytes	coat axons in the central nervous system (CNS) with their cell membrane, forming a specialized membrane differentiation called myelin, producing the so-called myelin sheath. The myelin sheath provides insulation to the axon that allows electrical signals to propagate more efficiently.
CNS	Ependymal cells	line the spinal cord and the ventricular system of the brain. These cells are involved in the creation and secretion of cerebrospinal fluid (CSF) and beat their cilia to help circulate the CSF and make up the blood-CSF barrier. They are also thought to act as neural stem cells.
NS	Radial glia	In the developing nervous system, radial glia function both as neuronal progenitors and as a scaffold upon which newborn neurons migrate. In the mature brain, the cerebellum and retina retain characteristic radial glial cells.
PNS	Schwann cells	Similar in function to oligodendrocytes, *Schwann cells* provide myelination to axons in the peripheral nervous system (PNS). They also have phagocytotic activity and clear cellular debris that allows for regrowth of PNS neurons.
PNS	Satellite cells	*Satellite glial cells* are small cells that surround neurons in sensory, sympathetic, and parasympathetic ganglia. These cells help regulate the external chemical environment. Like astrocytes, they are interconnected by gap junctions and respond to ATP by elevating intracellular concentration of calcium ions. They are highly sensitive to injury and inflammation, and appear to contribute to pathological states, such as chronic pain.
PNS	Enteric glial cells	Are found in the intrinsic ganglia of the digestive system. They are thought to have many roles in the enteric system, some related to homeostasis and muscular digestive processes.

B. Neurons

Anatomy and histology



Neurons are highly specialized for the processing and transmission of cellular signals. Given their diversity of functions performed in different parts of the nervous system, there is, as expected, a wide variety in their shape, size, and electrochemical properties. For instance, the soma of a neuron can vary from 4 to 100 micrometers in diameter.

- The soma is the body of the neuron. As it contains the nucleus, most protein synthesis occurs here. The nucleus can range from 3 to 18 micrometers in diameter.[5]
- The dendrites of a neuron are cellular extensions with many branches. This overall shape and structure is referred to metaphorically as a dendritic tree. This is where the majority of input to the neuron occurs via the dendritic spine.
- The axon is a finer, cable-like projection that can extend tens, hundreds, or even tens of thousands of times the diameter of the soma in length. The axon carries nerve signals away from the soma (and also carries some types of information back to it). Many neurons have only one axon, but this axon may—and usually will—undergo extensive branching, enabling communication with many target cells. The part of the axon where it emerges from the soma is called the axon hillock. Besides being an anatomical structure, the axon hillock is also the part of the neuron that has the greatest density of voltage-dependent sodium channels. This makes it the most easily excited part of the neuron and

the spike initiation zone for the axon: in electrophysiological terms it has the most negative action potential threshold. While the axon and axon hillock are generally involved in information outflow, this region can also receive input from other neurons.

- The axon terminal contains synapses, specialized structures where neurotransmitter chemicals are released to communicate with target neurons.

The canonical view of the neuron attributes dedicated functions to its various anatomical components; however dendrites and axons often act in ways contrary to their so-called main function.

Axons and dendrites in the central nervous system are typically only about one micrometer thick, while some in the peripheral nervous system are much thicker. The soma is usually about 10–25 micrometers in diameter and often is not much larger than the cell nucleus it contains. The longest axon of a human motor neuron can be over a meter long, reaching from the base of the spine to the toes.

Sensory neurons can have axons that run from the toes to the posterior column of the spinal cord, over 1.5 meters in adults. Giraffes have single axons several meters in length running along the entire length of their necks. Much of what is known about axonal function comes from studying the squid giant axon, an ideal experimental preparation because of its relatively immense size (0.5–1 millimeters thick, several centimeters long).

Fully differentiated neurons are permanently postmitotic; however, research starting around 2002 shows that additional neurons throughout the brain can originate from neural stem cells through the process of neurogenesis. These are found throughout the brain, but are particularly concentrated in the subventricular zone and subgranular zone.

Histology and internal structure

Numerous microscopic clumps called **Nissl substance** (or Nissl bodies) are seen when nerve cell bodies are stained with a basophilic ("base-loving") dye. These structures consist of rough endoplasmic reticulum and associated ribosomal RNA. Named after German psychiatrist and neuropathologist Franz Nissl (1860–1919), they are involved in protein synthesis and their prominence can be explained by the fact that nerve cells are very metabolically active. Basophilic dyes such as aniline or (weakly) haematoxylin [8] highlight negatively charged components, and so bind to the phosphate backbone of the ribosomal RNA.

The cell body of a neuron is supported by a complex mesh of structural proteins called neurofilaments, which are assembled into larger neurofibrils. Some neurons also contain pigment granules, such as neuromelanin (a brownish-black pigment that is byproduct of synthesis of catecholamines), and lipofuscin (a yellowish-brown pigment), both of which accumulate with age. Other structural proteins that are important for neuronal function are actin and the tubulin of microtubules. Actin is predominately found at the tips of axons and dendrites during neuronal development.

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There are different internal structural characteristics between axons and dendrites. Typical axons almost never contain ribosomes, except some in the initial segment. Dendrites contain granular endoplasmic reticulum or ribosomes, in diminishing amounts as the distance from the cell body increases.

s**ynapse**

*Specialized junctions with other cells that are along the length or at end of an axon.

*Act as transmission points for electrical impulses.

*Synapse can transmit action potential, or can polarize or depolarize the postsynaptic cell.

*Synapses at end of an axon or axon branches are swollen into a club shape, called **boutonsterminaux**.

*Those along length of axon result in **varicosities** (swellings) in the axon, called **boutons en passage**.

General structure of synapse

***terminal or presynaptic membrane** - this is part of the neuron plasmalemma

***synaptic gap** is present - this is a space between the presynaptic membrane of the axon and the plasmalemma of the cell that receives the synaptic input

***postsynaptic membrane** - part of plasmalemma of a cell that receives input

*high concentrations of small vesicles in bouton that contain neurotransmitter.

*when action potential reaches synapse, these vesicles are exocytosed at the presynaptic membrane and their contents (neurotransmitter) are released into the synaptic gap.

*neurotransmitter binds to receptors on postsynaptic membrane and propagates electrical impulse (action potential) or membrane charge change (polarization or depolarization) in post-synaptic cell.

Classification

Neurons exist in a number of different shapes and sizes and can be classified by their morphology and function.

The anatomist Camillo Golgi grouped neurons into two types;

type I with long axons used to move signals over long distances

type II with short axons, which can often be confused with dendrites.

Structural classification

Polarity

Different kinds of neurons:

1. unipolar neuron
2. bipolar neuron
3. multipolar neuron
4. pseudounipolar neuron

Most neurons can be anatomically characterized as:

- Unipolar or pseudounipolar: dendrite and axon emerging from same process.
- Bipolar: axon and single dendrite on opposite ends of the soma.
- Multipolar: two or more dendrites, separate from the axon:
  - Golgi I: neurons with long-projecting axonal processes; examples are pyramidal cells, Purkinje cells, and anterior horn cells.
  - Golgi II: neurons whose axonal process projects locally; the best example is the granule cell.
- Anaxonic: where axon cannot be distinguished from dendrites.

Other

Furthermore, some unique neuronal types can be identified according to their location in the nervous system and distinct shape. Some examples are:

- Basket cells, interneurons that form a dense plexus of terminals around the soma of target cells, found in the cortex and cerebellum.
- Betz cells, large motor neurons.
- Lugaro cells, interneurons of the cerebellum.
- Medium spiny neurons, most neurons in the corpus striatum.
- Purkinje cells, huge neurons in the cerebellum, a type of Golgi I multipolar neuron.
- Pyramidal cells, neurons with triangular soma, a type of Golgi I.
- Renshaw cells, neurons with both ends linked to alpha motor neurons.
- Unipolar brush cells, interneurons with unique dendrite ending in a brush-like tuft.
- Granule cells, a type of Golgi II neuron.
- Anterior horn cells, motoneurons located in the spinal cord.
- Spindle cells, interneurons that connect widely separated areas of the brain

Functional classification

Direction

- Afferent neurons convey information from tissues and organs into the central nervous system and are sometimes also called sensory neurons.
- Efferent neurons transmit signals from the central nervous system to the effector cells and are sometimes called motor neurons.
- Interneurons connect neurons within specific regions of the central nervous system.

Afferent and efferent also refer generally to neurons that, respectively, bring information to or send information from the brain region.

Action on other neurons

A neuron affects other neurons by releasing a neurotransmitter that binds to chemical receptors. The effect upon the postsynaptic neuron is determined not by the presynaptic neuron or by the neurotransmitter, but by the type of receptor that is activated. A neurotransmitter can be thought of as a key, and a receptor as a lock: the same type of key can here be used to open many different types of locks. Receptors can be classified broadly as *excitatory* (causing an increase in firing rate), *inhibitory* (causing a decrease in firing rate), or *modulatory* (causing long-lasting effects not directly related to firing rate).

The two most common neurotransmitters in the brain, glutamate and GABA, have actions that are largely consistent. Glutamate acts on several different types of receptors, and have effects that are excitatory at ionotropic receptors and a modulatory effect at metabotropic receptors. Similarly GABA acts on several different types of receptors, but all of them have effects (in adult animals, at least) that are inhibitory. Because of this consistency, it is common for neuroscientists to simplify the terminology by referring to cells that release glutamate as "excitatory neurons", and cells that release GABA as "inhibitory neurons". Since over 90% of the neurons in the brain release either glutamate or GABA, these labels encompass the great majority of neurons. There are also other types of neurons that have consistent effects on their targets, for example "excitatory" motor neurons in the spinal cord that release acetylcholine, and "inhibitory" spinal neurons that release glycine.

The distinction between excitatory and inhibitory neurotransmitters is not absolute, however. Rather, it depends on the class of chemical receptors present on the postsynaptic neuron. In principle, a single neuron, releasing a single neurotransmitter, can have excitatory effects on some targets, inhibitory effects on others, and modulatory effects on others still. For example, photoreceptor cells in the retina constantly release the neurotransmitter glutamate in the absence of light. So-called OFF bipolar cells are, like most neurons, excited by the released glutamate. However, neighboring target neurons called ON bipolar cells are instead *inhibited* by glutamate, because they lack the typical ionotropic glutamate receptors and instead express a class of inhibitory metabotropic glutamate receptors.[14] When light is present, the photoreceptors cease releasing glutamate, which relieves the ON bipolar

cells from inhibition, activating them; this simultaneously removes the excitation from the OFF bipolar cells, silencing them.

It is possible to identify the type of inhibitory effect a presynaptic neuron will have on a postsynaptic neuron, based on the proteins the presynaptic neuron expresses. Parvalbumin-expressing neurons typically dampen the output signal of the postsynaptic neuron in the visual cortex, whereas somatostatin-expressing neurons typically block dendritic inputs to the postsynaptic neuron.[15]

Discharge patterns

Neurons can be classified according to their electrophysiological characteristics:

- **Tonic or regular spiking**. Some neurons are typically constantly (or tonically) active. Example: interneurons in neurostriatum.
- **Phasic or bursting**. Neurons that fire in bursts are called phasic.
- **Fast spiking**. Some neurons are notable for their high firing rates, for example some types of cortical inhibitory interneurons, cells in globuspallidus, retinal ganglion cells.[16][17]

Classification by neurotransmitter production

- Cholinergic neurons—acetylcholine. Acetylcholine is released from presynaptic neurons into the synaptic cleft. It acts as a ligand for both ligand-gated ion channels and metabotropic (GPCRs) muscarinic receptors. Nicotinic receptors, are pentameric ligand-gated ion channels composed of alpha and beta subunits that bind nicotine. Ligand binding opens the channel causing influx of Na^+ depolarization and increases the probability of presynaptic neurotransmitter release. Acetylcholine is synthesized from choline and acetyl coenzyme A.
- GABAergic neurons—gamma aminobutyric acid. GABA is one of two neuroinhibitors in the CNS, the other being Glycine. GABA has a homologous function to ACh, gating anion channels that allow Cl^- ions to enter the post synaptic neuron. Cl^- causes hyperpolarization within the neuron, decreasing the probability of an action potential firing as the voltage becomes more negative (recall that for an action potential to fire, a positive voltage threshold must be reached). GABA is synthesized from glutamate neurotransmitters by the enzyme glutamate decarboxylase.
- Glutamatergic neurons—glutamate. Glutamate is one of two primary excitatory amino acid neurotransmitter, the other being Aspartate. Glutamate receptors are one of four categories, three of which are ligand-gated ion channels and one of which is a G-protein coupled receptor (often referred to as GPCR).

1. AMPA and Kainate receptors both function as cation channels permeable to Na^+ cation channels mediating fast excitatory synaptic transmission
2. NMDA receptors are another cation channel that is more permeable to Ca^{2+}. The function of NMDA receptors is dependant on Glycine receptor binding as a co-agonist within the channel pore. NMDA receptors do not function without both ligands present.
3. Metabotropic receptors, GPCRs modulate synaptic transmission and postsynaptic excitability.

Glutamate can cause excitotoxicity when blood flow to the brain is interrupted, resulting in brain damage. When blood flow is suppressed, glutamate is released from presynaptic neurons causing NMDA and AMPA receptor activation more so than would normally be the case outside of stress conditions, leading to elevated Ca^{2+} and Na^+ entering the post synaptic neuron and cell damage. Glutamate is synthesized from the amino acid glutamine by the enzyme glutamate synthase.

- Dopaminergic neurons—dopamine. Dopamine is a neurotransmitter that acts on D1 type (D1 and D5) Gs coupled receptors, which increase cAMP and PKA, and D2 type (D2, D3, and D4) receptors, which activate Gi-coupled receptors that decrease cAMP and PKA. Dopamine is connected to mood and behavior, and modulates both pre and post synaptic neurotransmission. Loss of dopamine neurons in thesubstantianigra has been linked to Parkinson's disease. Dopamine is synthesized from the amino acid tyrosine. Tyrosine is catalyzed into levadopa (or L-DOPA) by tyrosine hydroxlase, and levadopa is then converted into dopamine by amino acid decarboxylase.
- Serotonergic neurons—serotonin. Serotonin (5-Hydroxytryptamine, 5-HT) can act as excitatory or inhibitory. Of the four 5-HT receptor classes, 3 are GPCR and 1 is ligand gated cation channel. Serotonin is synthesized from tryptophan by tryptophan hydroxylase, and then further by aromatic acid decarboxylase. A lack of 5-HT at postsynaptic neurons has been linked to depression. Drugs that block the presynapticserotonin transporter are used for treatment, such as Prozac and Zoloft.

Neuronal signalling

Neuron's Resting State

In its resting state, an electrical gradient is maintained across the neuron's membrane, thereby creating a *resting membrane potential*. This section explains how this is maintained.

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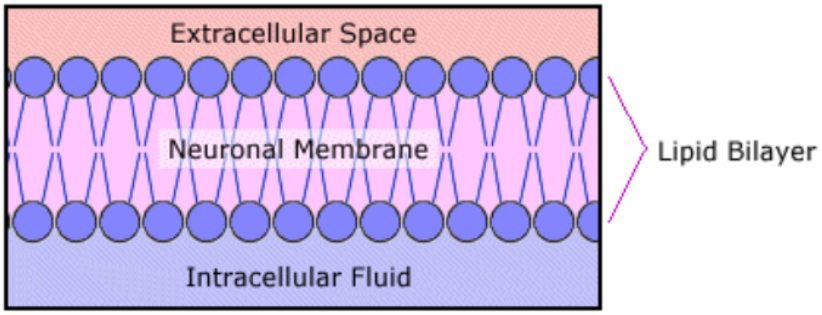
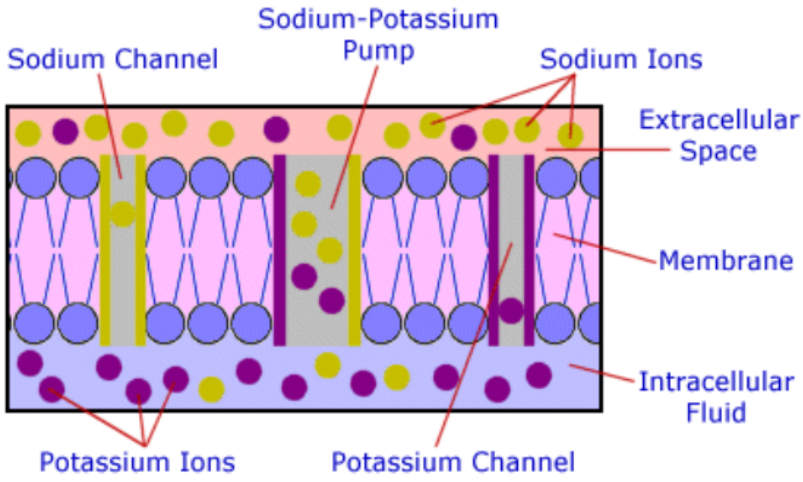
- Properties of neuronal membrane:



  - The neuron's membrane forms a separation between the extracellular space around the neuron and its intracellular fluid
  - The membrane is mostly impermeable, forming a barrier to many proteins, molecules, and other ions dissolved in the intracellular and extracellular fluids
  - It is *selectively permeable* to only a few ions, notably sodium (Na^+), potassium (K^+), and chlorine (Cl^-)
    - However, the membrane is not equally permeable to all: $K^+ > Cl^- >>> Na^+$, i.e., it is most permeable to K^+, less to Cl^-, and a lot less to Na^+.
  - The membrane is responsible for maintaining the neuron's *membrane resting potential*. This is defined as the voltage difference between the extracellular and intracellular spaces. This voltage difference is between –60 and –80 millivolts, but on average –70 mV
  - This transforms a neuron into the equivalent of a battery, allowing them to generate electrical signals

- Reasons for a membrane's resting potential:
  - Sodium-Potassium Pump



    - The membrane has protein (or enzyme) channels, or gaps, which forms a transmembrane pump.
    - These pumps use energy-storing molecules called *adenosine triphosphate* (ATP)
    - ATP actively pumps 3 Na^+ ions out of the cell, at the same time pumping 2 K^+ into the cell.
- After a while, a ionic concentration gradient is generated across the membrane, whereby more Na^+ ions are outside and more K^+ are inside
- Because of diffusion, the tendency is for Na^+ ions to travel back to the inside, and vice versa for K^+ ions
- There are nongated channels in the membrane that permit the passage of some Na^+ ions back into the neuron, and K^+ ions out of the neuron (again, using diffusion to achieve a concentration equilibrium), however, the membrane is not very permeable to Na^+ ions. Hence many more K^+ ions leave the cell than Na^+ ions enter. This causes an excess of negative charge in the cell.
- The K^+ ions continue to leak out until there is an equilibrium reached between the concentration gradient and the electric potential (i.e., the attraction of K^+ positive ions back to the negatively charged intracellular fluid)
- The voltage differential, again, is –70 mV on average

Neuronal Stimulation

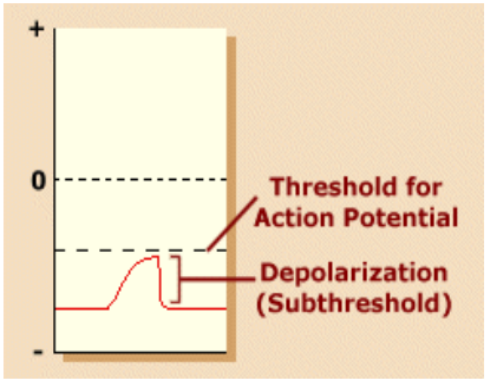
A number of factors contribute to a neuron's stimulation, which causes a change in the neural membrane's permeability

- *Mechano-sensitive channels* are affected by distortions or deformations in the membrane around it
- *Voltage-sensitive channels* are affected by the current voltage around the membrane
- *Ligand-sensitive channels* are affected by chemical agents (found on dendrites and postsynaptic cells)

Passive Potential

The moment a neuron's membrane is affected by some stimuli, the following happens:

- A chemical or physical change causes some Na^+ ion channels in the membrane to open temporarily
- Na^+ ions enter the cell because of the concentration gradient and electrostatic pressure, making the inside of the cell more positive (depolarization)
- Because of this electrical change, the K^+ ions are pushed out through the non-gated K^+ ion channels
- The current spreads passively as adjacent parts of the membrane also become depolarized
- The current is proportional to the size of the simulation, but passive potentials decay with time and distance from the source of the depolarization



- As long as the simulation does not cause a depolarization of more than 15 to 20 mV (-50 mV is the *treshhold* for an action potential), the electric current generated decays with distance and time, and is generally restricted to the area stimulated
- The cell eventually returns to its resting state
- This form of neuronal signaling is only effective over short distances. For example, neurons in the retina use passive potential to communicate with one another

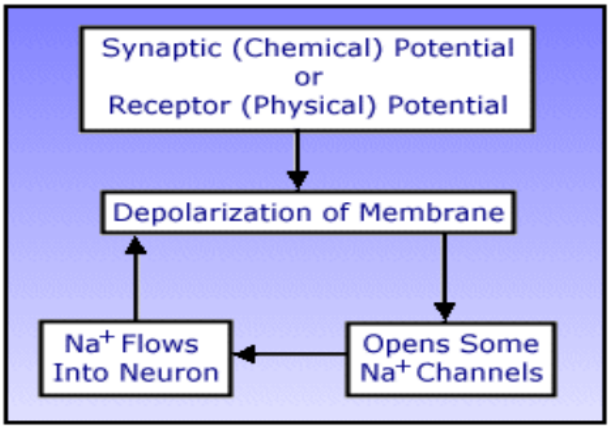
Action Potential

As long as the stimuli does not cause the membrane potential to reach -50 mV, only a passive current that diminishes with time and distance is generated through the neuron. However, if the stimuli is enlarged or additional stimuli is provided to the cell, a depolarization of more than 15 to 20 mV may occur (this is possible because the current is proportional to the size of the simuli).

A. Depolarization

If a passive potential depolarizes the membrane to about -50 mV, all Na^+ voltage-gated channels are opened:

- A combination of diffusion and electrostatic pressure causes a sudden rushing in, or *influx*, of Na^+ ions into the neuron's intracellular fluid
- This causes a further depolarization of the membrane, and more Na^+ voltage-gated channels are opened
- This is a rapid self-reinforcing cycle (which lasts about 25ms) that continues until all Na^+ voltage-gated channels are opened. It is known as the *Hodgkin-Huxley Cycle*



Hodgkin-Huxley Cycle

- Because the membrane has suddenly become 100% permeable, its membrane potential becomes very positive inside the neuron, about +50 mV.
- This massive depolarization is digital, i.e. all or none, and is independent of the stimulation intensity

B. Absolute Refractory Period

The moment the membrane potential hits +50 mV, all the Na^+ voltage-gated channels are closed and the K^+ voltage-gated channels are opened:

- This causes K^+ ions to flow out, or *efflux*, of the neuron, thereby causing a repolarization of the membrane. This period from the time the Na^+ voltage-gated channels are closed and the K^+ voltage-gated channels are opened to the time when the K^+ voltage-gated channels are closed again, is called the *absolute refractory period*
- During the absolute refractory period no further action potential can occur:
  - The Na^+ voltage-gated channels are completely closed
  - Hence the membrane cannot be depolarizated with an influx of Na^+ ions

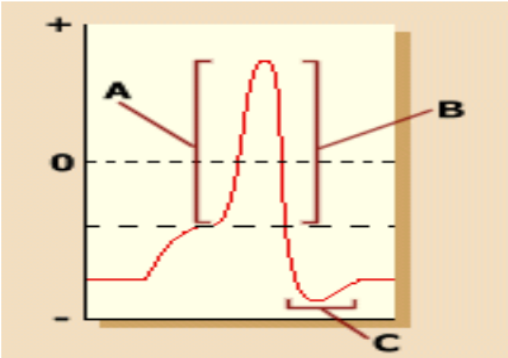
C. Relative Refractory Period

After the absolute refractory period, there is a period when both Na^+ and K^+ voltage-gated channels remain closed:

- This causes the membrane potential to be even more negative than at rest
- The membrane potential is now *hyperpolarized* ("hyper" means extra, super)
- It would take more stimuli to bring the potential to threshold in order to create another action potential

- This period is called the *relative refractory period*

Sections A, B, and C above are depicted graphically in the diagram below:



Comparison Between Passive Potential and Active Potential

Description	Passive Potential	Active Potential
Amplitude	Graded with stimulus intensity	Always the same size
Stimulation	Requires very little	Requires a 15-20 mV change
Summation	Adds the stimuli strengths	Only one potential at a time
Spread	Decay with distance	Actively regenerated
Duration	As long as the stimulus	Constant duration
Main channels used	Non-gated channels	Voltage-gated channels

Passive Conduction

Both passive potentials and active potentials propagate current in the intracellular fluid of the neuron.

- The passive potential operates like a graded analog signal
- It decays with time and distance:
  - The original intensity of the stimulus affects the size of the depolarizing current
  - The resistance of the membrane contributes to how much current leaks out
  - The conductivity of the axon is dependent on its diameter size (the larger the better)
- For most neurons, passive conduction is not good enough to conduct the current signal all the way down the axon to the terminal boutons.

- Another method is therefore needed to conduct a current signal down longer axons: *active conduction*.

Active Conduction

Because the action potential's depolarization is localized, it is not able to conduct the current signal very far. Axons therefore provide a method, called active conduction, to maintain the current with undiminished intensity by way of repeated action potentials. There are two forms of active conduction:

Unmyelinated Axons

- Axons without myelin sheaths surrounding them use many voltage gated Na^+ channels in proximity to one another
- An action potential depolarizes the surrounding area by the passive conduction of the depolarizing current
- The nearby Na^+ channels then open, which generates another action potential
- This process is repeated until the action potential reaches the terminal boutons
- Note: the action potential cannot travel backwards because of the refractory period

Myelinated Axons

- Rather than having many Na^+ channels in close proximity, axons also use a myelin sheath (in the form of Schwann cells in the PNS or oligodendrocytes in the CNS) to increase action potential speed
- The myelin around the axon prevents current leakage by increasing resistance in the axon
- The passive current therefore spreads further down the axon, until it reaches the gaps between the myelin sheaths (Nodes of Ranvier)
- The Nodes of Ranvier contains Na^+ channels, which fire another action potential upon depolarization from the passive current
- This 'jumping' of action potentials from node to node is called *saltatory conduction*
- Note: as before, the action potential cannot travel backwards due to the refractory period

Synaptic Transmission

Chemical Transmitters Carry the Signal Across Synapses & Neuromuscular Junctions

- A contact between 2 nerves is called a synapse
- At the synapse there is a break in electrical transmission (the action potential cannot cross)- instead chemicals are released that carry the signal to the next nerve
  - The release of chemical transmitters at nerve endings was first shown by Otto Loewi in the frog heart

- If the ions make the postsynaptic membrane more negative they produce an inhibitory postsynaptic potential (IPSP)
    - The major transmitters producing IPSPs are glycine and GABA (gamma amino-butyric acid)
- There are both excitatory and inhibitory nerves coming into most synapses

If There Are Enough EPSPs an Action Potential Will be Produced in the Postsynaptic Membrane

- 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
- IPSPs make the membrane potential more negative and cancel out EPSPs

The Transmitter is Broken Down and/or Recycled

- Once the signal has been delivered the transmitter must be removed so that new signals may be received
- In some cases the transmitter is broken down by an enzyme in the synapse
- In other cases the transmitter is recycled- it is transported back into the presynaptic nerve
- In still other cases these 2 methods are combined
- Some drugs inhibit the enzymes that break down transmitters: nerve gases, physostigmine
- Other drugs act by inhibiting recycling: prozac, cocaine

In the Central Nervous System Nerves Make Synapses with Thousands of Other Nerves

- Nerves in the central nervous system make synaptic contact with 1000 to 10,000 other nerves
- This allows nerve cells to be hooked together in complex patterns to perform tasks benefiting the animal
- In the brain synapses tend to cluster to form ganglia (gray matter of brain)
- Each nerve makes both excitatory and inhibitory synapses
- Whether or not a nerve fires is determined by summation of the EPSPs and IPSPs

There are Dozens of Transmitters in the Nervous System

- In this class we will deal with only a few types of transmitters: acetylcholine, epinephrine, norepinephrine and a few others
- There are dozens of other transmitters in the central nervous system (CNS) and new ones are being discovered every year:
    - Serotonin, dopamine, glutamate, secretin, endorphins, etc.
    - Even gas molecules such as nitric oxide (NO) can act as local transmitters
        - The gas types are not stored, but are made on demand
- A high percentage of pharmaceutical drugs affect the synapse or NMJs

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Synapses Are Believed to be the Sites of Learning and Memory

- Many learning exercises are known to increase transmission across certain synapses (potentiation). The potentiation can be for short or long term
- Long term potentiation involves protein synthesis, probably of receptors

Many Toxins and Diseases Affect Neuromuscular Junction & Synaptic Transmission

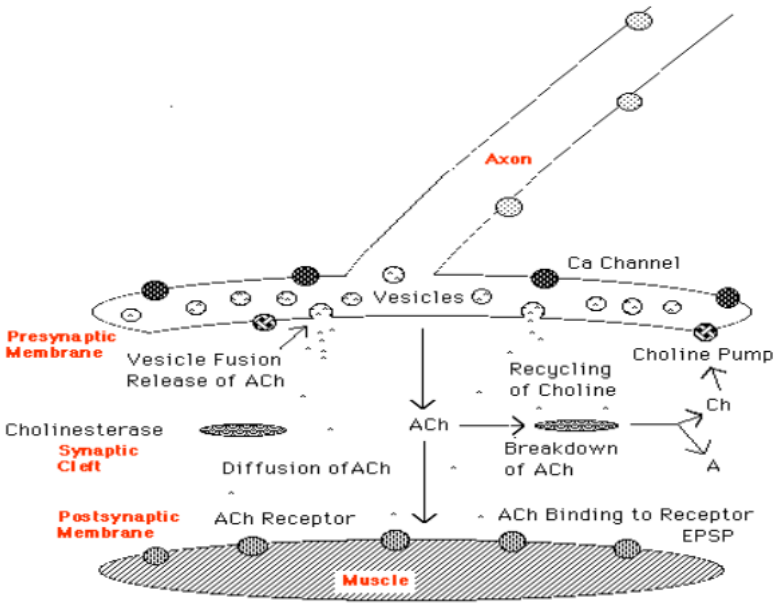
- NMJs and synapses are attacked by toxins and poisons:
  - ACh release in the NMJ is inhibited by botulinum toxin
  - Glycine release in the central nervous system (CNS) is inhibited by tetanus toxin
  - Black widow spider toxin, alpha-latrotoxin, stimulates fusion and depletion of transmitter vesicles
  - The plant poison, physostigmine, nerve gases and organophosphorus pesticides inhibit acetylcholinesterase, the enzyme that splits ACh into acetate and choline
  - The muscle ACh receptor is blocked by the South American arrow poison, curare
  - The plant drug, atropine, inhibits ACh receptors of the autonomic nervous system (but not the NMJ)
  - Strychnine binds to the glycine receptor protein and inhibits IPSPs in the spinal cord
  - Cocaine blocks the recycling of of dopamine and norepinephrine transmitters in the brain. This has an excitatory effect
- Low blood Ca will inhibit transmitter release
- Diseases affecting synapses and NMJs:
  - Eaton-Lambert syndrome: patient produces antibodies that attack his own Ca channels. This results in low Ca in the synapse and transmitter release is inhibited
  - Myasthenia gravis: another autoimmune disease which damages the receptor proteins for ACh
  - Parkinson's disease: cells in the substantianigra of the brain are deficient in the transmitter, dopamine
  - Clinical depression: associated with low amounts of the transmitter, serotonin, in parts of the brain

A Detailed Example: the Neuromuscular Junction

- We will consider the NMJ in detail because it is the best known junction. The diagram below outlines reactions in the NMJ.
- Transmission at this junction involves several steps:
  - 1) When an action potential (inhibited by tetrodotoxin) reaches the axon terminal it causes Ca channels to open. Ca^{2+} rushes into the cell because Ca^{2+} outside is much higher than Ca^{2+} inside
  - 2) The terminal region is loaded with vesicles containing the transmitter acetylcholine (ACh)
  - 3) Ca^{2+} causes some of the vesicles to fuse with the membrane and release their ACh (inhibited by botulinum toxin)

- 4) ACh diffuses across the junction and binds to the ACh receptor protein (inhibited by curare) in the postsynaptic membrane
- 5) Binding causes an ion channel to open
- 6) The flow of ions depolarizes the membrane, producing an EPSP. In muscle a single impulse usually causes enough depolarization to reach threshold
- 7) An action potential is generated in the muscle membrane
- 8) The muscle action potential causes release of Ca2+ from the sarcoplasmic reticulum of the muscle and this triggers muscle contraction
- 9) Back in the synapse the ACh is broken down to acetate and choline by the enzyme acetylcholinesterase (inhibited by physostigmine, nerve gases, organophosphate insecticides).
- 10) The choline is recycled. A choline pump transports it back into the nerve terminal and there it is converted back into Ach

Neuromuscular Junction



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Neurotransmitter System:

Neurotransmitters			
Substance	SiteofRelease	Effect	ClinicalExample
Acetylcholine(ACh)	CNSsynapses,ANS (atypeof synapses,andneuromuscular junctions	Excitatoryorinhibitory	Alzheimerdisease(atypeof seniledementia)isassociated withadecreaseinacetylcholine-secretingneurons.Myasthenia gravis(weaknesofskeletal muscles)resultsfroma reduction inacetylcholinereceptors.
Norepinephrine(NE)	SelectedCNSsynapses andsomeANSsynapses	Excitatory	Cocaineandamphetamines increasetherelease andblockthereuptakeofnorepinephrine, resultinginoverstimulationof postsynaptic neurons.
Serotonin	CNSsynapses	Generallyinhibitory	Itisinvolved withmood,anxiety, andsleepinduction.Levelsof serotoninareelevatedinschizophrenia (delusions,hallucinations,andwithdrawal). Drugsthatblockserotonintransporters, suchasprozac,areusedtotreat depression andanxietydisorders.
Dopamine	SelectedCNSsynapses (depressionof andsomeANSsynapses voluntarymotorcontrol)results	Excitatoryorinhibitory	Parkinsondisease fromdestructionofdopamine-secretingneurons.
Gamma-aminobutyric acid(GABA)	CNSsynapses	Inhibitory	DrugsthatincreaseGABA function havebeenusedtotreatepilepsy

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Glycine	CNSsynapsesInhibitory	Glycinereceptorsareinhibitedby the	poisonstrychnine.Strychnineincreases theexcitabilityofcertainneuronsby blockingtheirinhibition.Strychnine poisoningresultsinpowerfulmuscle contractions andconvulsions.Tetanus ofrespiratorymusclescancausedeath.
Endorphins	Descending Inhibitory Theopiatesmorphineandheroinbind painpathways toendorphinreceptorsonpresynaptic		neuronsandreducepainby blocking thereleaseofa neurotransmitter.