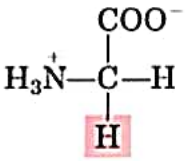
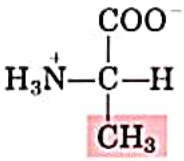
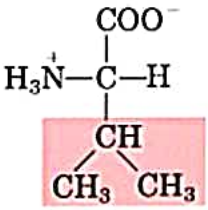
Nonpolar, aliphatic R groups



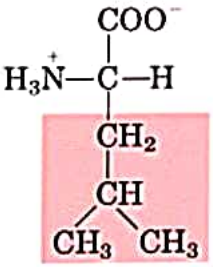
Glycine



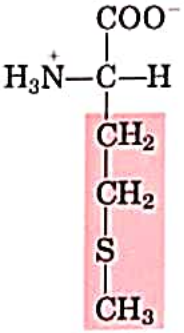
Alanine



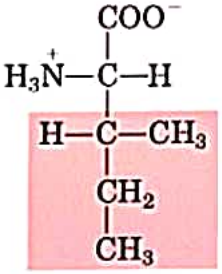
Valine



Leucine

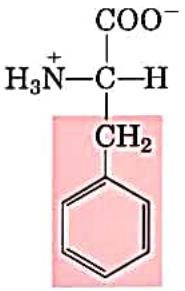


Methionine

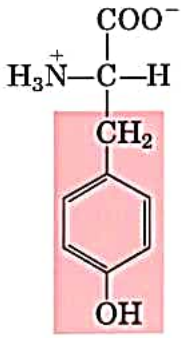


Isoleucine

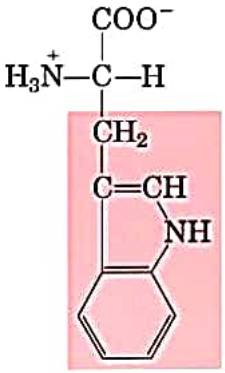
Aromatic R groups



Phenylalanine

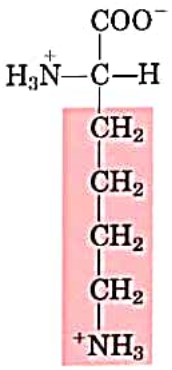


Tyrosine

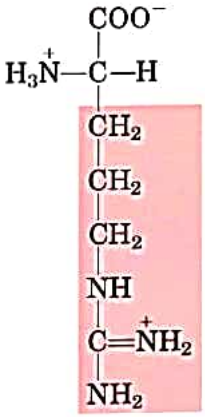


Tryptophan

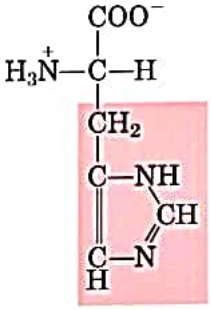
Positively charged R groups



Lysine

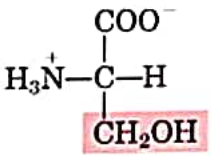


Arginine

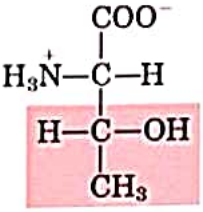


Histidine

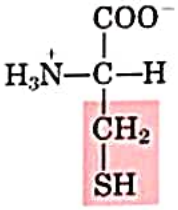
Polar, uncharged R groups



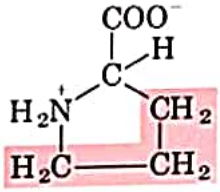
Serine



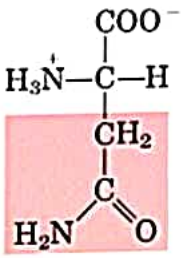
Threonine



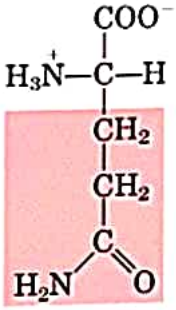
Cysteine



Proline

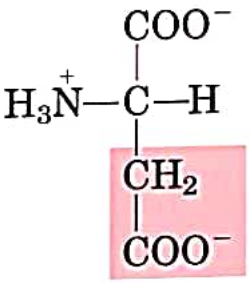


Asparagine

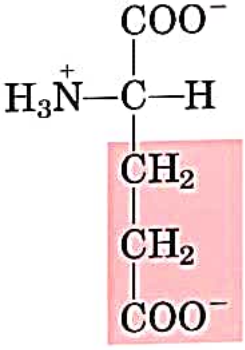


Glutamine

Negatively charged R groups



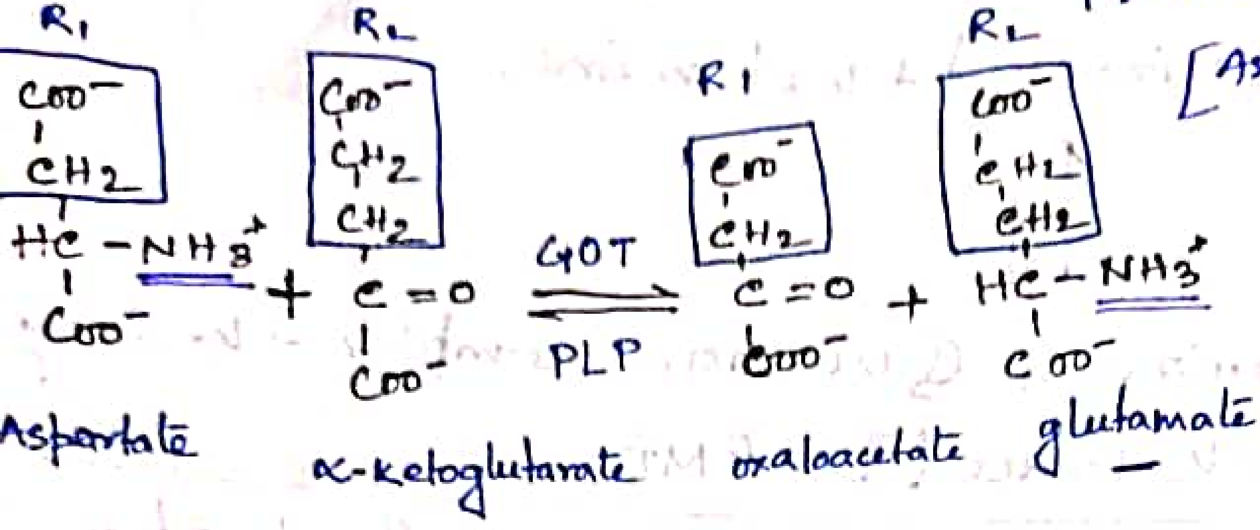
Aspartate



Glutamate

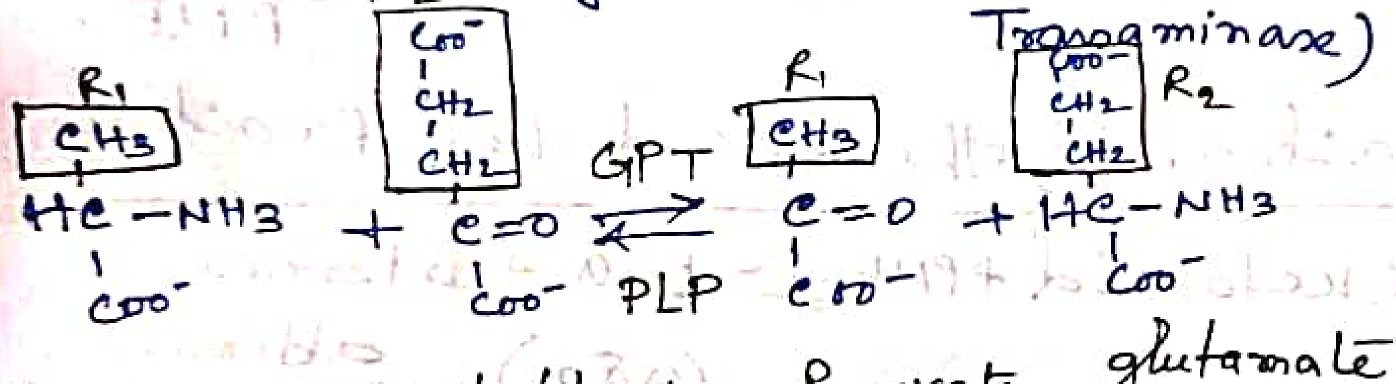
Trasamination

Trasamination by GOT (Glutamate oxaloacetate Trasaminase) [Aspartate trasaminase]



PLP is a B6 vitamin

- Trasamination by GPT (Glutamate Pyruvate Trasaminase)



* When B6 deficiant decrease trasaminase rate

* when lipid deposite in the heart tissue, and oxygen starvation occure, and degenerate the heart tissue called myocardial infection, aminotrasferase enzyme গুলো যখন heart cell থেকে blood এ বেরিয়ে আসে, তখন SGOT এবং SGPT tests করে দেখা হয় creatinine kinase এর concentration বাড়ছে। তাহলে heart damage hoyeche

is not followed by *US*, it soon ceases to elicit the response. This phenomenon is known as ***Extinction*** or ***Internal Inhibition***.

(ii) If the animal is disturbed by an external stimulus immediately after the *CS* is applied, the conditioned response may not occur. This is called ***External Inhibition***.

Thus the process of following up a *CS* with the basic *US* is termed ***reinforcement***.

6. Conditioned reflexes are difficult to form if the *US* proves *a pure motor response*; since the motor responses are also under voluntary control.
7. Conditioned reflexes are relatively easily formed if the US is associated with a pleasant or unpleasant effect. Here a repeated stimulus produces a greater response, a form of sensitization (page 892). For example,
   (i) Stimulation of the brain reward system is a powerful *US*; this is called *Pleasant* or ***positive reinforcement***; and
   (ii) Stimulation of the avoiding system or a painful shock to the skin is called *unpleasant* or ***negative reinforcement***.
8. ***Operant Conditioning***. *Operant* means to operate on the environment. This is a form of conditioning in which a naturally occuring response is strengthened by positive reinforcement (*reward*) or weakened by negative reinforcement (*punishment*). This is a classical example of simple form of learning based on phenomenon of *sensitization* and *habituation* (page 892). Experimentally, the animal is taught to perform some task in order to obtain a reward or avoid punishment. The *US* is the pleasant or unpleasant event, and the *CS* is a light or any signal that alerts the animal to perform the task.

   Conditioned motor responses that permit an animal to avoid an unpleasant event are called ***Conditioned Avoidance Reflexes***. For example, an animal is taught that by pressing a bar it can prevent an electric shock to the feet. Reflexes of this type are used mainly in testing tranquilizers and other drugs that affect behaviour.

Important Note

An alcoholic can be made to develop a strong aversion to alcohol if it is coupled to a drug that produces severe nausea or illness (*Food Aversion Conditioning*).

9. ***Discriminate Conditioning.*** When a conditioned reflex is first established, it can be produced not only by the *CS* but also by similar stimuli. However, if only one particular CS is reinforced and the similar stimuli are not, the animal can be taught to discriminate between different signals with great accuracy. This phenomenon is called *Discriminate Conditioning*.

Biochemical Basis of Conditioned Reflex

The biochemical events involved in synaptic plasticity (habituation, sensitization, post-tetanic potentiation and long-term potentiation) are described on page 891.

In conditioned reflex, the unconditioned stimulus (US) acts presynaptically on the endings of neurons activated by the conditioned stimulus (CS). This leaves free Ca^{2+} in the cell resulting in long-term change in the adenylate cyclase molecule, therefore, when this enzyme is activated by the CS, more cAMP is produced. This in turn closes K^+ channels and prolongs action potentials.

Physiological Basis of Conditioned Reflexes

One of the essential features of a conditioned reflex is the formation of a new functional connection in the nervous system. This may be caused by specific *nerve growth factors* released from the stimulated cells. For example, in *Pavlov classical experiments*, salivation in response to a bell ringing indicates that a functional connection has developed between the auditory pathways and the autonomic centers controlling salivation.

Site of formation of functional connections

The site of formation of new connection in the nervous system occurs at two levels:

1. intracortical level (mainly), and
2. subcortical level.

Evidences

(i) Conditioned reflexes can be built up with difficulty in decorticate animals.

(ii) When the *CS* is a complex sensory stimulus, the cortical sensory area for the sensory modality involved must be present.

(iii) Non-discriminative conditioned reflexes to simple sensory stimuli can be formed in the absence of the whole neocortex. This indicates that new functional connections can be formed at sub-cortical levels.

Important Note

The phenomenon resembling learning occurs at subcortical and spinal levels (synaptic plasticity - page 891); whereas more advanced type of learning, such as discriminating conditioning, are largely cortical phenomenon.

Clinical significance

1. By means of discriminative conditioning, dogs can

be taught to distinguish between different pitches of sounds, different colours, smells and other sensory modalities.

2. A large number of somatic, visceral and other neural changes can be made to occur as conditioned reflex responses. The conditioning of visceral responses is called ***Biofeedback***. The changes that can be produced include alteration in bowel movements, heart rate and blood pressure. Conditioned decrease in BP has been used for the treatment of hypertension.
3. The words like *Hare Rama* are associated with mental calmness, bliss and purity and so the emotions disappear. *Hare*, i.e. Haran means removal of grief; *Rama* i.e. attraction. (He also removes grief, is supreme attractor, the god.) Therefore, the words *Hare Rama* are the *CS* for control of rage (page 1072) (which is normally not easy to control).

Intercortical Transfer of Learning

1. If animals (cats/monkeys) are conditioned to respond to a visual stimulus with one eye covered and then tested with the blind fold transferred to the other eye, it performs the conditioned response. This is true even if the optic chiasma has been cut, making the visual input from each eye to go only to the ipsilateral cortex. However, if in addition, anterior and posterior commissures and corpus callosum are sectioned *(Split Brain Animal)*, **no** transfer of learning occurs. This demonstrates that the neural coding necessary for learning and memory has been transferred somehow to the opposite cortex via the commissures.
2. Similar results are seen in humans in whom either corpus callosum is congenitally absent or it has been sectioned surgically to control epileptic seizures (fits).

(Also refer to page 925 for *cortical plasticity*)

4, 6 and 8) and their connections.

LEARNING: CONDITIONED REFLEXES

The ability to alter behaviour on the basis of experience is called ***learning***.

Conditioned reflexes are an important type of learning. Two separate classes of reflexes are described by *Pavlov. I.P.* (1927) (of Russia): *inborn and acquired.*

The Inborn or **Unconditioned Reflex**. This reflex is present in all normal individuals, such as superficial, deep (or tendon) and organic reflexes.

Examples:

(i) *Superficial reflexes:* plantar and abdominal reflex (page 912),

(ii) *Deep (or tendon) reflexes:* knee and biceps jerk (page 904), and

(iii) *Organic reflexes:* deglutition (swallowing), defecation, sucking, grasping and micturition reflex.

The Acquired or Conditioned Reflex

Features

1. It is a *reflex response* to a stimulus that did not previously produce the response; however, it can be developed (acquired) by repeatedly pairing the stimulus with another stimulus that normally does produce the response.
2. It is, therefore, *peculiar* to the individual and refers to the fact that certain conditions must be present if this class of response is to develop.
3. It depends for its appearance on the formation of new functional connections in the CNS.

Example: **Pavlov's classical dog experiment** (Fig. 11.105.4).

(i) The introduction of food (***unconditioned stimulus***) into the mouth sets up *reflex* salivation in a dog. This is called ***unconditioned reflex***.

(ii) Application of a *neutral* stimulus like ringing of a bell alone produces *no* salivation.

(iii) Application of ringing of a bell just before the unconditioned stimulus (the taking of food) produces salivation. If this procedure is repeated several times, the ringing of a bell alone produces salivation. Therefore, the *initial* neutral stimulus finally develops (acquires) fresh properties i.e. new connections in the CNS and can now by itself produce salivation.

In this example, the flow of saliva in response to ringing of the bell (***conditioned stimulus***) is referred to as ***conditioned reflex***.

Mechanism of Development of Conditioned Reflex

The conditioned reflexes are always built up primarily on the basis of *inborn reflexes*. Habituation and sensitization (page 892) are simple form of learning in which the organism learns about a single stimulus. A classic example of such type of learning is a conditioned reflex. In more complex form of learning, the organism learns about the relation of one stimulus to another by means of 'synaptic plasticity' in the brain (page 891).

Factors which influence conditioned reflex to develop are:

1. The animal must be alert and in good health.
2. For conditioning to occur, the *conditioned stimulus (CS)* must begin to operate before the *unconditioned stimulus (US)* is applied. If the *CS* follows the *US*, no conditioned response develops.
3. The *CS* must be allowed to continue to act so as to overlap the *US*. Almost any stimulus, if suitably employed, may become a *CS*.
4. The conditioned response follows *CS* by the time the interval that separated the CS and US during trainnig. The delay between stimulus and response may be as long as 90 secs. When the time interval is more than 90 secs, the response is called as ***Delayed Conditioned Reflex***.
5. ***Necessity for Reinforcement***

   For a *CS* to retain its new properties, it is essential that it should always be followed by the *US*. Therefore,

   (i) If the *CS* is carried out several times alone and

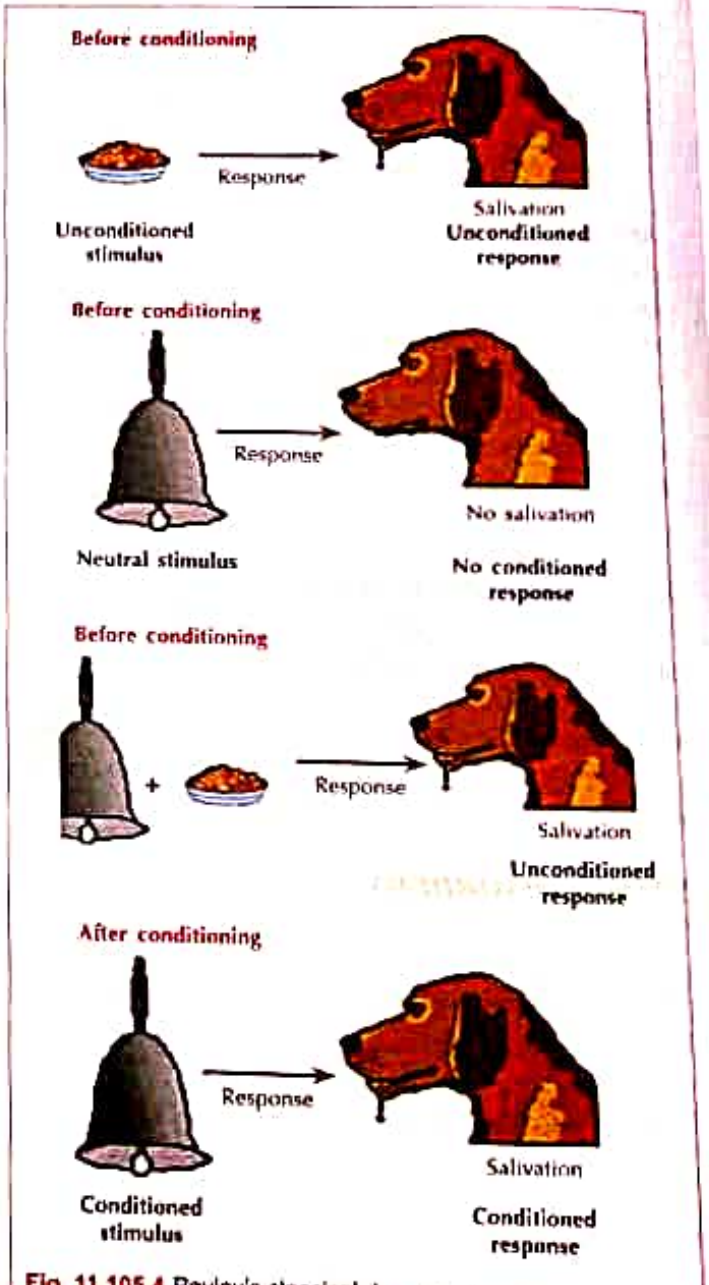


Fig. 11.105.4 Pavlov's classical dog experiment

(p. 163). EPP leads to formation of current sink (Fig. 5.22) and flow of charges from the adjacent parts of the muscle membrane, *i.e.*, sarcolemma. Therefore the MP in the adjacent sarcolemma decreases and when the firing potential is reached, it fires. Thus, an AP is formed in the muscle membrane and then travels in all direction. (AP in the motor nerve ending→Ca^{2+} entry→exocytosis of Ach→attachment with the receptors→ Na^+ entry→EPP→AP in the sarcolemma.)

The arrangement is such that a nerve impulse leads to release of a specific quantity of Ach which combines with sufficient number of receptors and leads to development of an EPP which can form AP in the muscle membrane.

The foldings in the end plate are essential for transmission as these help the Ach to act on a wide surface and to combine with large number of receptors. A given amount of Ach if injected by micropipette in one place on the end plate, fails to stimulate the muscle, as sufficient receptors are not involved. But the same amount of Ach, when applied by a brush over a wider area of the end plate, can stimulate the muscle.

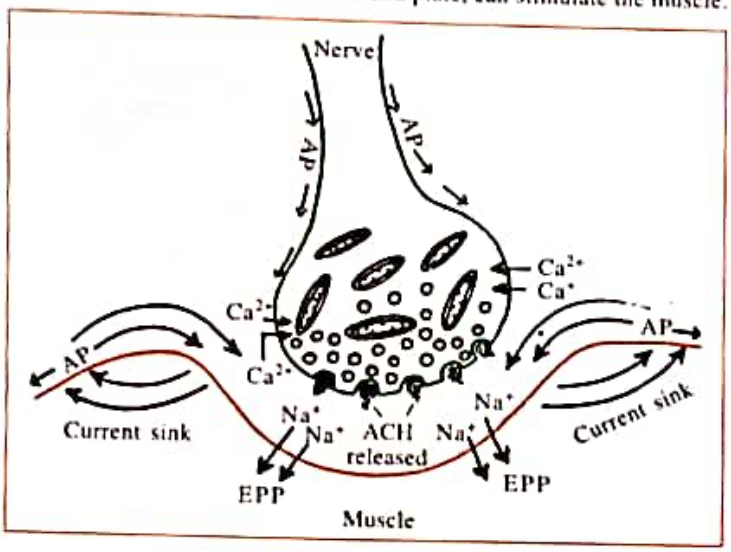


Fig. 5.22. *Neuromuscular transmission.*

If the amount of Ach released is less, the EPP developed dies locally and the muscle is not stimulated. One such EPP is called *miniature end plate potential* (MEPP) which develops normally in the motor end plate even in absence of nerve impulse. This is due to spontaneous release of small quantities of Ach (quantal release, quantum = smallest unit of energy) from the nerve ending. The Ach released in the junction is quickly destroyed after its action is over by the enzyme **cholinesterase** present locally and the receptors are kept free for combination with the Ach released in subsequent transmission.

Factors affecting Transmission

The factors which affect the neuromuscular transmission act at three levels. These are :

(i) the release of Ach,
(ii) destruction of Ach (*i.e.*, on cholinesterase), and
(iii) the Ach receptors.

Release of Ach

Release of Ach should be sufficient. If the amount is less there will be no muscle contraction. Summation may occur if another amount is released while the Ach released previously is still active. Ach release is prevented by botulinum toxin (the toxin produced by the bacteria, clostridium botulinum involved in food poisoning) which may lead to stoppage of neuromuscular transmission and even death.

Destruction of Ach

Normally Ach released at the junction is destroyed by the enzyme cholinesterase. If this does not occur, Ach accumulates and keeps the channels continuously open. It results in a continuous depolarisation, so, subsequent transmissions cannot occur and **depolarisation block** results.

This type of block of transmission is caused by agents like physostigmine, neostigmine, etc. Organophosphorus compounds like dyflos, parathion, etc., act in the same way but unlike the former group these agents cause permanent inactivation of the enzyme and ultimately death. Some compounds like carbachol, bethanichol, methacholine, etc. behave as Ach but these are destroyed very slowly. So, these compounds cause a persistent depolarisation. All these compounds, which cause depolarising block, lead to an initial strong muscle contraction (convulsion) and then paralysis.

Ach receptor

As stated above, for normal transmission to occur, sufficient number of receptors are needed. These receptors are decreased in **myasthenia gravis**, a crippling disease of muscle. This disease occurs due to formation of antibodies against nicotinic Ach receptors in the neuromuscular junction and subsequent destruction of these Ach receptors. So, neuromuscular transmission fails to occur; as a result, muscle contraction and thus the ability for movement is severely jeopardised.

Lambert-Eaton syndrome : It is a disease characterised by muscle weakness due to less Ach release from the motor nerve ending. It occurs due to less Ca^{2+} entry due to antibodies against some Ca^{2+} channels present here.

Some chemicals also lead to a decrease in the number of the effective receptors. These compounds have structural similarity with Ach and combine with the receptors but without depolarisation of the muscle. As the receptors are blocked, Ach cannot combine, so there is no transmission. The α-bungarotoxin present in snake venom (cobra group) acts in this way and leads to death. The famous arrow-head poison **curare**, once used by the natives of South America acts by blocking the Ach receptors in neuromuscular junction. Gallamine a synthetic drug also acts like curare.

Applied Physiology

Different chemicals as discussed above are used in treatment and also used in other causes (nerve gas, pesticides). The curare derivatives (the active compound of curare is called d-tubocurarine) are used as muscle relaxants. Prostigmine, neostigmine, etc., are used in the treatment of snake bite, myasthenia gravis, etc., *i.e.*, in diseases where either the receptors are blocked or are decreased in number. These agents help Ach to accumulate and to act through whatever amount of receptors is available.

Agents influencing neuromuscular transmission

(1) Which interfere Ach synthesis :
  Hemicholinium, triethylcholine.
(2) Which interfere release of Ach :
  Botulinum toxin, streptomycin.
(3) Which interfere the action of Ach :
  (a) Receptor blockers : Tubocurarine, gallamine.
  (b) Receptor stimulators : Decamethonium, suxamethonium.
(4) Which interfere cholinesterase activity :
  (a) Edrophonium. } Reversibly
  (b) Neostigmine, physostigmine. }
  (c) Dyflos, parathion : Irreversibly.

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Description

The somatic motor nerve which is going to supply a skeletal muscle breaks up into several branches (axon terminals) (Fig. 5.21A). Each terminal supplies one muscle fibre. The end of the terminal is swollen like a bulb **(terminal button/synaptic knob)** which fits into a depression on the muscle cell. The synaptic knobs contain acetylcholine (Ach) stored in clear vesicles. The related part of the muscle membrane (sarcolemma) is thickened and is called **motor end plate** which contains receptors for Ach. The motor end plate is folded to form the **junctional folds** (Fig. 5.21B). This folding increases the area of the motor end plate, so that it can accommodate sufficient number of Ach receptors (ligand-gated channels) for the transmission of the impulse. The space inside the junction, in between the nerve membrane and muscle membrane is called neuromuscular cleft or synaptic cleft.

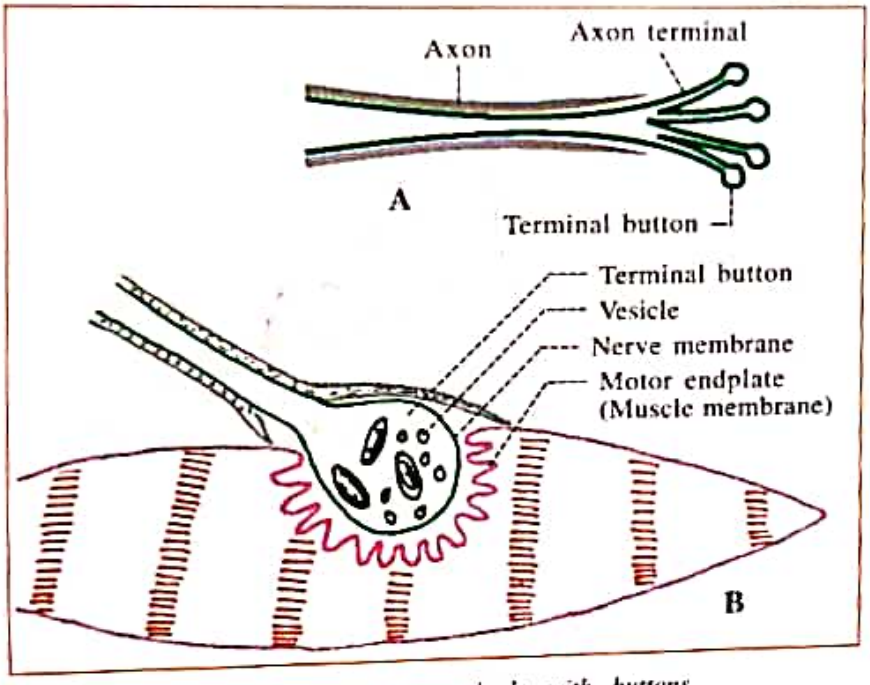
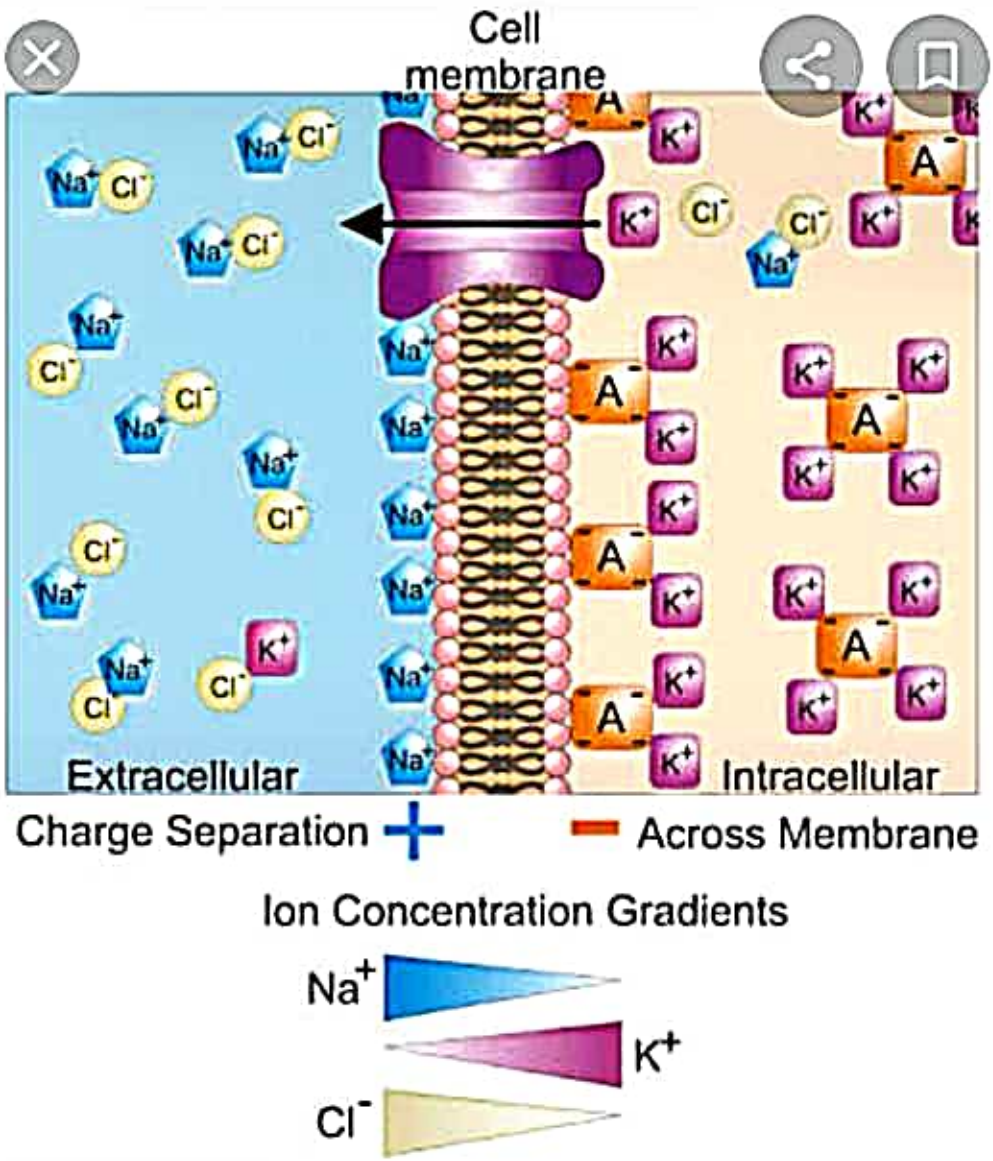


Fig. 5.21A. *Axon terminals with buttons.*
B. *Myoneural junction.*

Transmission

When a nerve impulse travels down the motor nerve up to its endings, there is Ca^{2+} entry into the synaptic knob. This is because of opening of voltage-gated Ca^{2+} channels by the AP. This Ca^{2+} leads to exocytosis of the vesicles through involvement of several proteins in the vesicular membrane as well as in the cell membrane and release of Ach into the synaptic cleft (Fig. 5.22). Ach molecules then cross the synaptic cleft within a millisecond or so and attach to the Ach receptors on the motor end plate. This combination leads to opening of channels in the centre of each receptor through which Na^+ enters into the muscle cell. All smaller ions like K^+ can also pass through but entry of Na^+ is quickest due to its higher inward gradient at RMP. (It may be recalled that inside of the cell is negative and has very low $[Na^+]$). Thus Na^+ enters both due to electrical and concentration gradient. This Na^+ entry leads to a local response, called **end plate potential (EPP)**, which means a change of MP of the end plate (muscle membrane) towards depolarisation. EPP is a local response



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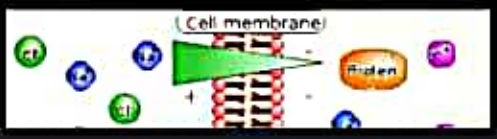

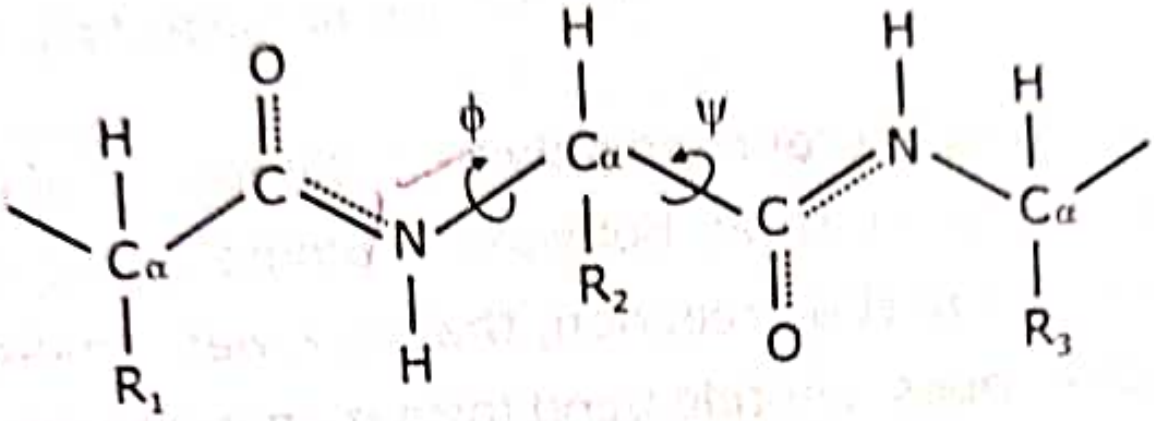

of adjacent amino acid residues are separated by thr
e peptide C—N bonds, because of their partial double-bor
tted about the N—C_α and the C_α—C bonds.

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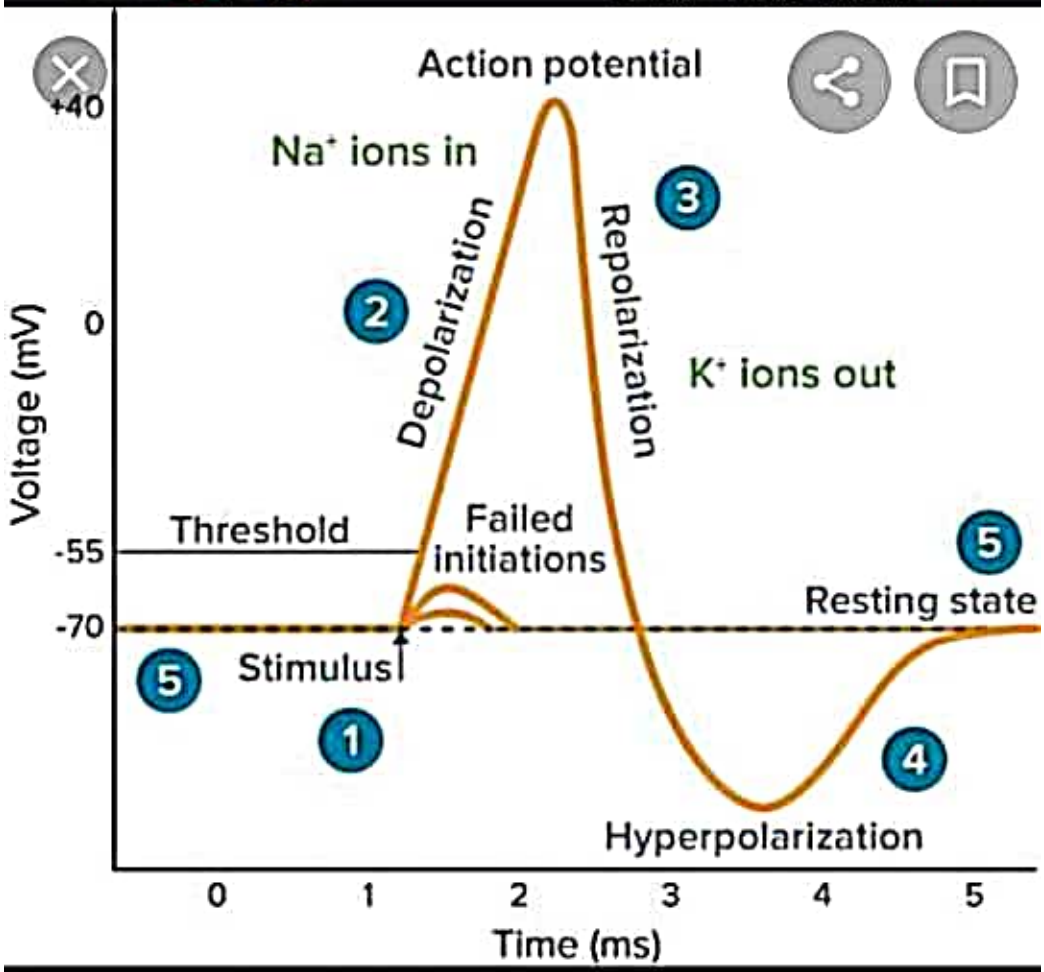

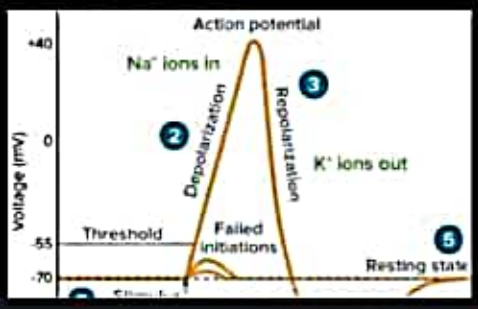

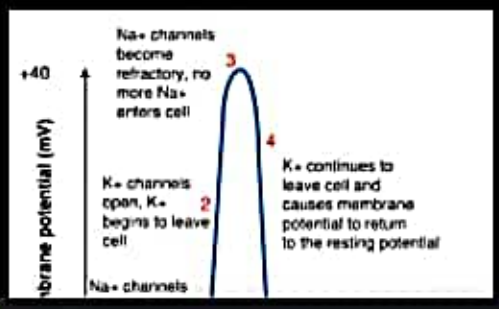

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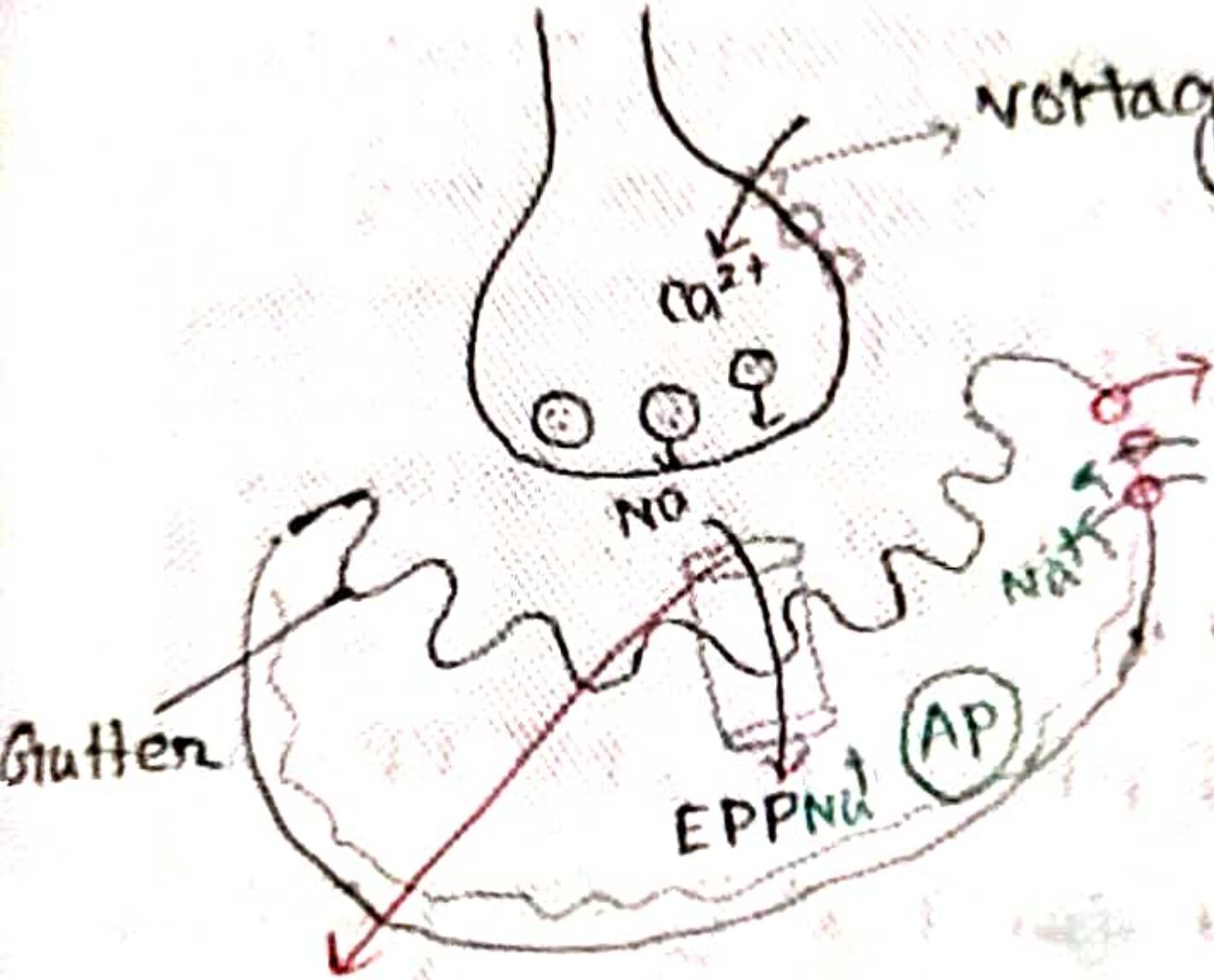

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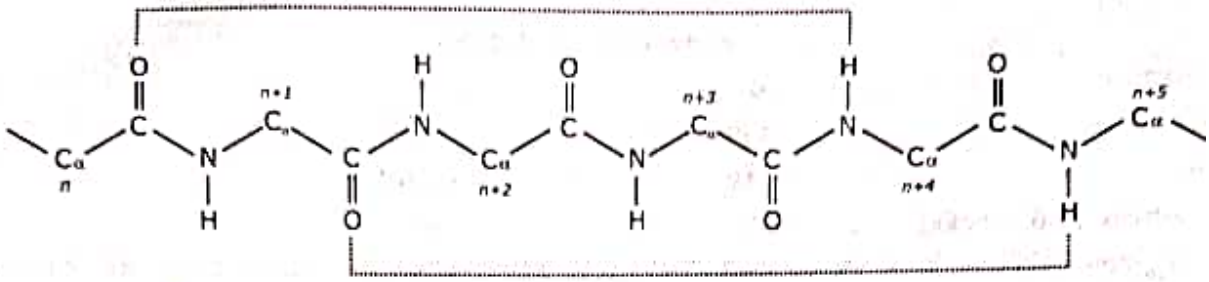
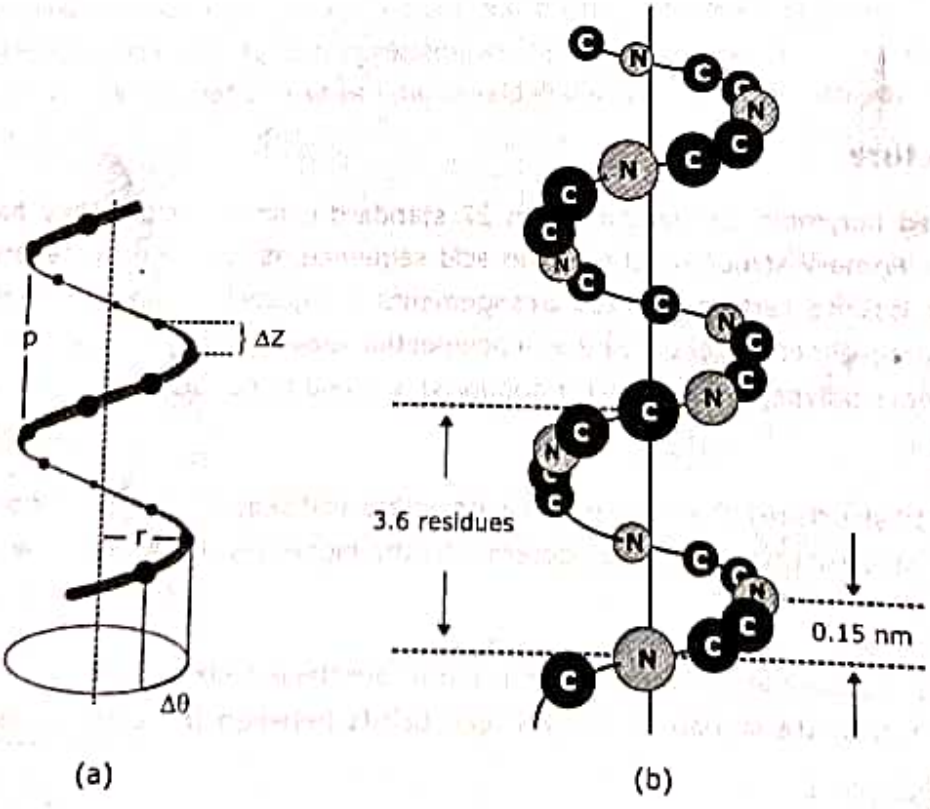


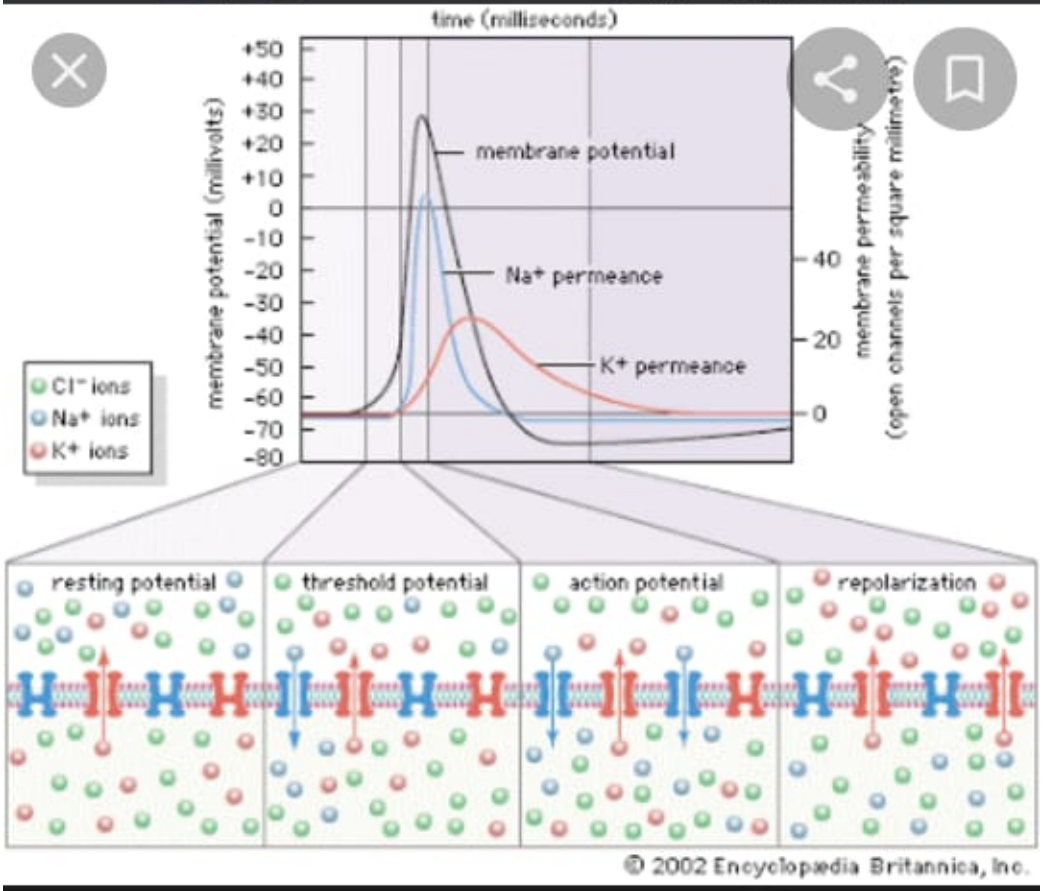
Figure 1.15 The hydrogen bonding arrangement in the α-helix.

for amino acids near the ends of an α-helix, all the main-chain CO and NH groups are hydrogen
ains of amino acids extend outward from the helix. All H bonds lie parallel to the helix axis and
direction.

s can be formed from either D- or L-amino acids, but a given helix must be composed entirely of
configuration. The α-helix cannot be formed from a mixed copolymer of D- and L-amino acids. L
rm either right or left handed α-helices.



re 1.16 (a) *Describing the geometry of α-helix*. The helix structure is defined by: the *pitch*, P (the
g the axis between successive turns), the radius, r, and the rise per residue, ΔZ. The number of
turn is equal to p/ΔZ. The angular difference between successive residues, Δθ=360
The right handed α-helix. A complete turn of the helix contains an average of 3.6 aminoacyl
the distance it rises per turn (its pitch) is 0.54 nm. The R groups of each aminoacyl residue in a
outward (not shown in the figure). In the α-helix the hydrogen bonds
n and are



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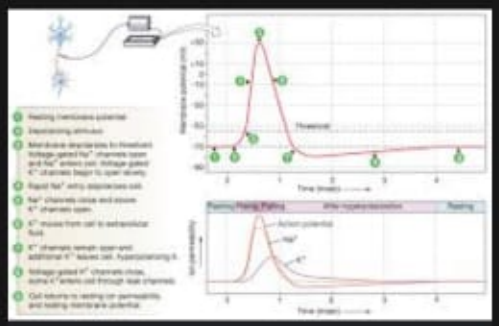
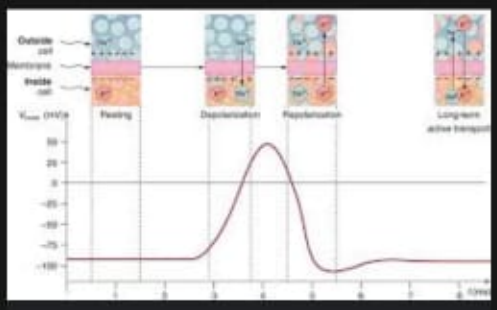


Action Potential Stages: Over...



Nerve Conduction–Electrocar...

Another important characteristic of the sodium channel inactivation process is that the inactivation gate will not reopen until the membrane potential returns to or near the original resting membrane potential level. Therefore, it is usually not possible for the sodium channels to open again without first repolarizing the nerve fiber.

Voltage-Gated Potassium Channel and Its Activation

The lower panel of Figure 9-2 shows the voltage-gated potassium channel in two states: during the resting state (left) and toward the end of the action potential (right). During the resting state, the gate of the potassium channel is closed and potassium ions are prevented from passing through this channel to the exterior. When the membrane potential rises from −90 millivolts toward zero, this voltage change causes a conformational opening of the gate and allows increased potassium diffusion outward through the channel. However, because of the slight delay in opening of the potassium channels, for the most part, they open just at the same time that the sodium channels are beginning to close because of inactivation. Thus, the decrease in sodium entry to the cell and the simultaneous increase in potassium exit from the cell combine to speed the repolarization process, leading to full recovery of the resting membrane potential within another few 10,000ths of a second.

Research Method for Measuring the Effect of Voltage on Opening and Closing of the Voltage-Gated Channels—the "Voltage Clamp"

The original research that led to quantitative understanding of the sodium and potassium channels was so ingenious that it led to Nobel Prizes for the scientists responsible, Hodgkin and Huxley. Figure 9-3 shows an experimental apparatus called a *voltage clamp*, which is used to measure flow of ions through the different channels. Two electrodes are inserted into the nerve fiber. One of these is to measure the voltage of the membrane potential, and the other is to conduct electrical current into or out of the nerve fiber. The investigator decides which voltage he or she wants to establish inside the nerve fiber. The electronic portion of the apparatus is then adjusted to the desired voltage, and this automatically injects either positive or negative electricity through the current electrode at whatever rate is required to hold the voltage, as measured by the voltage electrode, at the level set by the operator. When the membrane potential is suddenly increased by this voltage clamp from −90 millivolts to zero, the voltage-gated sodium and potassium channels open and sodium and potassium ions begin to pour through the channels. To counterbalance the effect of these ion movements on the desired setting of the intracellular voltage, electrical current is injected automatically through the current electrode of the voltage clamp to maintain the intracellular voltage at the required steady zero level. To achieve this, the current injected must be

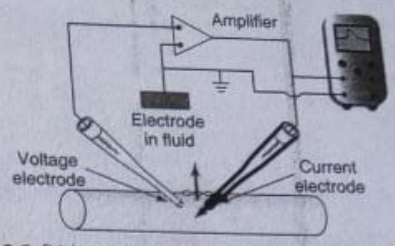


Figure 9-3 "Voltage clamp" method for studying flow of ions through specific channels.

equal to but of opposite polarity to the net current flow through the membrane channels. To measure how much current flow is occurring at each instance, the current electrode is connected to an oscilloscope that records the current flow, as demonstrated on the screen of the oscilloscope in Figure 9-3. Finally, the investigator adjusts the concentrations of the ions to other than normal levels both inside and outside the nerve fiber and repeats the study. This can be done easily when using large nerve fibers removed from some invertebrates, especially the giant squid axon, which in some cases is as large as 1 millimeter in diameter.

Another means for studying the flow of ions through an individual type of channel is to block one type of channel at a time. For instance, the sodium channels can be blocked by a toxin called *tetrodotoxin* by applying it to the outside of the cell membrane where the sodium activation gates are located. Conversely, *tetraethylammonium ion* blocks the potassium channels when it is applied to the interior of the nerve fiber.

Summary of the Events That Cause the Action Potential

Figure 9-4 shows, in summary form, the sequential events that occur during and shortly after the action potential. The bottom of the figure shows the changes in membrane conductance for sodium and potassium ions. During the resting state, before the action potential begins, the conductance for potassium ions is 50 to 100 times as great as the conductance for sodium ions. This is caused by much greater leakage of potassium ions than sodium ions through the leak channels. However, at the onset of the action potential, the sodium channels instantaneously become activated and allow up to a 5000-fold increase in sodium conductance. Then the inactivation process closes the sodium channels within another fraction of a millisecond. The onset of the action potential also causes voltage gating of the potassium channels, causing them to begin opening more slowly a fraction of a millisecond after the sodium channels open. At the end of the action potential, the return of the membrane potential to the negative state causes the potassium channels to close back to the

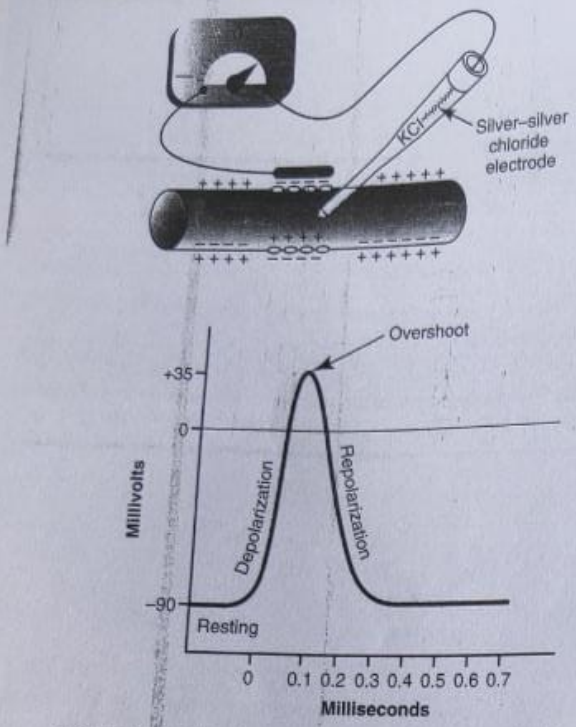


Figure 9-1 Typical action potential recorded by the method shown in the upper panel of the figure.

characteristics of two other types of transport channels through the nerve membrane: the voltage-gated sodium and potassium channels.

Rectification. The return of the membrane to its original ionic state is achieved through the continued action of the sodium–potassium electrogenic pump.

Voltage-Gated Sodium and Potassium Channels

The necessary factor in causing both depolarization and repolarization of the nerve membrane during the action potential is the *voltage-gated sodium channel.* A *voltage-gated potassium channel* also plays an important role in increasing the rapidity of repolarization of the membrane. *These two voltage-gated channels are in addition to the Na^+–K^+ pump and the K^+ leak channels.*

Voltage-Gated Sodium Channel—Activation and Inactivation of the Channel

The upper panel of Figure 9-2 shows the voltage-gated sodium channel in three separate states. This channel has two *gates*—one near the outside of the channel called the *activation gate* and another near the inside called the *inactivation gate.* The upper left of the figure depicts the state of

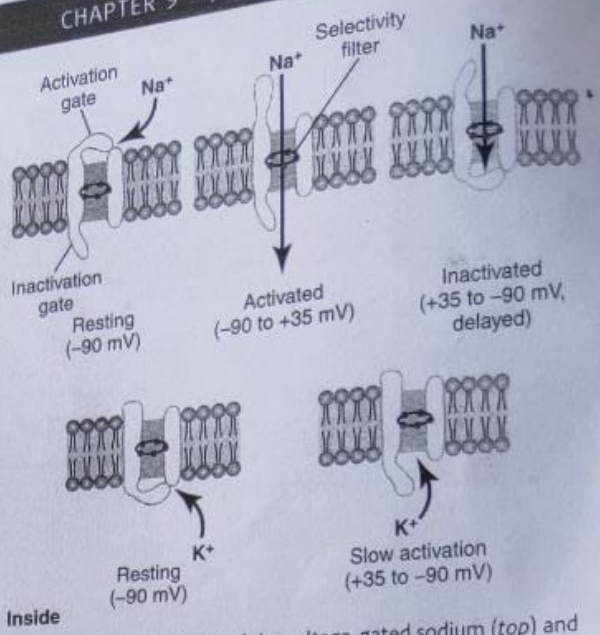


Figure 9-2 Characteristics of the voltage-gated sodium (*top*) and potassium (*bottom*) channels showing successive activation and inactivation of the sodium channels and delayed activation of the potassium channels when the membrane potential is changed from the normal resting negative value to a positive value.

these two gates in the normal resting membrane when the membrane potential is −90 millivolts. In this state, the activation gate is closed, which prevents any entry of sodium ions to the interior of the fiber through these sodium channels.

Activation of the Sodium Channel

When the membrane potential becomes less negative than during the resting state, rising from −90 millivolts toward zero, it finally reaches a voltage—usually somewhere between −70 and −50 millivolts—that causes a sudden conformational change in the activation gate, flipping it all the way to the open position. This is called the *activated state;* during this state, sodium ions can pour inward through the channel, increasing the sodium permeability of the membrane as much as from 500- to 5000-fold.

Inactivation of the Sodium Channel

The upper right panel of Figure 9-2 shows a third state of the sodium channel. The same increase in voltage that opens the activation gate also closes the inactivation gate. The inactivation gate, however, closes a few 10,000ths of a second after the activation gate opens. That is, the conformational change that flips the inactivation gate to the closed state is a slower process than the conformational change that opens the activation gate. Therefore, after the sodium channel has remained open for a few 10,000ths of a second, the inactivation gate closes, and sodium ions no longer can pour to the inside of the membrane. At this point, the membrane potential begins to recover back toward the resting membrane state, which is the repolarization process.

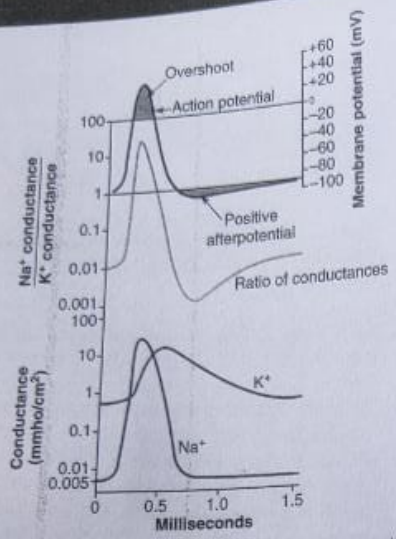


Figure 9-4 Changes in sodium and potassium conductance during the course of the action potential. Sodium conductance increases several thousand-fold during the early stages of the action potential, whereas potassium conductance increases only about 30-fold during the latter stages of the action potential and for a short period thereafter. (These curves were constructed from theory presented in papers by Hodgkin and Huxley but transposed from squid axon to apply to the membrane potentials of large mammalian nerve fibers.)

original status, but again, only after an additional millisecond or more delay.

The middle portion of Figure 9-4 shows the ratio of sodium conductance to potassium conductance at each instance during the action potential, and above this is the action potential itself. During the early portion of the action potential, the ratio of sodium to potassium conductance increases more than 1000-fold. Therefore, far more sodium ions flow to the interior of the fiber than do potassium ions to the exterior. This is what causes the membrane potential to become positive at the onset of action potential. Then the sodium channels begin to close and the potassium channels begin to open, so the ratio of conductance shifts far in favor of high potassium conductance but low sodium conductance. This allows very rapid loss of potassium ions to the exterior but virtually zero flow of sodium ions to the interior. Consequently, the action potential quickly returns to its baseline level.

Roles of Other Ions During the Action Potential

Thus far, we have considered only the roles of sodium and potassium ions in the generation of the action potential. At least two other types of ions must be considered: chloride anion and calcium ions.

Increased Permeability of the Sodium Channels When There is a Deficit of Calcium Ions. The concentration of calcium ions in the extracellular fluid also has a profound effect on the voltage level at which the sodium channels become activated. When there is a deficit of calcium ions, the sodium channels become activated (opened) by a small increase of the membrane potential from its normal, very negative level. Therefore, the nerve fiber becomes highly excitable, sometimes discharging repetitively without provocation rather than remaining in the resting state. In fact, the calcium ion concentration needs to fall only 50% below normal before spontaneous discharge occurs in some peripheral nerves, often causing *muscle "tetany."* This is sometimes lethal because of tetanic contraction of the respiratory muscles.

The probable way in which calcium ions affect the sodium channels is as follows: These ions appear to bind to the exterior surfaces of the sodium channel protein molecule. The positive charges of these calcium ions in turn alter the electrical state of the sodium channel protein itself, in this way altering the voltage level required to open the sodium gate.

Initiation of the Action Potential

Up to this point, we have explained the changing sodium and potassium permeability of the membrane, as well as the development of the action potential itself, but we have not explained what initiates the action potential.

A Positive-Feedback Cycle Opens the Sodium Channels. First, as long as the membrane of the nerve fiber remains undisturbed, no action potential occurs in the normal nerve. However, if any event causes enough initial rise in the membrane potential from −90 millivolts toward the zero level, the rising voltage itself causes many voltage-gated sodium channels to begin opening. This allows rapid inflow of sodium ions, which causes a further rise in the membrane potential, thus opening still more voltage-gated sodium channels and allowing more streaming of sodium ions to the interior of the fiber. This process is a positive-feedback cycle that, once the feedback is strong enough, continues until all the voltage-gated sodium channels have become activated (opened). Then, within another fraction of a millisecond, the rising membrane potential causes closure of the sodium channels and opening of potassium channels and the action potential soon terminates.

Threshold for Initiation of the Action Potential. An action potential will not occur until the initial rise in membrane potential is great enough to create the positive feedback described in the preceding paragraph. This occurs when the number of Na^+ ions entering the fiber becomes greater than the number of K^+ ions leaving the fiber. A sudden rise in membrane potential of 15 to 30 millivolts is usually required. Therefore, a sudden increase in the membrane potential in a large nerve fiber from −90 millivolts up

9 Action Potential of the Nerve

Learning Objectives

- Draw and label a typical nerve action potential.
- Describe the ionic basis of each of the phases.
- List the differences between the action potential and a local potential.
- Define refractory period and differentiate between absolute and relative refractory period.

Glossary of Terms

Depolarization A change in the resting membrane potential toward zero as a result of the influx of positive ions into the cell.

Repolarization The process by which the cell membrane potential is returned to its resting state after excitation.

Hyperpolarization A membrane potential that is even more negative than the potential at rest (in an unexcited state).

Threshold stimulus The minimum stimulus that results in the generation of an action potential.

Action potential The electrical response of the membrane to a threshold or greater than threshold stimulus.

Local response (potential) The potential that is developed at the cell membrane in response to a subthreshold stimulus.

Absolute refractory period The period during the action potential where the nerve cannot respond to a second stimulus, no matter how strong it is.

Relative refractory period The period during the action potential where the nerve can respond to a second stimulus, provided it is greater than threshold strength.

Nerve signals are transmitted by *action potentials*, which are rapid changes in the membrane potential that spread rapidly along the nerve fiber membrane. Each action potential begins with a sudden change from the normal resting negative membrane potential to a positive potential and then ends with an almost equally rapid change back to the negative potential. The duration of the nerve action potential as indicated in Figure 9-1 is 0.3 millisecond. To conduct a nerve signal, the action potential moves along the nerve fiber until it comes to the fiber's end.

The upper panel of Figure 9-1 shows the changes that occur at the membrane during the action potential, with transfer of positive charges to the interior of the fiber at its onset and return of positive charges to the exterior at its end. The lower panel shows graphically the successive changes in membrane potential over a few 10,000ths of a second, illustrating the explosive onset of the action potential and the almost equally rapid recovery.

The successive stages of the action potential are as follows.

Resting Stage. This is the resting membrane potential before the action potential begins. The membrane is said to be "polarized" during this stage because of the −90 millivolts negative membrane potential that is present.

Depolarization Stage. At this time, the membrane suddenly becomes permeable to sodium ions, allowing tremendous numbers of positively charged sodium ions to diffuse to the interior of the axon. The normal "polarized" state of −90 millivolts is immediately neutralized by the inflowing positively charged sodium ions, with the potential rising rapidly in the positive direction. This is called *depolarization*. In large nerve fibers, the great excess of positive sodium ions moving to the inside causes the membrane potential to actually "overshoot" beyond the zero level and to become somewhat positive. In some smaller fibers, as well as in many central nervous system neurons, the potential merely approaches the zero level and does not overshoot to the positive state.

Repolarization Stage. Within a few 10,000ths of a second after the membrane becomes highly permeable to sodium ions, the sodium channels begin to close and the potassium channels open more than normal. Then, rapid diffusion of potassium ions to the exterior re-establishes the normal negative resting membrane potential. This is called *repolarization* of the membrane.

To explain more fully the factors that cause both depolarization and repolarization, we will describe the special

Table 9-1 Differences Between a Local Potential and an Action Potential

	Local Potential	Action Potential
Nature of stimulus	Subthreshold	Threshold or suprathreshold
Type of potential change	Graded; depending on the strength of stimulus May be positive (depolarization, excitatory) or negative (hyperpolarization, inhibitory)	Fixed amplitude (all or nothing principle) Always positive (depolarization)
Propagation	Conducted over short distances with a reduction in magnitude of potential	Conducted over the entire cell membrane
Summation	Can be summated	Cannot be summated

Table 9-2 Difference Between Absolute Refractory Period and Relative Refractory Period

	Absolute Refractory Period	Relative Refractory Period
Definition	The period during the action potential where the nerve cannot respond to a second stimulus, no matter how strong it is	The period during the action potential where the nerve can respond to a second stimulus, provided it is greater than threshold strength
Duration	Whole of depolarization and about 1/3 of repolarization	Remainder of repolarization and hyperpolarization phase
Mechanism	A large number of the Na^+ channels are inactivated and cannot open until the membrane returns to the resting state	In the initial part of the relative refractory period some Na^+ channels are still inactivated Throughout the relative refractory period, K^+ conductance is high which opposes depolarization

to about −65 millivolts usually causes the explosive development of an action potential. This level of −65 millivolts is said to be the *threshold* for stimulation.

Local Potentials

Not all stimuli result in an action potential. Small stimuli may result in local changes in cell membrane potential that are below the threshold for the initiation of an action potential. These small changes in cell membrane potential are called local responses and can be differentiated from action potentials as outlined in Table 9-1.

Refractory Period

The nerve cannot respond to a second stimulus during much of the action potential and even longer. This is referred to as the refractory period of the nerve. In fact, the refractory period is further divided into an absolute refractory period and a relative refractory period. The difference between these two is highlighted in Table 9-2.

Bibliography

Alberts B, Johnson A, Lewis J, et al: *Molecular Biology of the Cell*, ed 3, New York, 2008, Garland Science.

Biel M, Wahl-Schott C, Michalakis S, Zong X: Hyperpolarization-activated cation channels: from genes to function, *Physiol Rev* 89:847, 2009.

Blaesse P, Airaksinen MS, Rivera C, Kaila K: Cation-chloride cotransporters and neuronal function, *Neuron* 61:820, 2009.

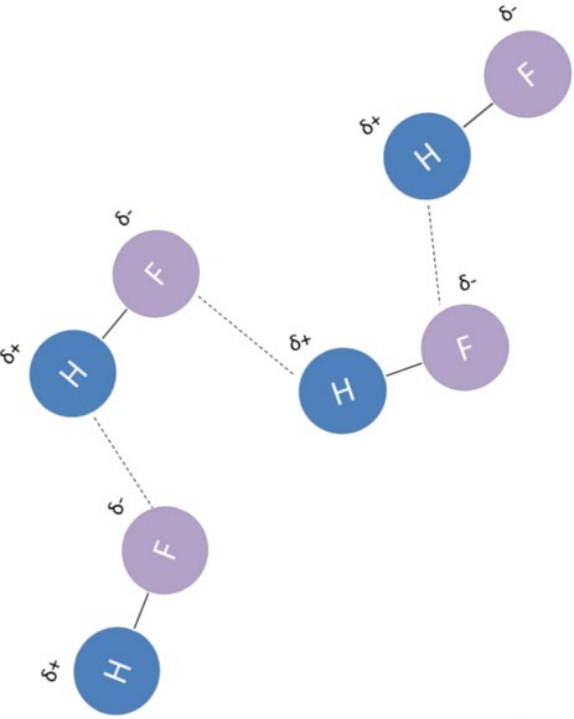
Dai S, Hall DD, Hell JW: Supramolecular assemblies and localized regulation of voltage-gated ion channels, *Physiol Rev* 89:411, 2009.

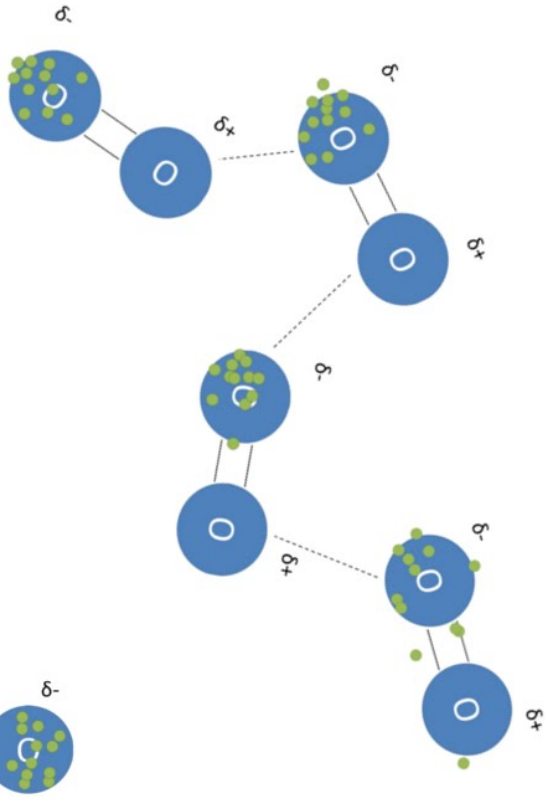
Hodgkin AL, Huxley AF: Quantitative description of membrane current and its application to conduction and excitation in nerve, *J Physiol (Lond)* 117:500, 1952.

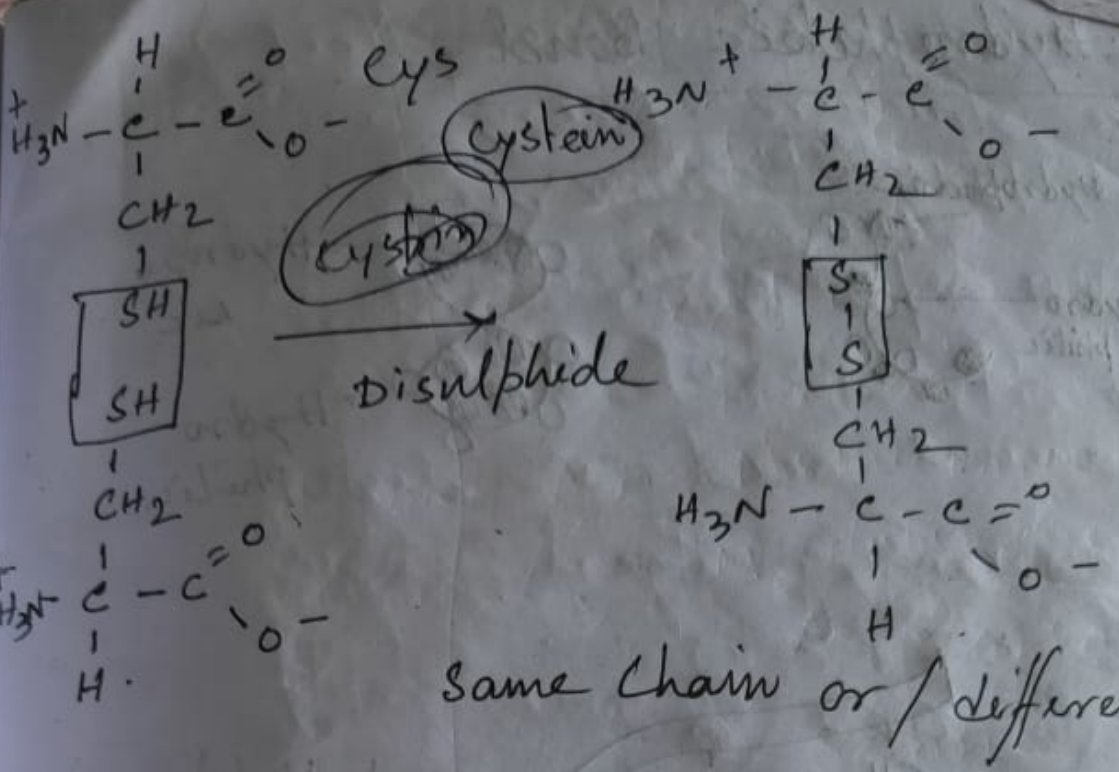
Kandel ER, Schwartz JH, Jessell TM: *Principles of Neural Science*, ed 4, New York, 2000, McGraw-Hill.

Vacher H, Mohapatra DP, Trimmer JS: Localization and targeting of voltage-dependent ion channels in mammalian central neurons, *Physiol Rev* 88:1407, 2008.

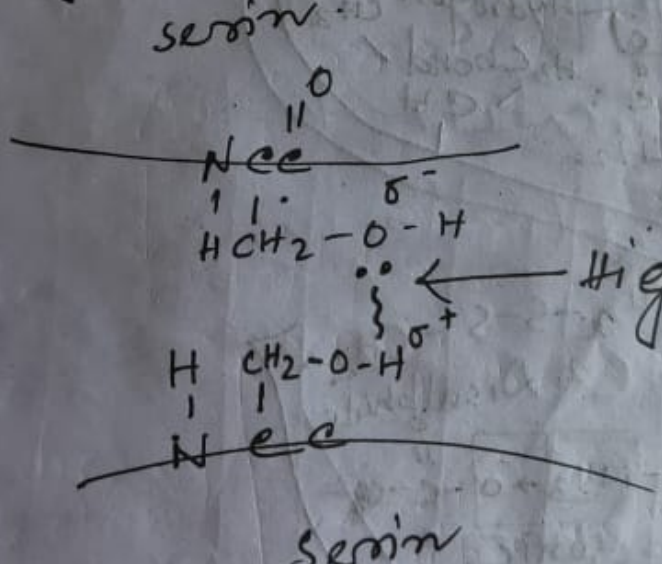
Van der Waals' Forces



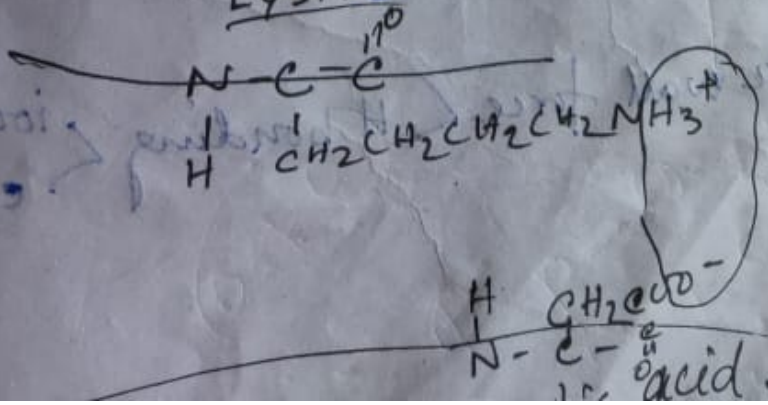




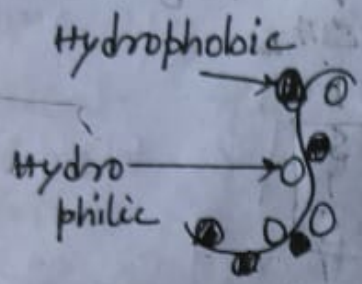
3. Hydrogen bond.

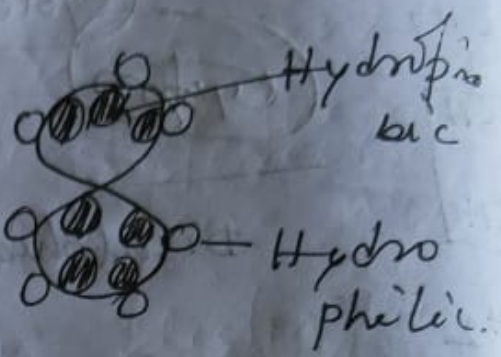


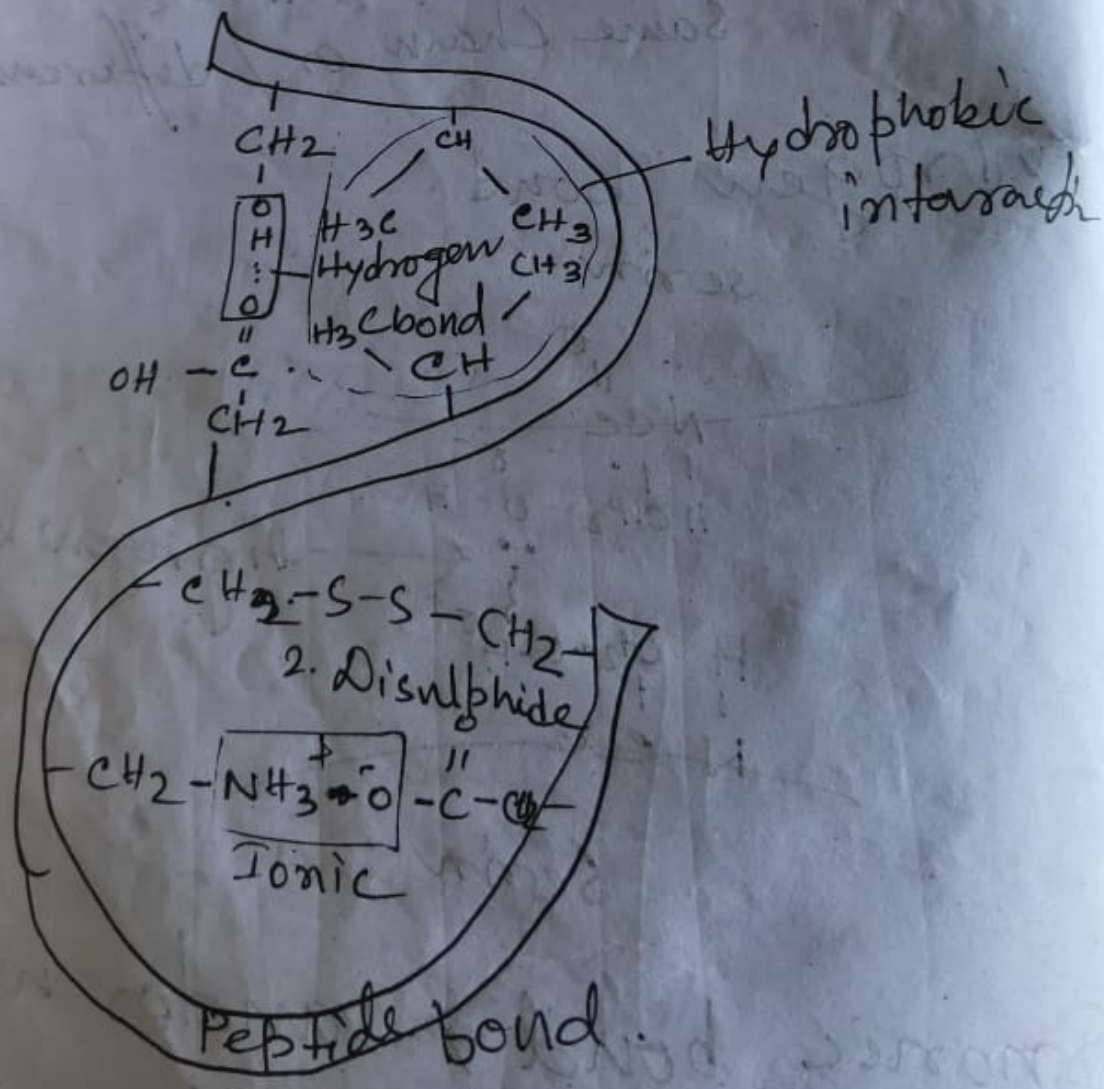
4. Inonic bond & vander walls force



5. Hydrophobic bond.





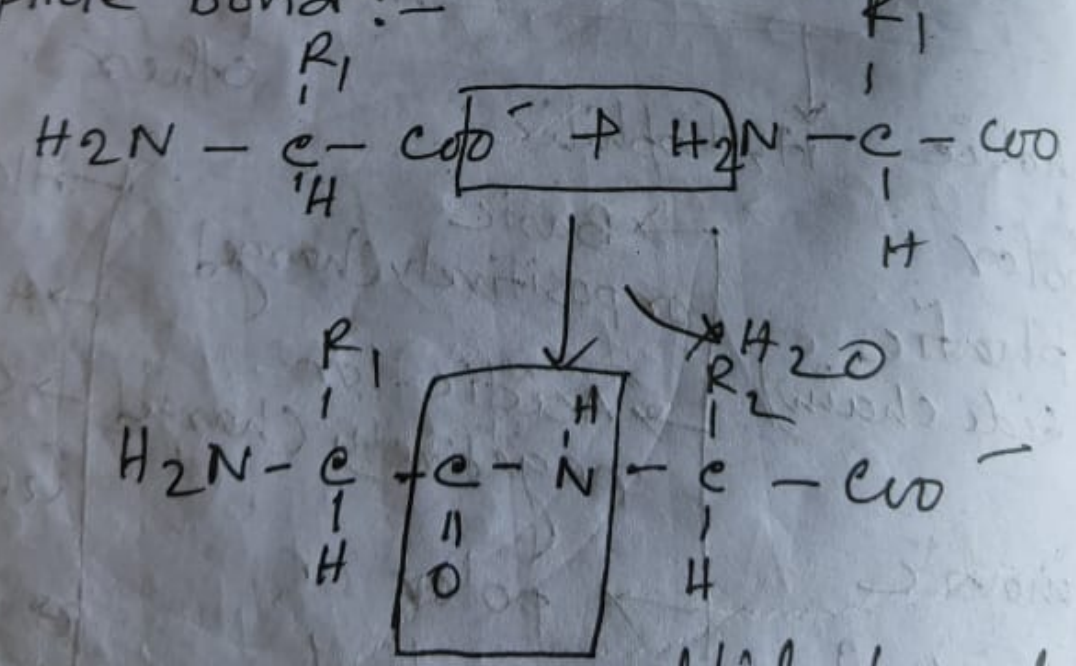


Bonds of Protein

- Prymari
  - * Covalent bonds
    1. Peptide
    2. Di-Sulphide
- Secondary
  1. Hydrogen
  2. Peptide
  3. Di-Sulphide
- Tertiary
  1. Hydrogen
  2. Hydrophobic
  3. Ionic
  4. vanderwalls forces
  5. Di-sulfide bond
- Quaternary

1. Hydrophobic → 1 → vanderwalls force. → 4
Hidrogen → 2
Ionic → 3
Disulfide → 5.

1. Peptide bond :-



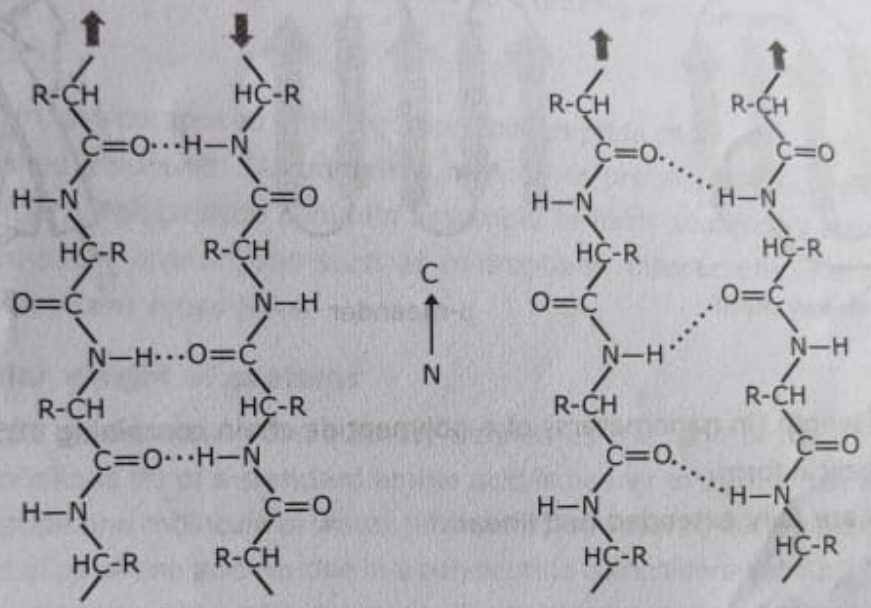
Peptide bond.

2. Disulphide bond.

cistin

heets

eets form when two or more polypeptide chain segments line up side by side. Each individual segment
o as a **β-strand**. Rather than being coiled, each β-strand is fully extended. The distance between
no acids along a β-strand is approximately 3.5 Å, in contrast with a distance of 1.5 Å along an α-helix.
eets are stabilized by interchain hydrogen bonds that form between the polypeptide backbone N—
groups of adjacent strands. Adjacent strand can be either *parallel* or antiparallel. In parallel β-pleat
ures, the polypeptide chains are arranged in the same direction. However in antiparallel β-plea
run in opposite directions. Antiparallel β-sheets are more stable than parallel β-sheets because
lrogen bonds form.



1.17 In an antiparallel sheet, adjacent strands run in opposite directions. Hydrogen bonds
CO groups connect each amino acid to a single amino acid on an adjacent strand. In paralle
nt strands run in the same direction. Hydrogen bonds connect each amino acid on one strand
nt amino acids on the adjacent strand. For each amino acid, the NH group is hydrogen bonde
oup of one amino acid on the adjacent strand, whereas the CO group is hydrogen bonded to
on the amino acid two residues farther along the chain.

ns have compact, globular shapes, requiring reversals in the direction of their polypeptide c
versals are accomplished by a common structural element called the *turn*. Turns, composed
s, are classified as a third type of secondary structure. These short, U-shaped secondary st
y a hydrogen bond between their end residues. Glycine and proline are commonly present i
ge side chain in glycine and the presence of a built-in bend in proline allow the polypeptide
tight U shape. Turns allow large proteins to fold into highly compact structures. In contras
turns and do not have regular secondary structure.
lassified according to the separation between the two end residues participating in hydrog
urn and γ-turn. In an **α-turn**, the donor and acceptor residues are separated by *four* pe
ve amino acid residues). H-bond forms between the carbonyl oxygen of residue (n) and the
(n+4). A **β-turn** (the most common form) is characterized by hydrogen
peptide bonds (n and n+3). Similarly