Biophysical Properties Of Voltage-gated Sodium Channels In Mammalian Neurons

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Abstract

Ion channels carry a significant importance for the human body, they're located in all of our cells and serve a critical role in controlling the electrical potential across cell membranes. They facilitate essential functions including neuromuscular and neuronal transmission, signal transduction, and the regulation of secretion and contractility. There are multiple types of ion channels embedded in the membrane, for example, ligand-gated channels, mechanically-gated channels, and voltage-gated channels. They are vital for physiological processes such as muscle contraction, nerve signaling, and maintaining cellular balance by regulating the flow of ions across membranes. There are various types of these ion channels and sodium channels are one of them, they are a subtype of voltage-gated ion channels. They play a vital role in the initiation of electrical signals in excitable cells such as neurons. These voltage-gated sodium channels are essential for the execution of normal physiological functions. They control the flow of sodium ions through the cell membrane and therefore play a significant part in generating action potentials in neurons. They are of significant importance to the human body and play a huge role in facilitating daily life processes.

1 Introduction

"It's the little details that are vital. Little things make big things happen." said John Wooden. Although the term 'voltage-gated sodium channels' might not be familiar one to many, their seemingly small size belies their profound impact on our physiological well-being. The function of these small channels is vital to human life, as they are indispensable for the execution of daily life activities and the proper functioning of essential bodily processes.

In this research paper, I will delve into the fascinating realm of ion channels, with a particular focus on the molecular structure of voltage-gated sodium channels. Ion channels play a critical role in a wide range of physiological processes,

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*Advised by: Arji Daou of the University of Chicago and therefore are significant for multiple scientific domains such as biology, medicine, neuroscience, among others. They are also crucial for a deeper understanding of various fundamental concepts, such as muscle physiology, action potentials, cardiac health, and disease mechanisms. Proficiency in the knowledge of ion channels not only enhances one's grasp of health and disease but also is essential for understanding life processes and improving medical research. Whether you are a scientist, researcher, or doctor, knowing about ion channels can deepen your understanding of the natural world and the fundamental principles governing biology.

Ion channels serve a critical role in controlling the electrical potential across cell membranes. They facilitate essential functions including neuromuscular and neuronal transmission, signal transduction, and the regulation of secretion and contractility. There are multiple types of ion channels embedded in the membrane, for example, ligand-gated channels, mechanically-gated channels, and voltage-gated channels. They are vital for physiological processes such as muscle contraction, nerve signaling, and maintaining cellular balance by regulating the flow of ions across membranes. Ligand-gated channels' permeability increases when a chemical ligand binds to the protein structure. Mechanically-gated channels activate in response to mechanical vibration or pressure. Voltage-gated channels, the focus of this research paper, modulate their opening and closing in response to changes in the cell membrane potential. This category comprises several subtypes, which include sodium, calcium, potassium, and chloride channels. The primary emphasis of this research paper will be on voltage-gated sodium channels.

2 Basic Membrane Biophysics

Voltage is defined as "an electromotive force or potential difference expressed in volts." According to the International Systems of Units, voltage's derived unit is volt (V), named in honor of the 18th–19th-century Italian physicist Alessandro Volta. Voltage is typically measured with a voltmeter, an instrument widely utilized in various aspects of life, such as home appliances, automobiles, power banks, and much more. Voltage is also utilized in nearly every part of our lives. It powers various lighting sources, kitchen appliances, transportation, medical devices, communication, and security systems, among others. In fact, voltage is so deeply ingrained in our daily routines that even the functioning of our brains relies on it. Neurons, specialized cells designed to transmit information throughout the body, depend on voltage changes to carry out their functions. When neurons are not actively transmitting signals, they maintain a resting membrane potential of approximately -70 mV (1 volt=1000 millivolts). The membrane potential is established by the differential ion concentration between the intracellular and extracellular fluids. Moreover, action potentials that contribute to electrical signaling in neurons are also generated due to specific changes in the membrane voltage. In short, voltage represents the measurement of electrical potential difference and is crucial to both everyday life functions and essential physiological processes.

The chemical element sodium which plays a critical role in neuronal functions has the atomic number 11 and is denoted with the symbol Na. Located in period 3 and group 1 of the periodic table, it is a part of the alkali metal group. It is characterized by its remarkable softness, high reactivity, excellent conductivity of electricity and heat, malleability, and a distinctive silvery-white appearance. Sodium is necessary for bodily functions such as regulating blood pressure, fluid and electrolyte balance, and the preservation of normal cellular homeostasis. Inadequate sodium levels in the body can result in nausea, vomiting, low energy, and in extreme cases, seizures. Sodium is also an important component of cellular activities, contributing to the generation of action potentials, depolarization, and the establishment of refractory periods. Furthermore, sodium has a major role in the sodium-potassium pump, which functions to preserve the sodium gradients and potassium gradients (K+) across the cell membrane at proper concentrations.

Neurons, the fundamental units of the nervous system, serve as specialized nerve cells responsible for transmitting signals throughout the human body. They are an integral part of both the central nervous system and the peripheral nervous system, and they are distributed strategically in specific regions. Neurons are found in key locations such as in the brain, the spinal cord, and throughout the rest of the body. They allow daily life functions such as breathing, walking, talking, eating, and much more. The structure of neurons comprises multiple parts including axons, dendrites, and the soma (cell body). The cell body, housing the nucleus and the cytoplasm, serves as the neuron's central hub. The soma's axon extends from the cell body and divides into multiple smaller branches until it ends at the nerve terminals. The axon's function is to rapidly transmit electrical signals from the soma to the terminal. It originates from the axon hillock, a part of the neuron made up of nerve fibers, connecting the start of the axon and the soma. The diameter of the axon remains mostly consistent throughout its length, this structure is maintained by a cytoskeleton. Dendrites which originate from the soma, are in most cases much shorter and thicker compared to axons. As they are highly branched this creates the ability to have a dense network of processes which is called the dendritic tree. Their structure can alter in a short period, not only does their form vary but their diameter can also change. Dendrites' function is to receive data and signals from other neurons. Their plasma membrane is acquired with specific proteins to enable it to perform its function. The dendrite can carry out its function as the proteins specialize the membrane in a certain way to allow the process. Synapses, neuronal junctions, are where neurons exchange information and interact with each other. Neurons have synaptic connections anywhere ranging from hundreds to thousands. They can have connections with themselves, nearby neurons, or neurons from differing parts of the brain.

There are three types of neurons: sensory neurons, motor neurons, and interneurons. Located in the dorsal root ganglion of the spinal nerve, sensory neurons' function is to process the stimuli coming from the sensory organs such as ears, eyes, nose, mouth, skin, and internal organs. These organs where sen-

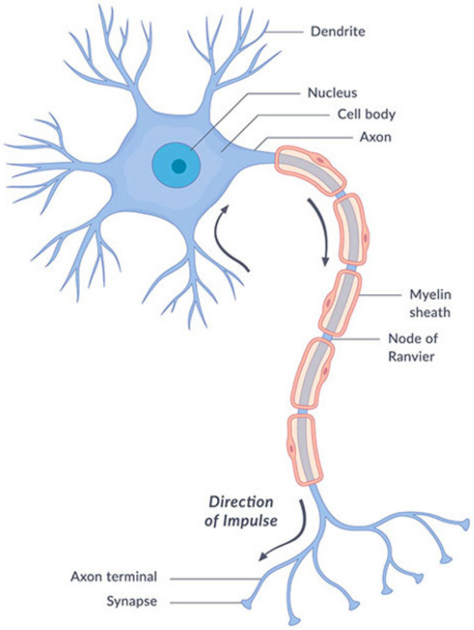

Figure 1: Neuron structure [Wha18]

sory receptors are located, monitor the external and internal environment of the body. Sensory neurons have specialized functions and depending on that they carry messages about touch, sound, taste, light, and scent. Neurons that are activated by such stimuli are called peripheral, the ones that respond to internal stimuli such as blood pressure, pain, and hunger are referred to as visceral neurons. Their shapes can also differ according to their functions. The other type of neurons, motor neurons are located in the spinal cord and the brain. They are divided into two subtypes upper motor neurons and lower motor neurons. They have different origins synapse points, pathways, neurotransmitters, and lesion characteristics. Motor neurons play a pivotal role in controlling muscle function and movement. They are made up of a variety of intricate circuits that are carefully regulated and allow for both voluntary and involuntary motions via innervating effector muscles and glands. The last neuron type is the interneurons, most are found in the the brain and the spinal cord, and others are within the autonomic ganglia. They make up most of the neurons in the human body. Interneurons are seen to be activated when a response to a stimulus has to be complex. All higher cognitive processes, like as learning, memory, cognition, and planning, depend on interneurons.

There is a difference between the membrane and the resting potential. The resting potential of a neuron is usually between -60 mV and -70 mV. In this state the neuron is not sending nor receiving any signals, it is simply at rest. Multiple ions have a significant impact on the cell's resting potential which are Cl-, Na+, K+, and Ca^2+ ions. There are ions distributed unequally both in the intracellular and extracellular medium of the neuron. They can move around freely and the transmission of a neuronal signal is entirely dependent on the movement of the ions. Their movement is guided through two main forces which are the electrostatic and diffusive forces. During the neuron's resting state the sodium ion concentration is higher on the outside of the cell compared to the inside. The concentration of potassium on the other hand is the opposite, it is more abundant on the inside than the outside. This ionic separation of mediums occurs due to the cell membrane which creates a chemical gradient across the membrane. The membrane potential is what indicates the voltage across the membrane at any given time, whether the neuron is rested or not. The membrane potential of a neuron is studied from the inside of the cell relative to the outside.

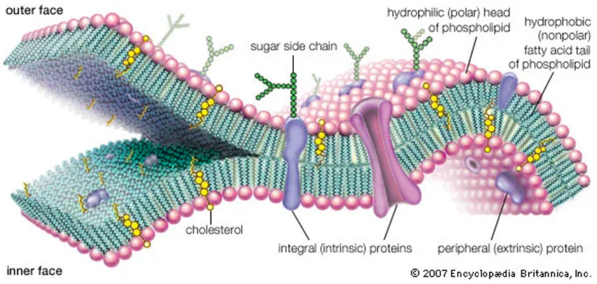

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Figure 2: Cell Membrane Structure [oE24]

A rapid series of voltage changes across a membrane is known as an action potential. Neurons communicate with each other using these quick changes in their membrane potentials. The relative ratio of extracellular to intracellular ions and the permeability of each ion together determine the membrane voltage. It is the result of different ion flows through multiple transporters and channels. Action potentials consist of four phases: depolarization, repolarization, hyperpolarization, and the refractory period. For this process to be generated a neuron needs to be stimulated which then leads to a change in the membrane potential. A nerve impulse sent to the neuron causes sodium cells to move into the cell. After the cell reaches a certain point, called the threshold, an action potential is fired which sends an electrical signal. It is an event caused by a depolarizing current. The threshold of neurons is generally around -55mV, more positive compared to their resting potential due to the positively charged sodium ions surging into the cell in response to a nerve impulse. Sometimes the nerve impulse sent to the neuron isn't strong enough to cross the threshold therefore doesn't result in an action potential, not all stimuli can cause action potentials to be fired. To summarize, during depolarization, which can also be called the rising phase, the internal charge of the cell becomes more positive due to the increasing amount of sodium ions entering the cell. After the membrane voltage reaches a certain point called the peak; the falling phase, repolarization, starts where the positively charged potassium ions start flowing out of the cell. The membrane voltage gets more negative as repolarization progresses and therefore after this phase, the membrane voltage is hyperpolarized. The voltage value is less than the resting potential of the cell during hyperpolarization. Eventually, the cell membrane reaches the resting potential which is -70 mV. This process is also why neurons cannot constantly fire action potentials, they have to go through certain phases to restore the original membrane voltage.

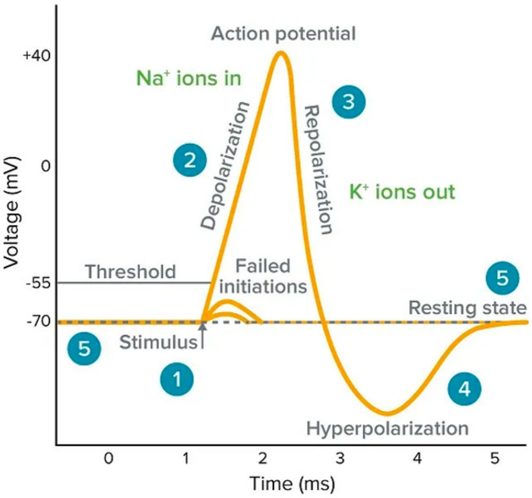

Figure 3: Voltage change during the firing of an action potential [Wha24]

3 Ion Channels, the unsung heroes of neurophysiology

3.1 Ion Channels

Ion channels serve a critical role in controlling the electrical potential across cell membranes. They facilitate essential functions including neuromuscular and neuronal transmission, signal transduction, and the regulation of secretion and contractility. They allow ions to travel from one end of the membrane to the other. The transport they catalyze can be much more rapid than carriers and pumps. There are multiple types of ion channels embedded in the membrane, for example, ligand-gated channels, mechanically-gated channels, and voltage-gated channels. They are vital for physiological processes such as muscle contraction, nerve signaling, and maintaining cellular balance by regulating the flow of ions across membranes. Some ion channels always remain open however generally they require a signal to direct them to open or close. Ligand-gated channels' permeability increases when a chemical ligand binds to the protein structure. Mechanically-gated channels activate in response to mechanical vibration or pressure. Voltage-gated channels, modulate their opening and closing in response to changes in the cell membrane potential. They are integral membrane proteins that are activated when the membrane potential is depolarized, causing a conformational shift that enables ion permeation. They are typically specific to one ion and allow only that specific one to cross the membrane. Therefore they have multiple categories comprised of several subtypes, which include sodium, calcium, potassium, and chloride channels.

Ion channels play a vital and indispensable role in human life. It is essential for various physiological processes as it provides a precise regulation of ion movement in the cells. As the plasma membrane is hydrophobic, it is impermeable to ions by itself, it requires mechanisms like ion channels to achieve an ion flow. Furthermore, action potentials are triggered as a direct result of ion channel functions, without the presence of ion channels, action potentials cannot be generated. Action potentials are of great importance for the human body as they propagate information in the nervous system. They play a significant role in neuron communication by assisting the propagation of signals, they are crucial for the flow of information between the cells. They are responsible for triggering muscle contractions. With a lack of action potentials, necessary signals would fail to reach the designated muscle, and the muscle not receiving the command to contract would cause muscle paralysis. This would impact the entirety of our voluntary movements such as the ability to talk, walk, swim, and all our daily life activities.

There are multiple ways to monitor ion channel functions. The most common is the use of electrophysiological techniques such as the patch clamp technique. The patch clamp method can determine the current flowing across the cell membrane as well as the potential of the membrane, it is an advanced electrophysiological approach. The study of the functions and dysfunctions of electrically excitable cells and their networks requires the use of electrophysiology. This patch clamp technique can be utilized to work on a variety of properties, ranging from kinetic activity of individual channels or cell firing activity. In this technique, tight contact is made with a small section of the membrane. This requires the cell to be enzymatically cleaned prior to the process. A glass, heat-polished micropipette with a small opening is placed in this selected area on the membrane. After the pipette makes contact with the neuronal membrane slight amount of suction is applied to the back of it so that a strong seal is established between the pipette and the membrane. The aim is to minimize the amount of ions that enter the pipette from outside the ion channel. This was one of the main challenges of this technique, if other ions leaked inside the pipette rather than the intended ones which came only from the ion channel this wouldn't provide us with accurate results. The current flowing through the pipette wouldn't be identical to the one flowing from the covered channel. The resulting electrical current from the flow of the ions can be measured with the pipette as an ultra-sensitive electronic amplifier is connected to it. With the results, it can be determined when a channel is in an open or closed state. There are multiple configurations of the patch clamp method to study ion channels, for example cell-attached, whole-cell, inside-out, and outside-out configurations. The cell-attached patch configuration is considered to be the least disturbing for the structure and environment of the cell membrane.

3.2 Voltage-gated Sodium Channels

One of the largest superfamilies of signaling proteins, voltage-gated ion channels, and their molecular relatives are common targets for medications used to treat human disorders. In their seminal series of studies published in The Journal of Physiology in 1952, Hodgkin and Huxley used the voltage clamp technique to identify the sodium current that starts the nerve action potential. In terms of Hodgkin and Huxley's discovery of their function and the subsequent discovery of the sodium channel protein itself, the voltage-gated sodium channels were the superfamily's original members. Although the VGSC was the first to be discovered from the ion channel superfamily, it is the family that has developed more recently. They are descended from similarly shaped Ca2+ channels with four homologous domains. Three distinguishing characteristics of VGSC were identified during Hodkin and Huxley's works which are fast inactivation, voltage-dependent activation, and selective ion conductance. There are multiple types of channels, mechanical-gated, ligand-gated, and voltage-gated which is the subsection VGSC belongs to. The voltage-gated sodium channels, composed of long protein chains to maintain their structure, play a vital role in the initiation of electrical signals in excitable cells such as neurons. They are essential for the execution of normal physiological functions. These channels are activated in response to a depolarization in the membrane. It controls the flow of the sodium ions through the cell membrane and therefore plays a significant part in generating action potentials in neurons. Voltage-gated sodium channels are typically composed of one to two beta subunits and an alpha subunit. The beta subunits have multiple functions such as voltage-dependence of channel gating and the modifying kinetics and the highly glycosylated alpha subunit constructs the conduction pore.

The alpha subunit which consists of the three main parts of three intracellular loops and the N-terminus and C-terminus, is the core subunit of the VGSC. It is the only principal subunit essential for function and folds into four internally homologous domains. These domains resemble a single alpha subunit of a voltage-dependent K+ channel. They each have six transmembrane segments, contain voltage sensors, and also have an additional pore loop between specific segments.

The mammalian brains' sodium channel proteins are made up of a complex of alpha subunits in association with one or more auxiliary beta subunits. In mammals, there are currently 10 types of VGSC that have been successfully identified. They were named according to the differences in the alpha subunit.

VGSC subtypes are distinct regarding structure, tetrodotoxin resistance, and tissue distribution. Although apart from one specific channel, Nav1.4, the other nine VGSC subtypes may currently be found in the nervous system their electrophysiological characteristics and relationship with nervous system diseases are unique.

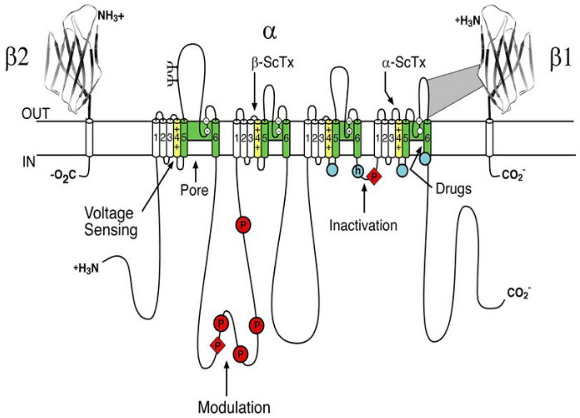

Figure 4: Voltage change during the firing of an action potential [WAC23a]

Voltage-gated sodium channels are a subtype of voltage-gated ion channels. Other voltage-gated channels include potassium, calcium, and chloride. They are all selectively permeable to the major physiological ions, K+, Ca2+, and Cl-. Similar to how VGSC regulates the movement of sodium ions across the cell membrane, potassium channels regulate the potassium ions. It also takes part in the generation of action potentials and neuronal communication. They are activated by the depolarization of the membrane, as the voltage gets closer to the peak of the action potential the VG potassium channels open, allowing potassium ions to rush out of the cell. Combined with the rapid Na+ channel inactivation, the K+ efflux causes the rapid repolarization of the membrane to end the action potential. These events bring the membrane voltage to its resting state, rapidly decreasing its potential after the peak. The voltage-gated calcium channels on the other hand serve the purpose of initiating neurotransmitter release at synapses. They open upon membrane depolarization and are typically closed during the resting potential. As the channels open they allow calcium ions to enter the presynaptic terminal. The influx of calcium ions is essential for the release of neurotransmitters at the synaptic terminals. Unlike the other voltage-gated ion channels, the VG chloride channels' function is to maintain the resting membrane potential. They are less common and their properties can vary among different cell types. They open in response to depolarization. All these channels are vital for maintaining the resting membrane potential as well as generating action potentials.

As the voltage-gated sodium channels' function is of such importance patients can be faced with serious neurological issues regarding mutations or malfunctioning in the channels. An increasing body of research demonstrates that the changes, mutations, or disruptions in the functions of these channels can result in severe difficulties considering the electrical stability of the cell membrane. These diseases or issues caused by the dysfunctions and defects in ion channels are called channelopathies, they can be either acquired factors or genetic. Common examples of channelopathies are epilepsy, migraine, and blindness. Epilepsy, also known as seizure disorder, is a common condition that causes frequent seizures. Mutations in the genes that encode multiple varieties of ion channels are considered to be the major cause behind the abnormal neuronal discharge. Epilepsy is considered a channelopathy as the abnormal neuronal discharge results in this brain dysfunction. Currently, Na+ channel inhibitors are the most commonly used clinical antiepileptic drugs which further highlight the correlation between epilepsy and voltage-gated sodium channels. Hyperexcitability is also a channelopathy as it results from the subtle alteration of sodium channel function due to mutations. However, the occurrence of these diseases also depends on the cell background in which the mutation is expressed. Myotonia is also a form of muscle channelopathy and they are a collection of diverse skeletal muscle channelopathies. It is when after a voluntary muscle contraction there is impaired muscle relaxation. When the muscles are relaxed after contraction, muscle stiffness occurs. All in all, mutations in and malfunctioning of sodium channels result in a variety of diseases which also highlights their importance for human life.

4 Conclusion

This study intends to thoroughly examine the voltage-gated sodium channels' functions, biophysical characteristics, and their properties in mammalian neurons; elucidating their crucial role in neuronal transmission, signal transduction, and the mechanism behind numerous neurological disorders. Ion channels overall are structures that are indispensable to human life, they assist numerous physiological processes such as neuronal transmission, signal transduction, and regulation of ion movement in the cell. They are vital for several scientific fields, including biology, medicine, and neuroscience, as they play a crucial part in a variety of physiological processes. Additionally, they are essential for a fuller comprehension of several fundamental ideas, including the physiology of muscles, action potentials, cardiac health, and disease causes. One of their most abundant roles is to allow ions to travel from one end of the membrane to the other. The transport they catalyze can be much more rapid than carriers and pumps. Action potentials are triggered as a direct result of ion channel functions, they are of great importance for the human body as they propagate information in the nervous system. Without ion channels, action potentials cannot be generated causing an impaired flow of information between the cells.

There are various types of ion channels embedded in the membrane, for example, ligand-gated channels, mechanically-gated channels, and voltage-gated channels. Voltage-gated channels open in response to changes in the membrane potential, they are all selectively permeable to the major physiological ions such as K+, Ca2+, and Cl-. Voltage-gated sodium for example controls the flow of the sodium ions through the cell membrane, resulting in the depolarization of the cell membrane. All these channels are vital for maintaining the resting membrane potential as well as generating action potentials. Although they might appear as a minimal part of our systems their seemingly small size belies their profound impact on our physiological well-being.

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