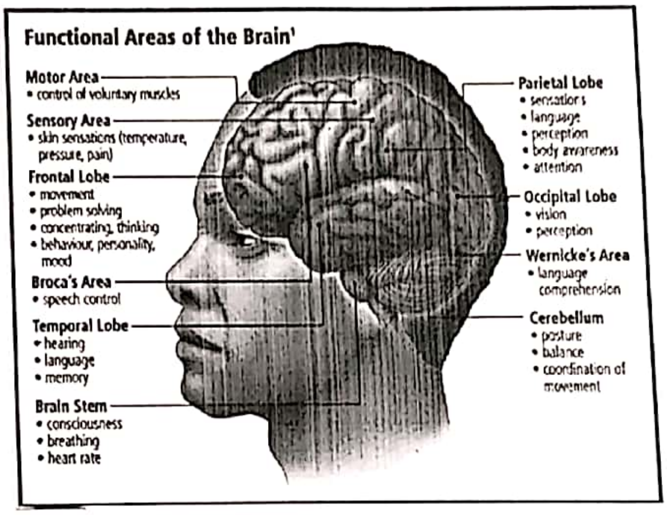
NEURONS AND POTENTIAL

Brain

The brain is a complex organ that controls thought, memory, emotion, touch, motor skills, vision, breathing, temperature, hunger and every process that regulates our body. Together, the brain and spinal cord that extends from it make up the central nervous system.

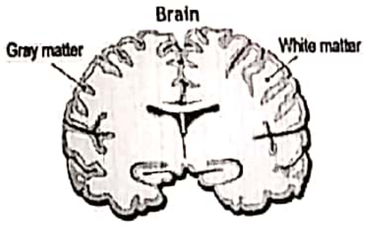
Composition of Brain

Brain consists of 60% fats and remaining 40% is a combination of water, protein, carbohydrates and salts. The brain is a not a muscle. It contains blood vessels and nerves, including neurons. In an adult human being its weighing is about 3 pounds.



Gray and white matter of brain Brain

Gray and white matter are two different regions of the central nervous system. In the brain, gray matter refers to the darker, outer portion, while white matter describes the lighter, inner section.



Gray matter is primarily composed of neuron, and white matter is made of axons .
Gray matter is responsible for processing and interpreting information, while white matter transmits that information to other parts of the nervous system.

Neurons

A neuron is a nerve cell, the basic building block of the nervous system. Neurons are similar to other cells, but there is one difference:- Neurons are specialized to transmit information throughout the body.

These are responsible for communicating information in both chemical and electrical forms. There are different types of neurons responsible for different tasks in the human body.

Neurons Vs. Other Cells

Similarities:-

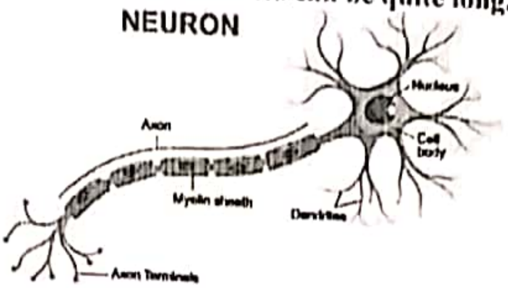
- both contain a nucleus that holds genetic information.
- both are surrounded by a membrane that protects the cell.
- The cell bodies of both cell types contain organelles like mitochondria, Golgi bodies, and cytoplasm.

Differences:-

- Neurons stop reproducing after birth. When neurons die they are not replaced.
- New connections between neurons form throughout life.
- Neurons have an axon and dendrites which transmit and receive information.
- Neurons release chemicals to communicate with other neurons.

Structure of a Neuron

There are three basic parts of a neuron: the dendrites, the cell body, and the axon. However, all neurons vary somewhat in size, shape, and characteristics depending on the function and role of the neuron.
Some neurons have few dendritic branches, while others are highly branched in order to receive a great deal of information. Some neurons have short axons, while others can be quite long.



Neurons can only be seen using a microscope and can be split into three parts:

1. Cell body (Soma) — this portion of the neuron receives information. It contains the cell's nucleus.
2. Dendrites — these thin filaments carry information from other neurons to the soma. They are the input part of the cell.
3. Axon — this carries information from the soma and sends it off to other cells. This is the output part of the cell. It ends with a number of synapses connecting to the dendrites of other neurons.
Both dendrites and axons are referred to as nerve fibers.
Axons vary in length. Some can be tiny, whereas others can be over 1 meter long. The longest axon is called the dorsal root ganglion (DRG), a cluster of nerve cell bodies that carries information from the skin to the brain. Some of the axons in the DRG travel from the toes to the brain stem — up to 2 meters in a tall person.

Types of neurons

Neurons vary in structure, function, and genetic makeup. In terms of function, scientists classify neurons into three broad types: sensory, motor, and interneurons.

1. Sensory neurons

Sensory neurons help in:

- **taste**
- **smell**
- **hear**
- **see**
- **feeling things**

Sensory neurons are triggered by physical and chemical inputs from environment. Sound, touch, heat, and light are physical inputs. Smell and taste are chemical inputs.
For example, stepping on hot sand activates sensory neurons in the soles of the feet. Those neurons send a message to the brain, which makes us aware of the heat.

2. Motor neurons:-

Motor neurons helps in movement including voluntary and involuntary movements.
These neurons allow the brain and spinal cord to communicate with muscles, organs, and glands all over the body.
There are two types of motor neurons: lower and upper.

(i) **Lower motor neurons carry signals from the spinal cord to the smooth muscles and the skeletal muscles.**
(ii) **Upper motor neurons carry signals between brain and spinal cord.**

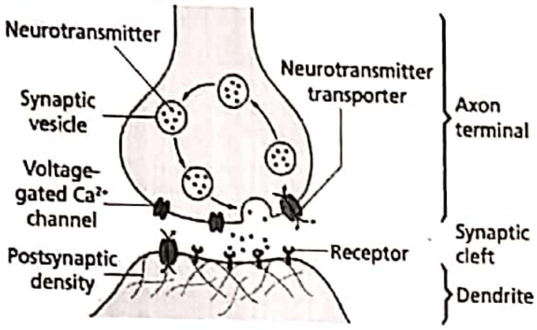
e.g. When we eat, lower motor neurons in spinal cord send signals to the smooth muscles in the esophagus, stomach, and intestines. These muscles contract, which allows food to move through digestive tract.

3. Interneurons:-

Interneurons are neural intermediaries found in the brain and spinal cord.
They're the most common type of neuron.
They pass signals from sensory neurons and other interneurons to motor neurons and other interneurons.
They form complex circuits that help to react to external stimuli.
e.g. when we touch something hot, sensory neurons in fingertips send a signal to interneurons in spinal cord. Some interneurons pass the signal on to motor neurons in hand, which allows us to move our hand away. Other interneurons send a signal to the pain center in the brain, and we experience pain.

Synapse Communication

Once an electrical impulse has reached the end of an axon, the information must be transmitted across the synaptic gap to the dendrites of the adjoining neuron. The electrical signal can almost instantaneously bridge the gap between the neurons and continue along its path.
Or neurotransmitters are needed to send the information from one neuron to the next.
Neurotransmitters are chemical messengers that are released from the axon terminals to cross the synaptic gap and reach the receptor sites of other neurons. In a process known as reuptake, these neurotransmitters attach to the receptor site and are reabsorbed by the neuron to be reused.



Neurotransmitters:-

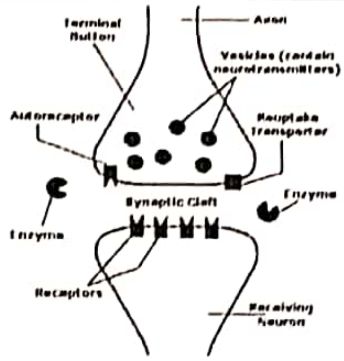
Neurotransmitters are essential part of our everyday functioning. More than 100 of neurotransmitters work as chemical messengers.
e.g.
1. Acetylcholine neurotransmitter is associated with memory, muscle contractions, and learning. A lack of acetylcholine in the brain is associated with Alzheimer's disease.
2. Endorphins is associated with emotions and pain perception. The body releases endorphins in response to fear or trauma. These chemical messengers are similar to opiate drugs such as morphine but are significantly stronger.
3. Dopamine is associated with thought and pleasurable feelings. Parkinson's disease is one illness associated with deficits in dopamine. Doctors may prescribe medications that can increase dopamine activity in the brain.
4. levodopa is converted into dopamine in the brain. They each carry their own relative benefits and side effects. Researchers also have found strong links between schizophrenia and excessive amounts of dopamine in certain parts of the brain.

Process to carry message by neurons

1. **Na+ channels open allowing Na^+ to flood into the cell, making it more positive.**
2. **Once the cell reaches a certain charge, K^+ channels open, allowing K^+ to flow out of the cell.**
3. **Na+ channels then shut but K^+ channels remain open allowing the positive charge to leave the cell. The membrane potential plunges.**
4. **As the membrane potential returns to its resting state, the K^+ channels shut.**
5. **Finally, the sodium/potassium pump transports Na+ out of the cell and K^+ back into the cell ready for the next action potential.**

How synapses work

Neurons communicate messages with each other and other tissues. They do not physically touch each other. There is always a gap between cells, called a synapse.
Synapses can be electrical or chemical i.e. the signal that is carried from the first neuron to the next is transmitted by an electrical or a chemical signal.
site of communication between two cells.
formed when an axon of a presynaptic cell
"connects" with the dendrites of a postsynaptic cell.



1. Chemical synapses

Once a signal reaches a synapse, it triggers the release of chemicals (neurotransmitters) into the gap between the two neurons; this gap is called the synaptic cleft.

The neurotransmitter diffuses across the synaptic cleft and interacts with receptors on the membrane of the postsynaptic neuron, triggering a response.

Chemical synapses are classified as:

Glutamergic — releases glutamine. They are often excitatory, meaning that they are more likely to trigger an action potential.

GABAergic — release GABA (gamma-Aminobutyric acid). They are often inhibitory, meaning that they reduce the chance that the postsynaptic neuron will fire.

Cholinergic — release acetylcholine. These are found between motor neurons and muscle fibers (the neuromuscular junction).

Adrenergic — release norepinephrine (adrenaline).

2. Electrical synapses

Electrical synapses are less common. Channels called gap junctions attach the presynaptic and postsynaptic membranes. In gap junctions, the post- and presynaptic membranes are brought much closer together than in chemical synapses, meaning that they can pass electric current directly.

Electrical synapses work much faster than chemical synapses. They are found in places where quick actions are necessary e.g. in defensive reflexes.

Chemical synapses can trigger complex reactions, but electrical synapses can only produce simple responses.

Electrical synapses are bidirectional i.e. information can flow in either direction.

Neurons are essential for every action that our body and brain carry out. They are responsible for the most basic of actions and the most intricate. Neurons are responsible for automatic reflex actions to deep thought.

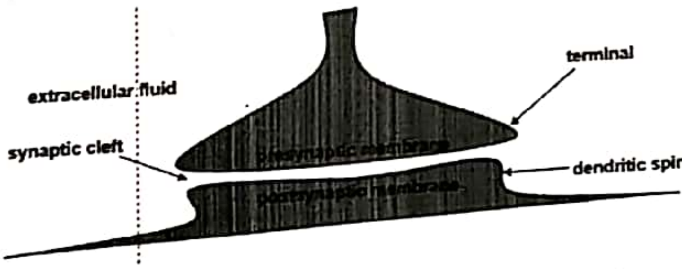
Comparing the Types of Synapses

Chemical Synapses

- Gap between: 20 nanometers
- Speed: Several milliseconds
- No loss of signal strength
- Excitatory or inhibitory

Electrical Synapses

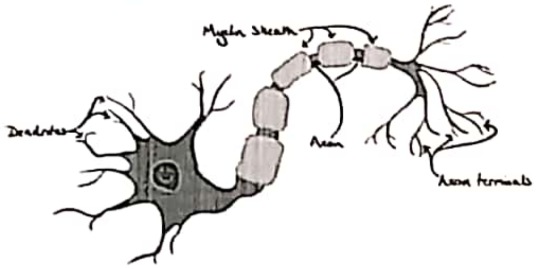
- Gap between: 3.5 nanometer
- Speed: Nearly instantaneous
- Signal strength diminishes
- Excitatory only



Action Potentials

This process of neuron communication utilizes electrical signals as well as chemical messengers. The dendrites of neurons receive information from sensory receptors or other neurons. This information is then passed to the cell body and on to the axon. Once the information has arrived at the axon, it travels down the length of the axon in the form of an electrical signal known as an action potential.

Human body has nerves that connect the brain to the organs and muscles. Nerves send electrical impulses called action potentials to different muscles allowing the concerned organ to respond. Neurons transfer information around the body through action potentials.



Concentration gradients

Concentration gradient is the difference in ion concentrations between the inside of the neuron and the outside of the neuron.

If there is higher concentration of positively charged ions outside the cell then there would be a large concentration gradient. The same would also be true if there were more of one type of charged ion inside the cell than outside. The charge of the ion does not matter, both positively and negatively charged ions move in the direction that would balance.

Resting membrane potential

Neurons have a negative concentration gradient most of the time i.e. there are more positively charged ions outside than inside the cell. This regular state of a negative concentration gradient is called resting membrane potential.

During the resting membrane potential there are:

- more sodium ions outside than inside the neuron.
- more potassium ions inside than outside the neuron.

The concentration of ions isn't static though! Ions are flowing in and out of the neuron constantly as the ions try to equalize their concentrations. The cell however maintains a consistent negative concentration gradient (between -40 to -90 millivolts).

- The neuron cell membrane is permeable to potassium ions, and so lots of potassium leaks out of the neuron through potassium leakage channels.
- The neuron cell membrane is partially permeable to sodium ions, so sodium atoms slowly leak into the neuron through sodium leakage channels.
- The cell maintain a negative resting membrane potential, so it pumps potassium back into the cell and sodium out of the cell at the same time.

Working of action potentials:

Action potentials are temporary shift from negative to positive in the neuron's membrane potential caused by ions suddenly flowing in and out of the neuron. During the resting state i.e. before an action potential, all of the gated sodium and potassium channels are closed. These gated channels are different from the leakage channels, and only open once an action potential has been triggered.

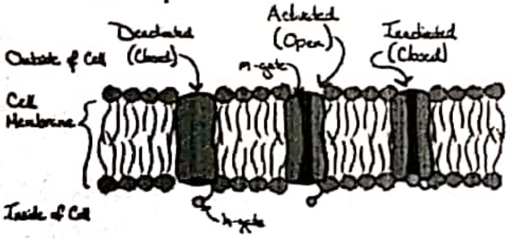
These channels are "voltage-gated" because they are open and closed depends on the voltage difference across the cell membrane.

- the activation gate is normally closed, and opens when the cell starts to get more positive.
- the deactivation gate is normally open, and shuts when the cells gets too positive.
- Activation gate is normally closed, but slowly opens when the cell is depolarized.

Voltage-gated sodium channels exist in one of three states:

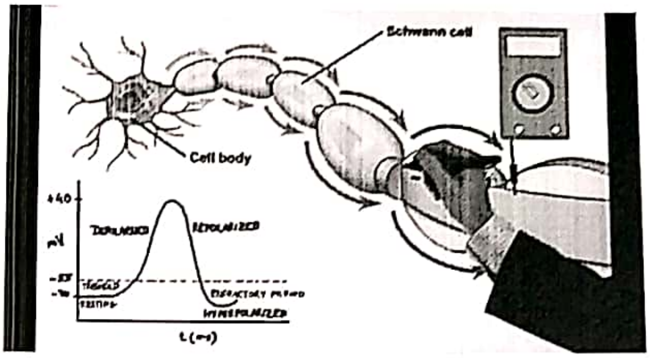
1. Deactivated (closed) - at rest, channels are deactivated. The gate is closed, and does not let sodium ions to pass.
2. Activated (open) - when a current passes through and changes the voltage difference across a membrane, the channel will activate and the gate will open.
3. Inactivated (closed) - as the neuron depolarizes, the gate swings shut and blocks sodium ions from entering the cell.

Voltage-gated potassium channels are either open or closed.



Main events taking place during an action potential:

1. A triggering event occurs that depolarizes the cell body. This signal comes from other cells connecting to the neuron, and it causes positively charged ions to flow into the cell body. Positive ions still flow into the cell to depolarize it, but these ions pass through channels that open when a specific chemical, known as a neurotransmitter, binds to the channel and tells it to open. Neurotransmitters are released by cells near the dendrites, often as the end result of their own action potential. These incoming ions bring the membrane potential closer to 0, which is known as depolarization. An object is polar if there is some difference between more negative and more positive areas. As positive ions flow into the negative cell and the cell's polarity decrease. If the cell body gets positive enough that it can trigger the voltage-gated sodium channels found in the axon, then the action potential will be sent.

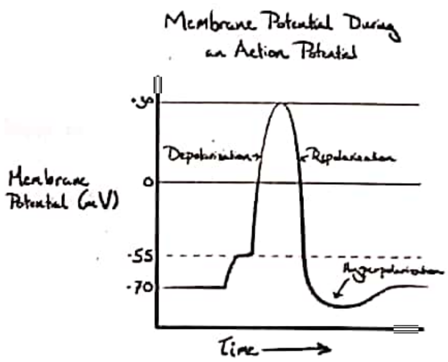


Main events taking place during an action potential:

2. **Depolarization -** makes the cell less polar. Voltage-gated sodium channels at the part of the axon closest to the cell body activate. This lets positively charged sodium ions flow into the negatively charged axon, and depolarize the surrounding axon.

3. **Repolarization** - brings the cell back to resting potential. The inactivation gates of the sodium channels close, stopping the inward movement of positive ions. At the same time, the potassium channels open. There is much more potassium inside the cell than out, so when these channels open, more potassium exits than comes in. This means the cell loses positively charged ions, and returns back toward its resting state.

4. **Hyperpolarization** - makes the cell more negative than its typical resting membrane potential. As the action potential passes through, potassium channels stay open a little bit longer, and continue to let positive ions exit the neuron i.e. cell temporarily hyperpolarizes, or gets more negative than its resting state. As the potassium channels close, the sodium-potassium pump works to reestablish the resting state.



Refractory Periods

Action potentials work on an all-or-none basis i.e. an action potential is either triggered, or not. A neuron will always send the same size action potential.

Action potential frequency.

When the brain gets excited, it fires off lot of signals. The stronger the signal, the higher the frequency of action potentials. There is a maximum frequency at which a single neuron can send action potentials, and this is determined by its refractory periods.

- Absolute refractory period: during this time it is not possible to send another action potential. No sodium will pass through i.e. no depolarization i.e. no action potential.

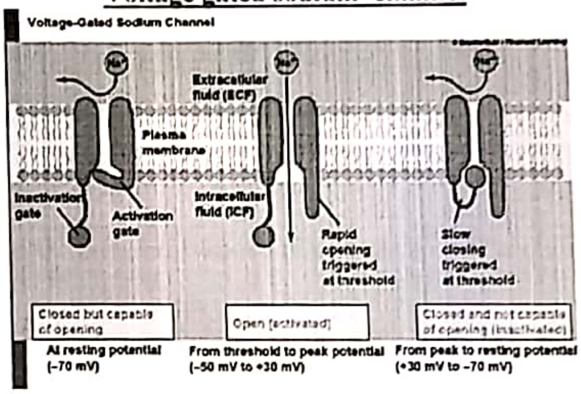
- **Relative refractory period:** during this time, it is not possible to send an action potential. This is the period after the absolute refractory period. The cell is hyperpolarized after sending an action potential. It would take even more positive ions than usual to reach the appropriate depolarization potential than usual e.g. cells in retina will send signals faster in bright light than in dim light.

Refractory periods also give the neuron to replenish the packets of neurotransmitter found at the axon terminal, so that it can keep passing the message along.
Action potential is the major signal sent down the axon, while graded potentials at the dendrites and cell body vary in size and influence whether an action potential will be sent or not. Graded potentials are small changes in membrane potential.

Graded Potentials	Action Potentials
At the dendrites and cell body	At the axon
Excitatory or inhibitory	Always excitatory
Smaller in size	Larger voltage difference
Triggered by input from the outside	Triggered by membrane depolarization
Many can happen at once	Only one at a time
Can come in different sizes	All-or-none

Voltage activation

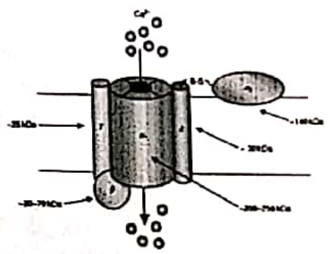
Voltage gated sodium channel



Voltage gated sodium channel
Voltage-gated sodium channels initiate action potentials in nerve, muscle, and other excitable cells.
Early studies described sodium selectivity, voltage-dependent activation, fast inactivation, and developed conceptual models for sodium channel function.

New researches are using a combination of biochemical, molecular biological, physiological, and structural biological approaches that has given the structure and function of sodium channels at the atomic level.
Structural models for voltage-dependent activation, sodium selectivity and conductance, drug block, and both fast and slow inactivation are studied at different levels.
Sodium currents were first recorded as part of the analysis of the action potential of the squid giant axon using the voltage clamp procedure by Hodgkin & Huxley in 1952.
They showed that electrical signals in nerves are initiated by voltage-dependent activation of sodium current that carries Na^+ inward and depolarizes the cell.
The sodium current then inactivates within 1–2 milliseconds, and electrical signaling is terminated by activation of the voltage-gated potassium current, which carries K^+ outward and re-establishes the original balance of electrical charges across the membrane.
Voltage sensitivity was proposed by Hodgkin and Huxley to depend on the movement of electrically charged particles, the gating charges, which were driven across the membrane by the change in voltage.

Voltage gated calcium channel



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Voltage gated calcium channel

Voltage-gated calcium channels (VGCCs) are a group of voltage-gated ion channels found in the membrane of muscle, glial cells, neurons, etc.

These channels are slightly permeable to sodium ions, so they are also called Ca^{2+}-Na^{+} channels.

Their permeability to calcium is about 1000-times greater than to sodium under normal conditions.

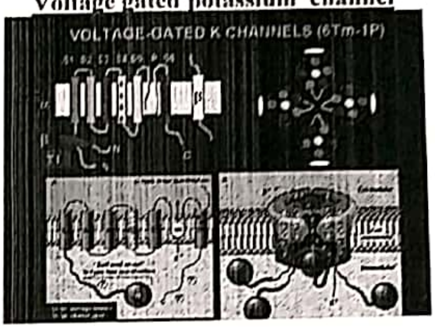
At resting membrane potential, VGCCs are normally closed. They are activated at depolarized membrane potentials.

The concentration of Ca^{2+} ions is normally several thousand times higher outside the cell than inside.

Activation of particular VGCCs allows a Ca^{2+} into the cell.

This results in activation of calcium-sensitive potassium channels e.g. excitation of neurons, up-regulation of gene expression, or release of hormones or neurotransmitters.

Voltage gated potassium channel



Voltage gated potassium channel

Voltage-gated potassium channels (VGKCs) are transmembrane channels specific for potassium and sensitive to voltage changes in the cell's membrane potential. During action potentials, they play a crucial role in returning the depolarized cell to a resting state.

Voltage-gated potassium channels are the largest ion channel family in the human genome.

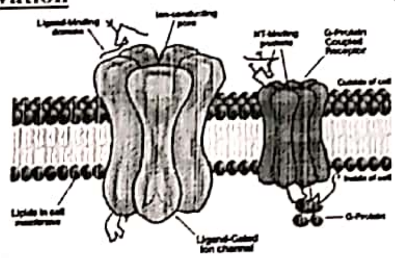
They have various functions like repolarization action potentials, setting membrane potential, dictating the duration or frequency of action potential, to modulation of Ca^{2+} signaling and cell volume, to control cellular proliferation and migration.

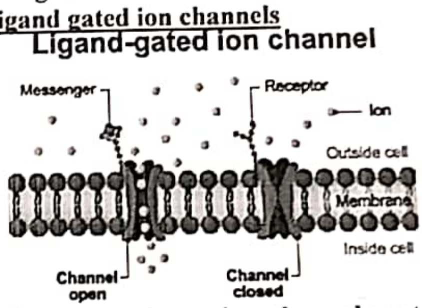
Voltage-gated potassium channels are products of 40 genes in 12 subfamilies, and the related channels are encoded by 8 genes in 4 subfamilies.

They conduct K^{+} ions in or out of the cell membrane depending on their functionality.

- **Ligand activation**

Ligand gated ion channels





Ligand-gated ion channels (LICs, LGIC), are group of transmembrane ion-channel proteins which open to allow ions such as Na^{+}, K^{+}, Ca^{2+}, and Cl^{-} to pass through the membrane in response to the binding of a chemical messenger called ligand. E.g. a neurotransmitter.

When a presynaptic neuron is excited, it releases a neurotransmitter from vesicles into the synaptic cleft. The neurotransmitter then binds to receptors located on the postsynaptic neuron. If these receptors are ligand-gated ion channels, a resulting conformational change opens the ion channels, which leads to a flow of ions across the cell membrane. This results in either a depolarization, for an excitatory receptor response, or a hyperpolarization, for an inhibitory response.

These receptor proteins are composed of at least two different domains:

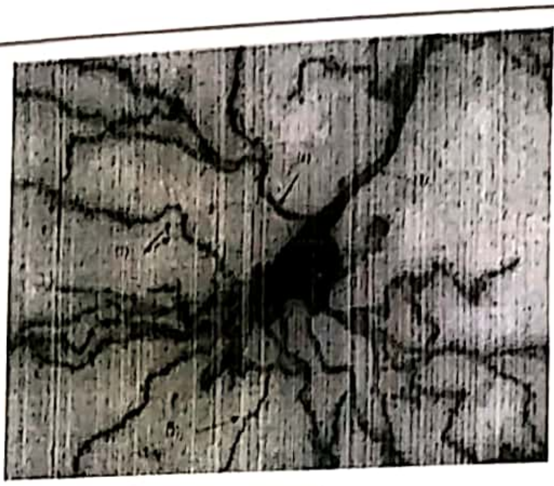
(i) a transmembrane domain which includes the ion pore.

(ii) an extracellular domain which includes the ligand binding location.

The function of such receptors located at synapses is to convert the chemical signal of pre - synaptically released neurotransmitter directly and very quickly into a post - synaptic electrical signal.

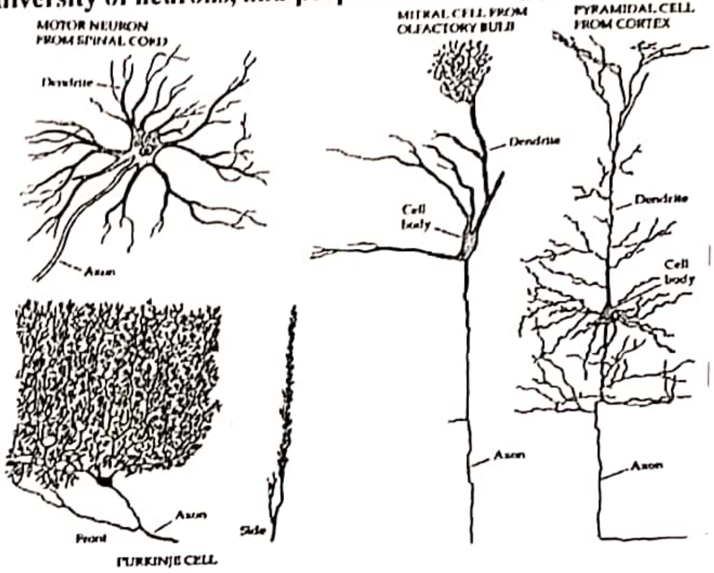
Many LICs are modulated by channel blockers, ions, or the membrane potential.

LICs are classified into three superfamilies which have no relationship: cys-loop receptors, ionotropic glutamate receptors and ATP-gated channels.



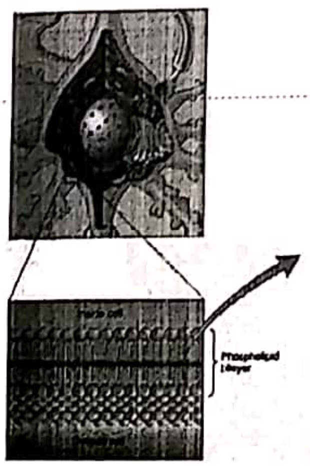
1) *Cell body*
2) *Axon*
3) *Apical dendrite*
4) *Basal dendrite*
5) *Synapses*

- **Neurons connect to each other via synapses**
- **Fast communication (a few milliseconds) occurs through Action Potentials**
- **Action Potentials release neurotransmitters at the synapse**
- **Neurotransmitters bind to "special gates" on the other side of the synapse and let in a "flood of charged particles" which start up a new electrical signal in the receiving neuron**
- **A bunch of neurons forming intricate connections allows us to think imaginatively**
- **There is a great diversity of neurons, and people are still struggling to classify them**



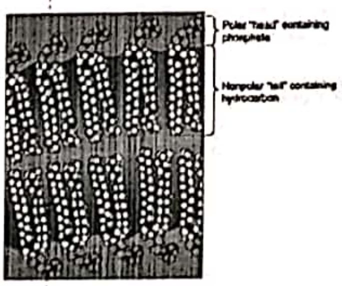
Electro-chemical properties of neurons

- **Membrane capacitance**

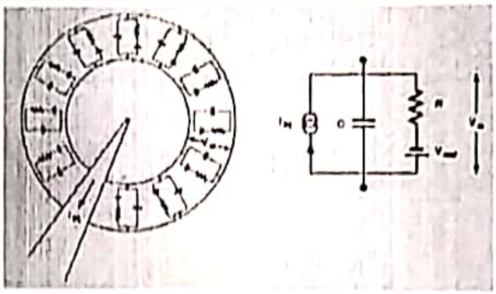


" parallel plate capacitor "

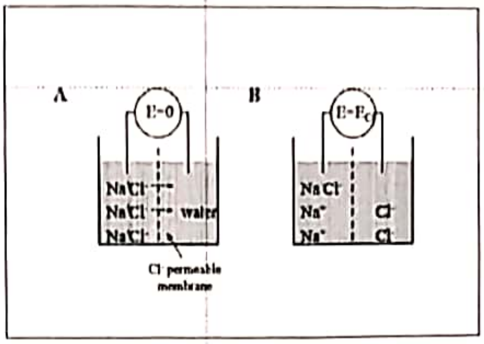
$$C = \frac{\varepsilon \varepsilon_0 A}{d}$$



- **Electrical circuit of a simple cell having:**
- **Capacitance *C***
- **Leak ion-channels R**
- **Membrane potential V_m** **[...keeping in mind that there are ions instead of electrons]**



- **Ions and electrochemical potentials:**
  (A) A Cl^- semi-permeable membrane separates a salty solution from water
  (B) As time passes, Cl^- diffuse, creating a potential difference



- **Nernst's equation for equilibrium potentials:**

$$E_{ion} = \frac{RT}{zF} \times \ln\left(\frac{[ion]_{out}}{[ion]_{in}}\right)$$

where z is the valence of the ion, R is the gas constant (8.315 J $K^{-1}mol^{-1}$), T is the temperature (K), F is Faraday's constant (96.485 C mol^{-1}) and $[ion]_o$ and $[ion]_i$ are the concentrations of the ion inside and outside of the cell respectively
The membrane potential of a simple cell can be calculated using this formula if the membrane is permeable only to one ion type.

- **Goldman-Hodgkin-Katz equation for equilibrium potentials:**
- **(generalization of Nernst's equation for membranes permeable to multiple ions simultaneously)**

$$V_m = \frac{RT}{F} \times \ln\left(\frac{\left(p_K\left[K^+\right]_o + p_{Na}\left[Na^+\right]_o + p_{Cl}\left[Cl^-\right]_i\right)}{\left(p_K\left[K^+\right]_i + p_{Na}\left[Na^+\right]_i + p_{Cl}\left[Cl^-\right]_o\right)}\right)$$

for example, the membrane relative permeability coefficients for the Squid Giant Axon are pK : pNa : pCl = 1.00 : 0.04 : 0.45 when the axon is at rest.

- Ion-channels: membrane-bound proteins conduct ions across the membrane are selective for certain ions they open/close in response to a wide range of stimuli:
  a) Electrical
  b) mechanical
  c) chemical
  d) thermal
  e) optical
  f) intracellular

1. **Ion-channels:**
2. **Leak-channels**
3. **Voltage-gated ion-channels**
4. **Ligand-gated ion-channels**
5. **Metabotropic ion-channels**

Ion channels are pore-forming membrane proteins that allow ions to pass through the channel pore. Their functions include establishing a resting membrane potential, shaping action potentials and other electrical signals by gating the flow of ions across the cell membrane, controlling the flow of ions across secretory and epithelial cells, and regulating cell volume.

Ion channels are present in the membranes of all cells.
Ion channels are one of the two classes of ionophoric proteins, the other being ion transporters.
The study of ion channels often involves biophysics, electrophysiology, and pharmacology, using techniques voltage clamp, patch clamp, immunohistochemistry, X-ray, crystallography, fluoroscopy, and RT-PCR.

Characteristics of ion channels

There are two characteristics of ion channels:-

1. The rate of ion transport through the channel is very high.
2. Ions pass through channels down their electrochemical gradient, which is a function of ion concentration and membrane potential.

Ion channels are located within the membrane.
They are narrow, water-filled tunnels that allow only ions of a certain size and charge to pass through. This is called selective permeability.
Some channels are permeable to the passage of more than one type of ion : positive (cations) or negative (anions).
In many ion channels, passage through the pore is governed by a "gate", which may be opened or closed in response to chemical or electrical signals, temperature, or mechanical force.
Ion channels are integral membrane proteins.

1. Voltage-gated ion channels.
2. Ligand gated ion channels.
3. Lipid gated ion channels.
4. Other Gated ion channels.

Classification of Ion channels on the basis of types of ions:-

1. Sodium ion channels.
2. Calcium ion channels.

Potassium ion channels.
Chlorine ion channels.

Toxins and Diseases

Toxins target ion channels e.g. voltage-gated sodium channel blocker which is produced by bacteria resident in blowfish.
Also a large number of therapeutic drugs like local anesthetics act directly or indirectly to modulate ion channel activity.
Inherited mutations in ion channel genes and in genes encoding proteins that regulate ion channel activity have been implicated in a number of diseases like diabetes mellitus and cardiac arrhythmias i.e. irregularities in heartbeat.

Role in research

Ongoing basic research on ion channels are to understand the structural basis for permeability, ion selectivity, and gating at the molecular level.
Researches are going on to study the cellular ion channel protein synthesis and degradation of channels.
Also compounds with greater importance for channels involved in pain, cardiovascular disease, and other pathological conditions are potential sources for drug development.