Chapter 1

Introductory Chapter: Ion Channels

Kaneez Fatima Shad, Saad Salman, Saifullah Afridi,
Muniba Tariq and Sajid Asghar

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.80597

1. Introduction

Ion channels are remarkable proteins, present in the lipid bilayer membrane of both animal and plant cells and their organelles, such as nucleus, endoplasmic reticulum, Golgi apparatus, mitochondria, chloroplasts, and lysosomes.

When we google the word "ion channel," about 80,000,000 results pop up within 0.45 s. Scientists have been working on these amazing transmembrane proteins since the beginning of the last century, which has resulted in three sets of Nobel prizes in 1963, 1991, and 2003.

Sir John Carew Eccles, Alan Lloyd Hodgkin, and Andrew Fielding Huxley in 1963 received Nobel Prize for Physiology and Medicine for their discoveries concerning the ionic mechanisms involved in excitation and inhibition in the peripheral and central portions of the nerve cell membrane [1, 2]. Similarly, Erwin Neher and Bert Sakmann in 1991 proved that cell membranes have individual ion channels through which tiny currents can pass, which are big enough to generate communications between pre- and postsynaptic neurons by converting chemical or mechanical events into electrical signals [3, 4]. The Nobel Prize in Chemistry for 2003 was shared between two scientists Agre [5] and Roderick MacKinnon [6] who have made fundamental discoveries concerning how water and ions move through cell membranes.

In this book, we have **nine** very diverse and informative chapters including this introductory chapter on the importance of both cations and anions passing through these ion channels.

First chapter is the introductory chapter which briefly overview the other eight chapters included in this book, as well as discusses the diversity and classification of ion channels, nature and number of gating for these ion channels along with shedding some light on Channellopathies. **Second chapter** deals with the voltage-gated sodium channels in drug discovery. Sodium channels are the very first one to be discovered when Hodgkin and Katz were

performing their experiments on squid axons showing that there would be no action potential if sodium ions are not present in the extracellular fluid. In this chapter, genetic evolution and subtype distribution of this super family of voltage-gated sodium (Nav) channels are introduced, and there is a discussion about how the changes in the structure alter their functions. **Third chapter** argues the modulation of Nav by small and large molecules, along with the discussion on the major challenges for the Nav-targeted drug discoveries. **Fourth chapter** is taking us to a striking journey about how the genetic mutations bring change in their product proteins and resultant disorders such as Dravet syndrome. SCN1A gene is responsible for this condition and there is a word of caution for the medical practitioners to not prescribe sodium channel blockers for the epileptic patients with this mutation, as the medicine will aggravate their condition. **Fifth chapter** is about potassium channels: there are many different types of the potassium channels (many more than sodium ion channels). In this chapter, authors have discussed the role of two gap junction proteins—connexins and pannexins—in maintaining the homeostasis of potassium ions, taking cochlea as an example. Mutation in gap junction gene results in 50% of prelingual, recessive deafness. Authors developed a novel method for the early detection of the genetic mutations for the inner ear impairment. **Sixth chapter** is dealing with the structure and function of L-type calcium channels and how voltage-gated calcium channels (VGCCs) manage the electrical signaling of cells by allowing the selective-diffusion of calcium ions in response to the changes in the cellular membrane potential. Among the different VGCCs, the long-lasting or the L-type calcium channels (LTCCs) are prevalently expressed in a variety of cells, such as skeletal muscles, ventricular myocytes, smooth muscles, and dendritic cells and form the largest family of the VGCCs. Their wide expression pattern and significant role in diverse cellular events have made these channels the major targets for drug development. **Seventh chapter** is about the regulation of pain through calcium channels. In this chapter, authors present a large body of clinical, biochemical, biophysical, pharmacological, and genetic evidences pointing toward calcium-permeable channels as the key players in pain conditions. The primary goal of this chapter is to present an overview of the different classes of calcium-permeable channels and how they change to modulate the sensation of pain in acute and chronic states. **Eighth chapter** deals with the transient receptor potential (TRP) ion channels, from their distribution to their assembly. TRP ion channel superfamily is widely distributed from neuronal to nonneuronal tissues by serving as cellular sensors. TRP subunits can form both homomeric and heteromeric channels which are present either in the same subfamily or in the different subfamilies and diversify TRP channel functions. **Ninth chapter** discusses about the types of anionic and chloride channels present in the mitochondria. There are many types of chloride channels present in mitochondria, but two types are of major interest, i.e., one which is present in the inner mitochondrial membrane, responsible for the oscillations of membrane potential and the chloride intracellular ion channel (CLIC) localized in the cardiac mitochondrial membranes. These anion channels are very important both in health and diseased conditions. These channels are important for the regulation of PH and ROS along with the synchronization of the mitochondrial membrane potential.

In the following pages of Chapter 1, we will be looking at the role of gating in ion channels for the maintenance of normal physiology and how any of these alterations in the gating result in the channelopathies.

Before going any further, we would like to acknowledge the sculpture called the birth of an idea. It is a 1.5-m tall figurine of KcsA potassium channel, made up of wires and blown glass, representing the channel's lumen [7, 8]. This statue was commissioned to Julian Voss-Andreae by Nobel Prize winner Roderick Mackinnon.

There are three main types of ion channels, i.e., voltage-gated, extracellular ligand-gated, and intracellular ligand-gated along with two groups of miscellaneous ion channels. These ion channels are responsible for the transmission of signals between nerve and other types of electrically active cells [9, 10] through synapses and gap junctions [11, 12]. Alterations in the electrical potential of presynaptic neurons initiate the release of neurotransmitters from the vesicles in the synaptic cleft [13]. These chemicals move toward the postsynaptic cells through the diffusion and occupy their specific receptor sites on membranes and generate the electrical potential by opening ion channels [14]. Removal of neurotransmitters from the synaptic cleft is essential to avoid any effect on the nearby cells [14–16]. Cell signaling by neurotransmitters is far more adaptable and versatile as compared to the gap junctions [17].

2. Distinctive features of ion channels and ion transporter proteins

More than 106 ions are transported in a second through the ion channels without the help of metabolic energy like ATP, cotransport, or the active transport mechanism [18]. There are two types ion channels, nonselective or large pore and selective (archetypal) or small pores [19, 20]. Ions typically pass through the channel pores in the form of a single file almost as fast as they move through a free solution. In most of the ion channels, the passage across the pores is governed by a "gate." The gate may be opened or closed in response to different factors such as: electrical signals, chemical signals, temperature, and the mechanical force [14, 15, 18]. In summary, ion channels are the integral membrane proteins which are usually present as assemblies of many subunit proteins [16, 19]. In most voltage-gated ion channels, α subunit is the pore-forming subunit, while β and γ are the auxiliary subunits [21].

2.1. Diversity and classification of ion channels

There are many different types of ion channels distributed in each cell of our body; for example, in the cells of inner ear alone, there are about 300 ion channels [22]. Ion channels are mainly classified [23, 24] on the basis of the following:

1. The nature of gating;
2. The types of ions passing through the said gates;
3. The number of the gates.

2.1.1. Classification by gating

Ion channels could be classified on the basis of gating, i.e., type of stimuli responsible for their opening and closing. Electrical gradient across the plasma membrane are responsible for the

opening and closing of voltage-gated ion channels [25, 26]; however, binding of the ligands to the channels is responsible for the activation and deactivation of ligand-gated ion channels [29].

2.1.1.1. Voltage-gated

The opening and closing of the voltage-gated ion channels are dependent on the membrane potential, which can be divided into the following subtypes [25–28].

2.1.1.2. Ligand-gated

These channels are also known as the ionotropic receptors and get opened in response to specific ligand molecules binding to the extracellular domain of the receptor proteins [28–30]. Binding of the ligand causes a conformational change in the channel protein that ultimately leads to the opening of the channel gate and subsequent ion flux across the plasma membrane occurs [31, 32]. Cation-permeable "nicotinic" acetylcholine receptors, ionotropic glutamate-gated receptors, acid-sensing ion channels (ASICs), ATP-gated P2X receptors, and the anion-permeable γ-aminobutyric acid-gated GABA receptors are a few examples of ligand-gated channels [29, 31, 33].

2.1.1.3. Other gating

Activation and inactivation of ion channels by second messengers are included under this heading. Some examples are:

Photon-mediated light-gated channels are activated and deactivated in response to light and are synthesized in the laboratory. Some light-sensitive channels are present in nature such as channelrhodopsin. Photoreceptor proteins are also sensitive to light and are G protein gated too.

Cyclic nucleotide-gated channels are activated by hyperpolarization and are permeable to monovalent and divalent cations such as K^+, Na^+, and Ca^{2+}.

Temperature-gated channels are the members of the transient receptor potential ion channel superfamily and are opened by hot or cold temperatures.

3. Channelopathies

Genetic and autoimmune disorders of the ion channels cause channelopathies. If a mutant gene encodes an ion channel protein that is present on the cell membrane of heart, muscles, or brain, it results in the development of diseases in these organs [34, 35]. For example, if a gene encoding Na^+ channel is mutated, then the protein for that channel will be defected and will be incapable to function properly; for example, in myotonia, there is delayed muscle relaxation after voluntary contraction. The abnormal Na+ channels are not able to deactivate, thus initiating repeated membrane depolarizations and resultant muscle contractions. Similarly, abnormality of the K^+ and Ca^{2+} channels in the brain can cause epilepsy. The repeated nerve firings result in convulsions and fits, known as epileptic seizures [36]. Generally, the cell repolarization is effected due to a defect in the voltage-gated ion channels such as K^+, Ca^{2+}, Cl^-, and Na^+. Similarly, any impediment in the Nav can lead to hyperkalemic periodic

paralysis [36, 37]. Stress, alarm, or strenuous activity can stimulate paramyotonia congenital (PC), potassium-aggravated myotonia (PAM), generalized epilepsy with febrile seizures plus (GEFS+), and episodic ataxia (EA), marked by acute bouts of extreme discoordination with or without myokymia [36, 37]. Similarly, familial hemiplegic migraine (FHM) and spinocerebellar ataxia are due to mutation in one or more of the 10 different genes encoding the potassium channels, which also causes a ventricular arrhythmia syndrome called the Long QT syndrome. This mutation ultimately affects the cardiac repolarization [38]. Another type of ventricular arrhythmia is caused by the mutations in genes coding for the voltage-gated sodium channels, and is known as the Brugada syndrome. Likewise, a mutation in the CFTR gene, which encodes for the chloride channel, causes cystic fibrosis [39].

Defect in the transient receptor potential cation channel, mucolipin subfamily (TRPML1) channel, due to a mutation in any of its genes results in mucolipidosis type IV [34, 40, 41]. Some very vital events occur in the cancer cells due to the mutations and overexpression of genes encoding the ion channels; for example, glioblastoma multiform is marked by an increase in the number of receptors for glioma big potassium (gBK) channels and the CIC-3 chloride channels enabling the glioblastoma cells to move within the brain causing the diffuse growth patterns of these tumors.

Author details

Kaneez Fatima Shad[1]*, Saad Salman[2,3], Saifullah Afridi[3,4], Muniba Tariq[3] and Sajid Asghar[2]

*Address all correspondence to: ftmshad@gmail.com

1 University of Technology Sydney, Sydney, Australia

2 Government College University, Faisalabad, Pakistan

3 The University of Lahore, Islamabad, Pakistan

4 Centre for Advanced Drug Research (CADR), COMSATS Institute of Information Technology (CIIT), Abbottabad, Pakistan

References

[1] Hodgkin AL, Huxley AF. Action potentials recorded from inside a nerve fibre. Nature. 1939;**144**:710

[2] Hodgkin AL, Huxley AF. A quantitative description of membrane current and its application to conduction and excitation in nerve. The Journal of Physiology. 1952;**117**:500-544

[3] Neher E, Sakmann B. Single-channel currents recorded from membrane of denervated frog muscle fibres. Nature. 1976;**260**:799

[4] Neher E, Sakmann B, Steinbach JH. The extracellular patch clamp: A method for resolving currents through individual open channels in biological membranes. Pflügers Archiv. 1978;**375**:219-228

[5] Agre P, King LS, Yasui M, Guggino WB, Ottersen OP, Fujiyoshi Y, et al. Aquaporin water channels–from atomic structure to clinical medicine. The Journal of Physiology. 2002;**542**:3-16

[6] Mackinnon R. Determination of the subunit stoichiometry of a voltage-activated potassium channel. Nature. 1991;**350**:232

[7] Voss-Andreae J. Protein sculptures: Life's building blocks inspire art. Leonardo. 2005;**38**:41-45

[8] Voss-Andreae J. Quantum sculpture: Art inspired by the deeper nature of reality. In: Aesthetics of Interdisciplinarity: Art and Mathematics. Basel, Switzerland: Springer; 2017

[9] Nusser Z. Creating diverse synapses from the same molecules. Current Opinion in Neurobiology. 2018;**51**:8-15

[10] Stewart MG, Popov VI, Kraev IV, Medvedev N, Davies HA. Structure and Complexity of the Synapse and Dendritic Spine. The Synapse. Cambridge, Massachusetts, United States: Elsevier; 2014

[11] Ashery U, Bielopolski N, Lavi A, Barak B, Michaeli L, Ben-Simon Y, et al. The Molecular Mechanisms Underlying Synaptic Transmission: A View of the Presynaptic Terminal. The Synapse. Cambridge, Massachusetts, United States: Elsevier; 2014

[12] Raghavachari S, Lisman J. Synaptic Transmission: Models; 2009

[13] Whalley K. Synaptic building blocks. Nature Reviews Neuroscience. 2018;**1**:388-389

[14] Burch A, Tao-Cheng JH, Dosemeci A. A novel synaptic junction preparation for the identification and characterization of cleft proteins. PLoS One. 2017;**12**:e0174895

[15] Lewis S. Synaptic transmission: A hare as well as a tortoise. Nature Reviews Neuroscience. 2018;**19**:183

[16] Ohtaka-Maruyama C, Okamoto M, Endo K, Oshima M, Kaneko N, Yura K, et al. Synaptic transmission from subplate neurons controls radial migration of neocortical neurons. Science. 2018;**360**:313-317

[17] Cervera J, Pietak A, Levin M, Mafe S. Bioelectrical coupling in multicellular domains regulated by gap junctions: A conceptual approach. Bioelectrochemistry. 2018;**123**:45-61

[18] Li Y, Wang S, He G, Wu H, Pan F, Jiang Z. Facilitated transport of small molecules and ions for energy-efficient membranes. Chemical Society Reviews. 2015;**44**:103-118

[19] Mandala V, Gelenter MD, Hong M. Transport-relevant protein conformational dynamics and water dynamics on multiple timescales in an archetypal proton channel-insights from solid-state NMR. Journal of the American Chemical Society. 2018;**140**:1514-1524

[20] Tu YH, Cooper AJ, Teng B, Chang RB, Artiga DJ, Turner HN, et al. An evolutionarily conserved gene family encodes proton-selective ion channels. Science. 2018;**359**:1047-1050

[21] Oyrer J, Maljevic S, Scheffer IE, Berkovic SF, Petrou S, Reid CA. Ion channels in genetic epilepsy: From genes and mechanisms to disease-targeted therapies. Pharmacological Reviews. 2018;**70**:142-173

[22] Gabashvili IS, Sokolowski BH, Morton CC, Giersch AB. Ion channel gene expression in the inner ear. Journal of the Association for Research in Otolaryngology. 2007;**8**:305-328

[23] Zdebik AA, Wangemann P, Jentsch TJ. Potassium ion movement in the inner ear: Insights from genetic disease and mouse models. Physiology. 2009;**24**:307-316

[24] Zhang AH, Sharma G, Undheim EA, Jia X, Mobli M. A complicated complex: Ion channels, voltage sensing, cell membranes and peptide inhibitors. Neuroscience Letters. 2018;**679**:35-47

[25] Brenowitz S, Duguid I, Kammermeier PJ. Ion Channels: History, Diversity, and Impact. Cold Spring Harbor Protocols; New York, United States. 2017. pdb. top092288

[26] Dreyer I, Müller-Röber B, Köhler B. Voltage-gated ion channels. Annual Plant Reviews. 2004;**15**:169-215

[27] Tikhonov DB, Zhorov BS. 3D Structures and Molecular Evolution of Ion Channels. Evolutionary Physiology and Biochemistry-Advances and Perspectives. London, United Kingdom: InTech; 2018

[28] Collingridge GL, Olsen RW, Peters J, Spedding MA. Nomenclature for ligand-gated ion channels. Neuropharmacology. 2009;**56**:2-5

[29] Maathuis F. Ligand-gated ion channels. Annual Plant Reviews. 2018;**15**:216-246

[30] Lev B, Murail S, Poitevin F, Cromer BA, Baaden M, Delarue M, Allen TW. String method solution of the gating pathways for a pentameric ligand-gated ion channel. In: Proceedings of the National Academy of Sciences. 2017b;**114**:E4158-E4167

[31] Lev B, Murail S, Poitevin F, Cromer BA, Baaden M, Delarue M, Allen TW. Gating pathways for a pentameric ligand-gated ion channel solved by atomistic string method simulations. Biophysical Journal. 2017a;**112**:475a

[32] Hu H, Nemecz À, Renterghem CV, Fourati Z, Sauguet L, Corringer PJ, Delarue M. Crystal structures of a pentameric ion channel gated by alkaline pH show a widely open pore and identify a cavity for modulation. In: Proceedings of the National Academy of Sciences. 2018;**115**:E3959-E3968

[33] Sauguet L, Shahsavar A, Poitevin F, Huon C, Menny A, Nemecz À, Changeux JP, Corringer PJ, Delarue M. Crystal structures of a pentameric ligand-gated ion channel provide a mechanism for activation. In: Proceedings of the National Academy of Sciences. 2014;**111**:966-971

[34] Caterina MJ. An Introduction to Transient Receptor Potential Ion Channels and Their Roles in Disease. TRP Channels As Therapeutic Targets. New York, United States: Elsevier; 2015

[35] Zorina-Lichtenwalter K, Parisien M, Diatchenko L. Genetic studies of human neuropathic pain conditions: A review. Pain. 2018;**159**:583

[36] Millichap JJ, Cooper EC. KCNQ2 potassium channel epileptic encephalopathy syndrome: Divorce of an electro-mechanical couple? Epilepsy Currents. 2012;**12**:150-152

[37] Horvath GA, Demos M, Shyr C, Matthews A, Zhang L, Race S, et al. Secondary neurotransmitter deficiencies in epilepsy caused by voltage-gated sodium channelopathies: A potential treatment target? Molecular Genetics and Metabolism. 2016;**117**:42-48

[38] Lolicato M, Arrigoni C, Mori T, Sekioka Y, Bryant C, Clark KA, et al. K2P2. 1 (TREK-1)-activator complexes reveal a cryptic selectivity filter binding site. Biophysical Journal. 2018;**114**:303a-304a

[39] Themistocleous AC, Ramirez JD, Serra J, Bennett DL. The clinical approach to small fibre neuropathy and painful channelopathy. Practical Neurology. 2014;**14**:368-379

[40] Sexton JE, Cox JJ, Zhao J, Wood JN. The genetics of pain: Implications for therapeutics. Annual Review of Pharmacology and Toxicology. 2018;**58**:123-142

[41] Spillane J, Kullmann D, Hanna M. Genetic neurological channelopathies: Molecular genetics and clinical phenotypes. The Journal of Neurology, Neurosurgery, and Psychiatry. 2016;**87**:37-48