Action Potential

3

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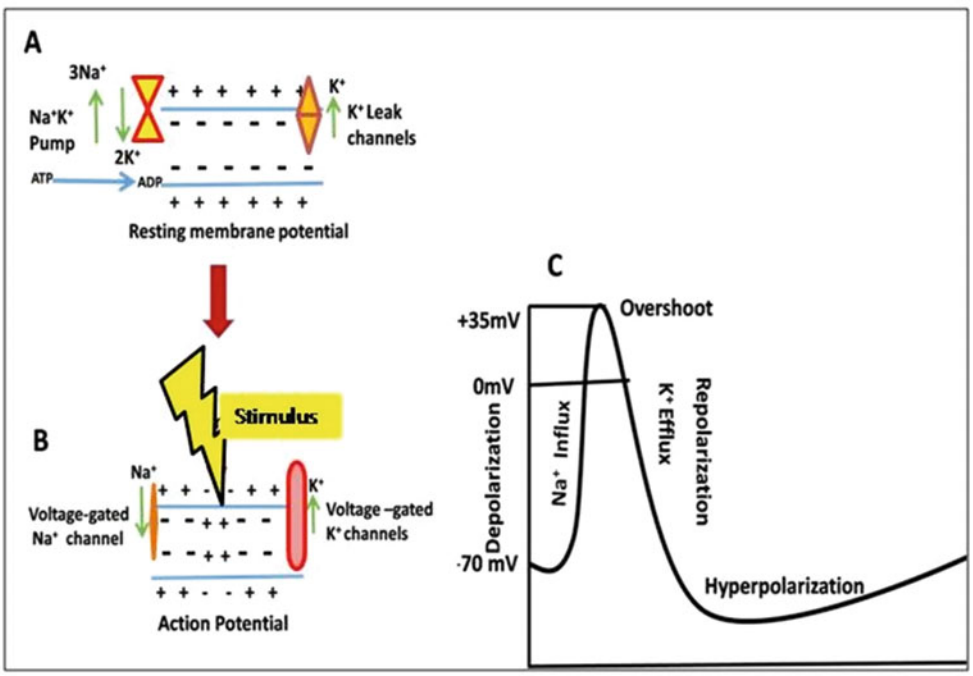
Abstract

The nerve axons and muscle fibers exhibit the property of excitability by which they can transmit signals along their membranes. At rest, potential differences develop across the unit membranes owing to differences in the concentration of ions and their selective permeability towards specific ions. An action potential can be generated by a threshold stimulus that can depolarize the resting nerve and activate the voltage-gated ion channels. An action potential consists of four phases depolarization, overshoot, repolarization, and hyperpolarization. Once developed, an action potential propagates with undiminished strength until it reaches the end of the nerve fiber.

Graphical Abstract



Description of the graphic: The exchange of ions and establishment of the resting membrane potential (**a**). Application of stimulus and generation of action potential (**b**). Graphical representation of action potential in nerve axonal membrane (**c**)

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Keywords

Resting membrane potential · Action potential · Polarized state · Depolarization · Repolarization

Learning Objectives

- Ionic basis of resting membrane potential (RMP) in a neuronal membrane.
- Generation of action potential and its phases.
- Characteristics of action potential.
- Basis of refractoriness in the neuronal membrane after the action potential.
- Factors that determine the propagation and conduction velocity of action potential.

Every cell of the body has electrical potentials across its cell membranes. Additionally, some cells such as the nerve axons and muscle fiber exhibit the property of excitability by which they are able to transmit signals along their membranes. The excitability or rapid changes in electrochemical impulses exhibited by certain cells of the body is governed by the principles of membrane theory or ionic hypothesis. The theory is based on the ability of the cellular membrane to respond to changes in the membrane permeability to ions. The membrane theory states that potentials develop across the unit membranes owing to differences in the concentration of ions and their selective permeability towards specific ions. The understanding of the fundamentals of nerve cell excitability are based on the finding by Hodgkin and Huxley (1952) whose experiments with the squid giant axons gave the first insights into the generation of action potential and the kinetics of ion channels. The membrane potential is an essential feature of all body cells both excitable and non-excitable. Recent studies highlight the indispensable role of membrane potentials in regulating several important functions of the body such as the biological rhythms; specifically the circadian rhythm. It denotes the events that repeat cyclically over 24 h period and is coordinated by the superior chiasmatic nucleus of the hypothalamus. The depolarization and a consequent fall in action potential firing lead to changes in the membrane potential of neurons in the superior chiasmatic nucleus. Contrary to the popular belief, here depolarization leaves the cell membrane less excitable leading to a decrease in action potential generation. The pineal glands respond to these changes by secreting melatonin which mediates the cyclic events. The membrane potential is essential for various sensory perceptions such as vision, hearing, taste, and olfaction. The neuroendocrine cells of the body located in the hypothalamus, pituitary, thyroid gland, and pancreas are excitable and secrete hormones that regulate basic body functions. The excitability of neuroendocrine cells is driven by action potential which occurs as rapid oscillation bursts induced by Ca^{+} ions influx followed by a period of rest. This depolarization due to calcium ion influx leads to the secretion of hormones from the concerned cell types.

3.1 The Diffusion Potential and Membrane Potential

The diffusion of ions across the cell membrane due to their concentration gradients creates the diffusion potential. The potassium ions are of higher concentration inside the cell membrane in comparison to the outside; they diffuse outside due to this concentration gradient leaving the negatively charged ions behind. This causes electropositive charges to accumulate outside and electronegativity develops inside the membrane. The diffusion potential then develops across the membrane which prevents further efflux of potassium ions from inside despite the existence of a high concentration gradient. The value of diffusion potential is −94 mV in a nerve fiber of mammalian origin. In case the membrane is selectively permeable only to sodium ions, the diffusion of sodium ions will occur towards the inside of the membrane since the concentration of sodium ions is much more in the ECF than in the ICF. This diffusion of positive ions inside will cause electropositivity inside and electronegativity on the outer side of the cell membrane thereby diffusion potential will rise to +61 mV which will block the further influx of sodium ions. The diffusion potential at which the net diffusion of a particular ion across a membrane is prevented is known as the Nernst potential which can be determined using the Nernst Equation as given

$$E_{\text{ion}} = 2.303 \frac{RT}{ZF} \log \frac{[\text{ion}]_{\text{o}}}{[\text{ion}]_{\text{i}}}$$

As this value increases, it indicates a greater tendency for the ion to diffuse which means a greater Nernst potential is required to prevent further diffusion of ions.

When the membrane is permeable to more than one ion then the diffusion potential relies on several parameters; the charge of individual ions, their concentrations on either side of the membrane, and the membrane permeability to these ions. The membrane potential on the inside of the cell membrane can then be calculated by applying the Goldman equation also known as the Goldman-Hodgkin-Katz equation as given. The ions involved are sodium, potassium, and chloride. These three ions are predominantly involved in the maintenance of the membrane potential of muscle fibers and nerve fibers.

$$V_m = -\frac{RT}{F} \ln \frac{P_{Na}[Na^+]_i + P_K[K^+]_i + P_{Cl}[Cl^-]_o}{P_{Na}[Na^+]_o + P_K[K^+]_o + P_{Cl}[Cl^-]_i}$$

The selective permeability of the membrane to particular ions determines the membrane potential. If the membrane is selectively permeable only to sodium ions and impermeable to the other ions, i.e., potassium and chloride, the membrane potential will be determined by the sodium ion concentration gradient and will be equal to the sodium ion Nernst potential. The same principle applies to other permeant ions as well.

3.1.1 Ionic Basis of Resting Membrane Potential (RMP)

Before understanding the action potential, it is very important to have an idea about the resting membrane potential. The cell membrane of most cells maintains an ionic concentration difference operated by the "*Na^+K^+ pump*" and the potassium "*leak*" channel systems. The "*Na^+K^+ pump*" actively pumps out sodium ions from the intracellular fluid to the extracellular fluid and draws in potassium ions against the concentration gradient. This pump exchanges three sodium ions for every two potassium ions and thus develops a negative potential inside the cell membrane. A large difference in ionic concentration also develops across the membrane in the resting stage by the "*Na^+K^+ pump*." The concentration of sodium and potassium ions inside the cell membrane is 14 mEq/L and 140 mEq/L while their concentration outside is 142 mEq/L and 4 mEq/L, respectively. The potassium "*leak channel*" functions opposite to the "*Na^+K^+ pump*" as this ion channel favors the movement of sodium ions into the ICF and potassium ions into the ECF by following the chemical gradient but are 100 times more permeable to potassium ions than to sodium ions. These two systems work together to maintain a steady state across membranes. This net results in a positive charge outside the cell membrane and a negative charge on the inner side. This potential difference (denoted as V_m) in the inside and outside the cell membrane at rest is known as the resting membrane potential (RMP). The magnitude of the RPM can be determined by the Nernst equation as given:

$$E_{ion} = 2.303 \frac{RT}{ZF} \log \frac{[ion]_o}{[ion]_i}$$

where $[ion]_o$ and $[ion]_i$ are the concentration of particular ions in the ECF and ICF, respectively.

In the nerve cell, the RMP is −70 mV.

The voltmeter is used to measure the membrane potential. It is a highly sophisticated instrument through which minute changes in potential difference across the membrane can be detected.

3.2 Action Potential

The Resting membrane potential is a dynamic process that functions continuously to maintain a steady ionic balance in the cell wherein the ions moving through the membranes due to their concentration gradient are again being actively pumped back against their concentration gradient. This state is also known as the "polarized state" of the cell membrane. The process occurs inherently in all excitable cells such as the nerve axon and muscle fibers. Whenever a stimulus is applied over the cell membranes at resting membrane potential, the polarity of the membrane at the particular spot of application gets reversed, i.e., the outside becomes negative and the inside becomes positive. This "depolarization state" of the cell membrane is known as action potential and it signals the onset of cellular activity.

An **action potential** is therefore a very fast and transient change in the resting membrane potential due to a stimulus. This property exhibited by neurons and muscle cells is also referred to as excitability.

3.2.1 Characteristics of Action Potential

The duration of action potential in a nerve axon is very short (about 1 ms). They follow the all-or-none law, i.e., if the stimulus is below the threshold level, the depolarization does not occur. However, once the stimulus reaches adequate strength, the action potential develops and propagates throughout the entire length of the cell membrane with undiminished strength. The size of the action potential also remains unchanged on increasing the intensity of the stimulus above the adequate level. The response is regenerative by nature since the excitation developed in a particular patch of an axon is capable of exciting the next part and so on. The impulse propagates in the form of a wave at a constant speed and amplitude along the complete length of the axon by permeability changes of the axonal membrane to sodium and potassium ions in each axonal segment. Action potential plays a vital role in transmitting information to and from the central nervous system that is mediated by the propagation of action potential through the nerve cell axons.

3.2.2 The Phases of Action Potential

The action potential is comprised of several components (Fig. 3.1). Once a stimulus reaches the threshold value it leads to the generation of an action potential. For a nerve fiber, if a stimulus of adequate strength is applied, the RMP of −70 mV can reach up to −60 mV, the so-called threshold level. The immediate response is the depolarization phase or

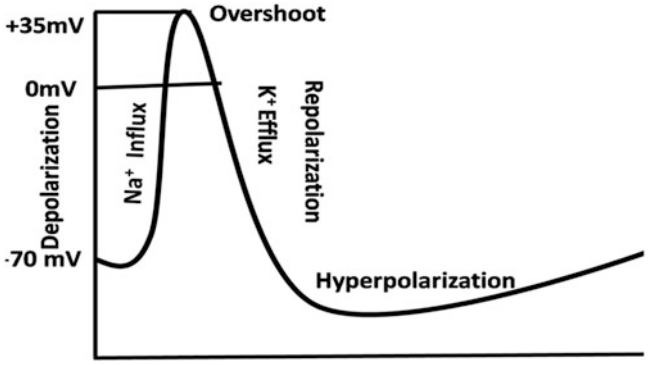

Fig. 3.1 Generation of action potential in a nerve axonal membrane. (Adapted from Guyton and Hall Textbook of Medical Physiology 12th Edition)

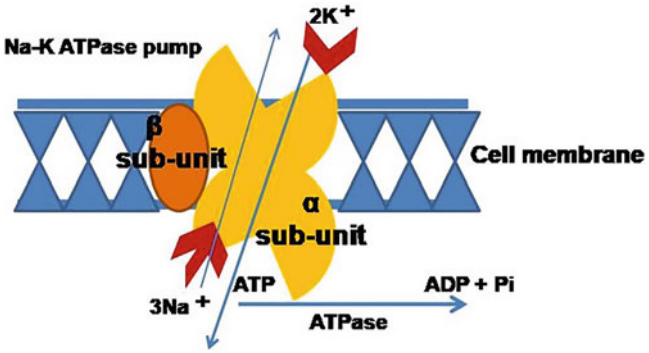

Fig. 3.2 Functioning of the Na-K ATPase pump. (Adapted from Guyton and Hall Textbook of Medical Physiology 12th Edition)

the upstroke whereby the membrane potential reaches a more positive state from a negative state. In a nerve fiber, the membrane potential of −60 mV can sharply reach 0 mV during the depolarization phase. In the next phase, the membrane potential reaches the peak amplitude beyond 0 mV. This is known as the overshoot which can be up to +30 to +40 mV. The potential then returns to the resting membrane potential of about −70 mV and is known as the repolarization phase. It may also reach a more negative phase beyond the resting membrane potential, known as hyperpolarizing after potential or the undershoot and again subsequently return to its original RMP.

3.2.3 Ionic Basis of Action Potential

The resting membrane potential of the nerve fiber is determined by the active transport of sodium and potassium ions through the "*Na^+K^+ pump*" and by the leakage of potassium ions through the *K^+ leak channels* located in the nerve membrane. The "*Na^+K^+ pump*" continuously pumps out sodium ions to the outside and potassium ions to the inside of the cell. For every three sodium ions that are pumped out, two potassium ions are taken inside leading to a net deficit of positive ions; thus, causing a negative potential inside. This phenomenon leads to the creation of a large concentration gradient for both ions. The *K^+ leak channels* are more permeable to potassium ions in comparison to sodium ions and thus potassium may leak outside. This permeability difference influences the resting membrane potential. Moreover, there are other ion channels; the voltage-gated sodium and potassium channels which specifically permit the particular ion only. The voltage-gated Na^+ ion channels which permit only Na^+ ions remain practically closed during resting conditions or at RMP.

The Na-K ATPase pump or "*Na^+K^+ pump*" is also an electrogenic pump that is responsible for maintaining a potential difference (i.e., outside positive and inside negative) across the cell membrane (Fig. 3.2). This function is essential to almost all cells of the body for regulation of cellular volume and for transmitting signals across nerve and muscle fibers. This pump also maintains the concentration of sodium and potassium ions on either side of the cell membrane. The Na-K ATPase pump is a complex structure composed of two protein subunits, the α and β subunits. The α subunit is the bigger one with a molecular weight of approx. 100,000 while the β subunit, the smaller one, has a molecular weight of 55,000. This carrier protein complex is present in the cell membrane and extends extracellularly and intracellularly. The α subunit has several important functions. The part of the α subunit that extends intracellularly has three sodium ions binding receptor sites. The α subunit also has an ATPase activity near the vicinity of receptor sites for sodium ions. While the portion that protrudes outside has two potassium ions binding sites. Whenever this carrier protein binds with three sodium ions present inside the cell and two potassium ions present outside the cell membrane, ATPase becomes activated which cleaves the ATP molecule to form ADP by releasing a high-energy phosphate bond. This energy leads to conformational alteration of the carrier protein which leads to the expulsion of three sodium ions to the outside, simultaneously drawing in two potassium ions within the cell. Thus, for each cycle of the pump, there is a net deficit of one positive ion within the cell. This creates a negative potential within the cell membrane as more positive ions are pumped out in comparison to those that enter the cell. This pump may function reversibly depending on sodium, potassium electrochemical gradients, and the relative concentrations of ADP, ATP, and phosphate.

The development of action potential is attributable to the changes in the relative permeability of the neural membrane to sodium and potassium ions. When a stimulus is applied to the nerve cell membrane, the membrane potential becomes less negative and this leads to the activation of the voltage-gated Na^+ channels which open and draw in a large amount

of Na^+ ions by the electrochemical gradients earlier established by the "*Na^+K^+ pump*" and the *K^+ leak channels* at rest. As Na^+ ion enters the cell it immediately changes the relative voltage inside the cell membrane from more negative to less negative. Very few Na^+ ions channels open at the beginning marking the start of depolarization, which has a positive effect and stimulates further opening of a large number of Na^+ channels causing massive entry of positive ions into the cell. This ultimately reverses the RMP from negative to positive and a steep rise in action potential is observed. The membrane potential reaches 0 mV and then overshoots to +30 mV. Soon the voltage-gated Na^+ ion channels begin to close and the voltage-gated K^+ ion channel opens. Driven by the concentration gradient, the K^+ ions start to diffuse out of the cell into the ECF. A drop in the inflow of Na^+ ions combined with the vigorous exit of K^+ ions drives the membrane potential back toward its resting voltage, i.e., to −70 mV. The Potassium ions continue to leak out until they reach the equilibrium and this leads to hyperpolarization.

Know More. . . . . .
In the cardiac muscle fibers, repolarization does not occur immediately after depolarization, instead just after the spike, the potential remains fixed for several milliseconds at a plateau stage and finally undergoes repolarization. This occurs due to the slow opening of voltage-gated calcium–sodium channels which allows the prolonged influx of calcium ions leading to the plateau formation and contraction of the cardiac muscles.

3.2.3.1 Threshold Stimulus, Chronaxie, Utilization Time, and Rheobase

Whenever a nerve fiber is stimulated by a subthreshold stimulus, no action potential is generated. However, on gradually increasing the strength of the stimulus, at a particular point, a response or action potential is produced when the stimulus is applied for an indefinite duration of time. Thus, the strength of stimulus that upon application for an indefinite period can generate a response is known as Rheobase. The minimum strength of the stimulus which can elicit an action potential is the threshold stimulus. Utilization time denotes the minimum duration of time that is just sufficient to generate excitation when Rheobasic strength of the current is applied to the excitable cell such as nerve and muscle fiber. When a stimulus having double the strength of Rheobase is applied to the nerve or muscle, the time taken for the response to happen is termed Chronaxie. While Rheobase denotes the strength of stimulus or current, Chronaxie denotes the time in seconds.

3.2.4 Refractory Period

After the occurrence of an action potential, the nerve cannot be stimulated for the generation of another action potential for a brief period of time. This nonresponding period is known as the absolute refractory period. This period overlaps with the depolarization phase and the two-third of the repolarization phase. Since all the voltage-gated sodium channels are in a transition stage from open to inactivation, it is impossible to start a new action potential at this stage. At the end of the absolute refractory period, the nerve can respond to a stimulus to generate an action potential but of much smaller size, provided the stimulus is of much larger strength, i.e., by a suprathreshold stimulus. This period of partial responsiveness is known as the relative refractory period. As all the voltage-gated sodium channels are closed now, depolarization is possible at this stage.

3.2.5 Propagation of Action Potential

The action potential developed at one particular point of the cell membrane leads to the excitation of adjacent segments which propagates the action potential along the membrane with undiminished strength until it reaches the end of the nerve fiber. Thus, new action potentials are repeatedly regenerated in a subsequent segment of the neuronal membrane. As action potential develops at a spot, the relative permeability to sodium ions increases and positive charges accumulate inside. These charges are attracted by the adjacent segment which is negative relative to the outside or at RMP. The positive charge moves to the next segment and triggers an action potential there. This is referred to as electrotonic current spread and the current is known as electrotonic current. The velocity of conduction of action potential depends on the resistance to the flow of current both internally and across the axonal membrane. It also depends on the capacitance or storage ability of the axonal membrane. The thickness of the axon determines the velocity of propagation of action potential. It is faster in myelinated nerves since salutatory conduction occurs only over the node of Ranvier and action potential jumps from one node to another. Myelination also decreases the capacitance thus conduction velocity increases. In an unmyelinated nerve, the conduction takes a much longer time since each part of the nerve membrane have to undergo depolarization for propagation. The propagation of action potential occurs only in the forward direction away from the stimulus. As the segment remains in the refractory period after the generation of action potential, backward propagation does not occur.

3.2.6 Ion Channels and Ion Channel Modulators

The membrane potential and the generation of the action potential are intimately intertwined with the functioning of ion channels. The ion channels are pore-forming proteins in the cell membrane that permit the passive flow of ions across the cell membrane. Most of the ion channels are gated, which means they can switch between open and closed states in response to particular stimuli. The voltage-gated ion channels open in response to changes in voltage or potential differences across the cell membrane. The ligand-gated ion channel opens upon binding to ligands that can be neurotransmitters or other molecules. The mechanically gated channels operate in response to changes in mechanical stimuli such as stretch and swelling. These ion channels allow the passage of cations, such as potassium, sodium, calcium, and anions such as chloride. The working of several ion channels is based on protein phosphorylation and dephosphorylation. In addition to the gated channels, the cell membrane also has leakage channels that practically remain always open permitting the selective movement of potassium ions from inside to outside the cell due to the concentration gradient. This causes the efflux of potassium ions from inside to outside the cell resulting in the development of negative potential within the cell. As soon as this reaches an equilibrium state the further efflux of potassium ions is prevented. This phenomenon is responsible for establishing the resting membrane potential of the cell. The electrochemical gradients dictate the direction of individual ion flow across the cell membrane. While sodium and calcium ion generally flows inside the cell exerting a depolarizing effect, potassium ions usually moves out of the cell causing the cell to repolarise. The chloride ions moving into the cell is responsible for causing hyperpolarization. The ion channels are composed of several protein units and subunits. Typically the pore-forming subunit is constituted by the α subunit, while the auxiliary subunits are formed by the β and γ subunits. Studies suggest that some drugs functions by binding to the α-subunits of the ion channels thereby modulating their activity. These drugs are usually small molecules that might obstruct the pore, disturb the interactions of the proteins with the several subunits, etc. Some of the drugs modulating the functions of the ion channels are enlisted here

- Amiodarone and Dofetilide are voltage-gated K^+ channel blockers that delay the repolarization of action potentials in cardiac cells and neurons and are commonly prescribed in the treatment of atrial and ventricular fibrillation.
- Nicorandil and Diazoxide are K^+ channel openers that cause hyperpolarization thereby preventing the entry of calcium ions in vascular smooth muscle cells and pancreatic β-cells. These drugs are used in treating angina and hypoglycemia, respectively.
- Some local anesthetics such as Lidocaine and Tetracaine selectively block the voltage-gated Na^+ channels thereby preventing the generation and propagation of action potential.
- Amlodipine and nifedipine are used in the treatment of hypertension and angina work by blocking the voltage-gated calcium channels which relaxes the vascular smooth muscle.

3.2.7 Channelopathies

Ion channels are gaps across cell membranes that allow the passive diffusion of ions. These can be classified into Sodium (Na^+), Potassium (K^+), Calcium (Ca^{2+}), and Chloride (Cl^-) ion channels depending upon the ions for which they are selectively permeable. Ion channels transport ions depending on the electrochemical gradient. There are various types of ion channels such as ligand-gated ion channels, voltage-gated, mechanical-gated, such as stretch-activated and also temperature-activated, i.e., heat- or cold-activated channels. They hold immense importance in regulating several important functions such as the generation of electrical signals, chemical signaling, muscle contraction, transepithelial transport of ions and molecules, hormone secretion, maintenance of cell volume, and cell proliferation. Mutations in genes that encode the proteins of ion channels such as voltage-gated potassium, sodium, calcium, and chloride channels and also autoimmune diseases are implicated in several diseases of the ion channels known as channelopathies. Table 3.1 gives an overview of the diseases due to mutations of proteins in ion channels.

Table 3.1 Genetic disorders of ion channels/channelopathies

Sl. no	Type of ion channel	Gene affected	Disease	Characteristics
1.	Voltage-gated Na^+ ion channel (skeletal muscle)	SCN4A in the α subunit of the ion channel	Hyperkalemic periodic paralysis and myotonia	In Hyperkalemic periodic paralysis, there are sudden episodes of muscle weakness or paralysis between normal muscle activities. In Myotonia there is a delay in the relaxation of muscles after contraction.
2.	Voltage-gated Na^+ ion channel (neuronal)	SCN1B and SCN1A for the β1 and α subunit of the ion channel, respectively	Epilepsy is accompanied by febrile seizures	Epilepsy is bursts of synchronized discharges causing seizures.
3.	Voltage-gated Na^+ ion channel (cardiac muscle)	SCN5A in α subunit of the ion channel leading to complete channel inactivation	Long QT syndrome	Cardiac disorder with arrhythmia and syncope leading to sudden death.
4.	Voltage-gated potassium channel (neural)	KCNA1/Kv1.1 in the α subunit of the ion channel	Episodic ataxia with myokymia syndrome	Uncontrolled muscle contractions/movements (myokymia) with brief ataxia.
5.	Voltage-gated potassium channel (renal)	KCNJ1 gene	Bartter's syndrome	Severe depletion of intravascular volume.
6.	Voltage-gated calcium channel	*CACNA1F*	Congenital stationary night blindness	
7.	Chloride channel	CFTR	Cystic fibrosis	Copious mucous secretion in the lungs and pancreas leads to constant inflammation and finally death.

Learning Outcomes

- **Resting membrane potential and action potential**: The resting membrane potential in the neuronal membrane is around −70 mV. This potential difference is created due to the activity of the "*Na^+K^+ pump*" which actively pumps out three sodium ions for every two potassium ions. A large difference in ionic concentration also develops across the membrane in the resting stage by the "*Na^+K^+ pump*." Whenever a threshold stimulus is applied to the neuronal membrane at resting membrane potential, an action potential develops that is characterized by a very fast and transient change in the resting membrane potential. The activation of voltage-gated sodium ion channels leads to a massive influx of sodium ions causing depolarization of the membrane. These ion channels inactivate spontaneously while the voltage-gated potassium channels begin to open whereby the membrane becomes much more permeable to potassium than to sodium leading to the efflux of potassium. This phrase denotes the repolarization phase of the action potential which may lead the membrane potential to a more negative value than the RMP and cause the hyperpolarization phase.
- **Refractory period**: The brief period after the occurrence of an action potential when the nerve cannot be stimulated for the generation of another action potential is the absolute refractory period. At the end of the absolute refractory period, the nerve can respond to a stimulus to generate an action potential but of much smaller size, provided the stimulus is of much larger strength, i.e., by a suprathreshold stimulus. This period of partial responsiveness is known as the relative refractory period.
- **Propagation of action potential**: The propagation of action potential occurs only in the forward direction away from the point of stimulus. The action potential developed at one particular point is repeatedly regenerated in a subsequent segment of the neuronal membrane which propagates along the membrane with undiminished strength until it reaches the end of the nerve fiber.

Exercises

Objective Questions

Q1. Which ion plays a major role in the maintenance of RMP?
Q2. What are the forces that influence ionic influx and efflux across the cell membrane?
Q3. What is the approximate value of resting membrane potential in a nerve fiber?
Q4. What causes depolarization of cell membrane?
Q5. Name the different phases of the action potential.
Q6. What causes the plateau during the action potential of cardiac muscles?

Q7. What are the two phases of the refractory period?
Q8. Why action potential cannot be generated during the absolute refractory phase?
Q9. How does the propagation of action potential occur?
Q10. Why does action potential conduction occur faster in myelinated nerve fibers?

Subjective Questions

Q1. Describe the ionic basis of resting membrane potential.
Q2. Outline the ionic basis of action potential in a nerve membrane.
Q3. Elaborate on the all or none law as applicable for action potential propagation.
Q4. Why does the action potential propagate only in the forward direction?
Q5. Explain the factors influencing the propagation of action potential in a neuronal membrane.

Answers to Objective Questions

A1. Potassium ions
A2. The concentration gradient and electrical gradient
A3. −70 mV
A4. Threshold stimulus causing activation of voltage-gated sodium channels and influx of sodium ions
A5. Depolarization, overshoot, repolarization, hyperpolarization
A6. The slow influx of calcium ions
A7. The absolute and relative refractory period
A8. Absence of resting membrane potential, inactivation of voltage-gated sodium channel
A9. Electrotonic current
A10. Less resistance to current flow due to large diameter, saltatory conduction, and less capacitance

Keywords for the Answer to Subjective Questions

A1. "*Na^+K^+ pump*," potassium "*leak*" channel.
A2. Activation of voltage-gated Na^+ channels, depolarization, activation of voltage-gated potassium pump, repolarization.
A3. Subthreshold stimulus, threshold stimulus.
A4. Refractoriness.
A5. Resistance to current flow, capacitance.

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