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ION CHANNELS–SOME BASIC AND APPLIED ASPECTS

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THE CELL MEMBRANE

Each of the hundred trillion cells in human body is enveloped by a biological membrane, which is known as plasma membrane.[1] This membrane separates the cellular fluid (i.e. intracellular fluid or cytosol) from the fluid surrounding the cells (i.e. extracellular fluid) or acts as a partition between sub-cellular organelles within the same cell. Such a biological membrane acts as a barrier for free passage of substances between the fluid compartments. However, this barrier is only partial. While lipid soluble substances can readily cross the membrane, water and water soluble molecules (e.g., ions, glucose, urea, etc) cannot do so. The partial nature of this membrane can be explained by its molecular structure.[2] Most of the membranes are composed of two layers of lipid with small amounts of embedded proteins (see *fig. 1*). These protein molecules form pores within the lipid bilayer and allow the movement of water soluble substances. It is actually these aqueous pores that are known as "ion channels".[2] These channels allow the movement of charged particles i.e. "ions" such as sodium (Na^+), potassium (K^+), calcium (Ca^+), chloride (Cl^-) etc across the plasma membrane.[3]

Types of ion channels: Ion channels are molecular basis of electrical signaling in all of the excitable tissues of the body. Physiological processes like contraction of heart and skeletal muscles, secretion of endocrine glands, T cell activation, and operations of nervous system require proper functioning of ion channels.[4] There are more than 100 types of ion channels in a living cell.[3] They may be classified by the nature of their gating (opening/closing), the species (or the type) of ions passing through these gates, the number of gates (pores) and

localization of proteins.[5] The widely followed classification of ion channels based upon gating is shown in *fig – 2*.

Gating of ion channels: Majority of ion channels are dynamic. They exist in open as well as closed states.The mechanism which allows ion channels to open and close in response to a specific stimulus is known as "gating".[6] Upon stimulation, the channel protein is thought to rearrange itself insuch a way that the central pore which spans the biological membrane opens and allows the ionic movement.[6]

If the stimulus is in the form of a change in electrical gradient across the plasma membrane, then it is an example of "voltage gated" channel (VGIC). If binding of a certain small molecule to the channel protein opens up the ion channel, then the channel is labeled is "ligand gated" (LGIC).[3] In some instances, the secondary messengers produced within the cell in response to stimuli could also influence ionic movement (indirect gating by second messengers). While most of the ion channels are gated, some remain "ungated" and these function as "leak channels".[6]

Voltage Gated Ion Channels (VGIC): These channels are usually present in excitable cells of the body like neurons, cardiac and skeletal muscle etc. Theyare generally composed of several subunits, which are arranged in such a mannerthat there is a central pore through which ions can travel.[7] The VGICs have an inbuilt voltage sensor, which can detect even minute changes in electrical gradients across the membrane.[1]

A typical VGIC exists in three states, viz. a) open and active b) open but inactive and c) closed (see *fig- 3*). During the closed (or resting) state, the central pore remains closed and does not allow any ionic movement. Rapid changes in electrical potential of the membrane near the voltage sensor of VGIC will trigger some conformational changes within the channel protein that opens up the pore. Thus, the VGIC opens up and becomes active, allowing ionic movement.[7] The ionic movement could be either entry of ions within the cell or efflux (exit) of ions outside the cell depending upon electrical gradient created along the plasma membrane. Most VGICs are selective and allow only a particular type of ion to pass through them e.g., K^+ or Na^+. However, there are some other VGICs which exhibit a relative selectivity only i.e. they allow any of the cations (positively charged ions) or anions (negatively charged ions) to pass through them.[1]

Ligand gated ion channels (LGICs)

LGICs are membrane proteins which open in response to binding witha ligand viz a chemical messenger. They play an important role in nerve impulse transmission and intracellular signaling. LGICs are composed of an extracellular ligand binding unit and a transmembrane pore forming unit. LGICs act as receptors for most of the neurotransmitters, where they could be located within the cell or on the surface of plasma membrane.[8]

While extracellular LGICs have ligand binding domain on the cell surface, intracellular LGICs have this within cytoplasm or upon subcellular organelles like endoplasmic reticulum. Ion channels operated by ligands like GABA ($GABA_A$ receptors), glycine, serotonin ($5HT_3$ receptors), nicotine (nicotinic acetylcholine receptors), glutamate (AMPA, NMDA and kinate receptors) are extracellular and ATP-sensitive K^+ channel, phosphoinositol bisphosphate receptors are intracellular.[8] A typical example of opening of LGIC is shown in *fig – 4a and 4b*.

Leak channels

They are known as leak channels because they always remain in open state and ions can readily pass through them continuously. The movement of ions is governed here by concentration or electrical gradients of traversing ion. They are primarily responsible for maintenance of resting membrane potential within the excitable cells. An example of leak channel is inwardly rectifying K^+ channel [9,10] (refer *fig- 5).*

The ion channels can also be classified according to the type of ion passing through them like sodium, potassium, calcium, chloride, non-selective cationand proton channels. Sodium, potassium and calcium channels are essentially “cationic” channels. While chloride ion channels are “anionic” channels. The channels with a significant clinical relevance are discussed below.

Sodium Channels: Existence of ion channels was explained by Alan Hodgkin and Andrew Huxley with the help of voltage gated Na^+ channels ($VGNa^+ch$). This hypothesis won them a Nobel prize in 1952.[11] Na^+ channels are classified either as voltage-gated ("voltage-sensitive", or "voltage-dependent", $VGNa^+ch$) or ligand-gated. Distribution of $VGNa^+ch$ outweighs the ligand gated channels. Ligand gated Na^+ channels are found in the neuromuscular junction as nicotinic cholinergic receptors where the ligand isan acetylcholine molecule.

$VGNa^+$chcomprises of a pore forming α subunit and two regulatory β subunits; α subunit protein contains 4 domains and forms a Na^+ ion selective pore and β subunits are proteins which span all across the membrane. A set of charged amino acids of α subunit forms the voltage sensor and causes conformational changes in channel protein when more positive voltages are reached [12] $VGNa^+$ch are most commonly present in excitable tissues like neurons, skeletal and cardiac myocytes and they play a vital role in transmission of electrical impulses or muscle contraction.[13] While blockers of $VGNa^+$ch (pheytoin sodium, carbamazepine, sodium valproate etc) are widely used in clinical practice [14], activators (e.g., acotinide, batrachotoxin, etc) and modulators (conotoxin, scorpion venom toxin) are used only for experimental purposes.[12]

Increased activity of $VGNa^+$ch results in hyperexcitability of tissues that leads to disorders such as epilepsy or cardiac arrhythmias.[15] Hence, drugs which block $VGNa^+$ch find a place in treatment of these diseases. $VGNa^+$ch blockers might also find application in diseases such as chronic pain syndromes, neurodegenerative disorders etc in future.[16] Applied pharmacology of $VGNa^+$ch blockers is presented in *table 1*.

Potassium Channels: Potassium channels are the most widely distributed ion channels.[17] They are virtually found in all types of cells in body and help in controlling a wide variety of cell functions such as neuronal and cardiac muscle activity, vascular tone, secretion of hormones etc. K^+ channel re-establishes resting membrane potential of excitable tissues.[18] Hence, they are important in decreasing their excitability. K^+ channels are grouped into 3 major classes based upon their physiological properties and pharmacological applications as follows.[18]

a. Voltage – gated K^+ channels
b. Inwardly rectifying K^+ channels
c. Tandem pore domain K^+ channels

Voltage gated K^+ channels, like other voltage gated ion channels open and closes in response to change in electric gradient. They allow entry of K^+ ions from the cell (in opposite direction to inward rectifying K^+ channels).[1] These channels are found in cardiac myocytes and play an important role in cardiac action potential.[19] Class III anti-arrhythmic drugs (like amiodarone, bretylium, dofetilide, ibutilide) act by blocking voltage gated K^+ channels, thus, delaying the repolarization phase and prolonging the action potential duration.[20] As a result, they are useful in improving the survival and reducing the mortality due to sudden cardiac

death or ventricular fibrillation.[20] Recently, these channels are also thought to be important in regulating neuronal excitability. Retigabine is an example of novel antiepileptic drug that acts by blocking the voltage – gated K^+ channels.[21]

Inwardly rectifying K^+ channels allow the K^+ ions to pass inwards much more readily than outwards. The important subtype of these channels is ATP-sensitive K^+ channels, which regulate duration of cardiac action potential, secretion of insulin from pancreas and vascular smooth muscle relaxation.[22] Oral hypoglycemic agents like sulphonylureas (tolbutamide, glybenclamide, glipizide, etc) and meglitinide analogues (rapaglinide, nataglinide) inhibit ATP-sensitive K^+ channels on β cells of pancreas and provoke the release of insulin, thereby leading to its hypoglycemic effect.[23] Drugs like diazoxide, minoxidil, nicorandil and cromakalim produce vascular smooth muscle relaxation or vasodilatation by opening the K^+ channels, making them useful in vascular disorders like angina pectoris, hypertension, cerebral vasospasm and arteritis.[24]

The most recently discovered K^+ channels are tandem pore domain K^+ channels which are a subtype of leak channels. Together with inwardly rectifying channels, they help in re-establishing negative resting membrane potential of excitable tissues. Certain subtypes of these channels are activated by volatile anesthetic agents like halothane.[25]

At present, active research is being carried out to establish the role of K^+ channels in varied disorders like bipolar disease, bronchial asthma, bladder instability, multiple sclerosis, etc. Drugs like ezogabine have shown mood stabilizing effects in animals.[26, 27, 28] Dalfampridine is one of the K^+ channel blocker which has shown its efficacy in treatment of multiple sclerosis.[29]

Calcium Channels: Cellular functions like muscular contraction (in case of skeletal, cardiac and smooth muscles), secretion of hormones, nerve transmission, enzyme activity, gene expression, and other biochemical processes operate directly or indirectly by influencing intracellular calcium ion concentration.[30]

It has now become clear that a wide range of functions are carried out due to diversity of the types of Ca^{2+} channels on the membrane of individual cells. There are two basic types of calcium ion channels, voltage-dependent and ligand-gated. Voltage gated Ca^{2+}channels are highly selective for Ca^{2+}ions.[30] They allow Ca^{2+}ion movement inside the cell whenever the

plasma membrane is depolarized. The resulting accumulation of Ca^{2+}ions in the cytoplasm acts as a chemical trigger or secondary messenger.[30] On the other hand, ligand gated Ca^{2+}channels are relatively non-selective and conduct various cations along with Ca^{2+}ions. Malfunctioning of glutamate receptors (NMDA type) in neurodegenerative disorders causes excess neuronal excitability because of massive Ca^{2+} influx within the neuronal cells.[31] *Table 2* depicts major types and therapeutic targets of Ca^{2+}channels.

Chloride channels: Amongst the group of anionic channels, Cl^- ion channels are clinically most relevant. Cl^- ion channels form an integral part of inhibitory neurotransmitters like GABA (gamma-amino-butyric acid).[32] Additionally, they play a key role in maintaining acid-base balance and resting membrane potential in excitable cells, cellular proliferation and differentiation.Drugs like benzodiazepines and barbiturates bind to GABA receptor-chloride channel complex and facilitate the movement of Cl^- ions within the neurons. Therefore, benzodiazepines are used in anxiety neuroses, insomnia and epilepsy.[32]

Disorders of ion channels

In 1989, cystic fibrosis was identified as the first ion channel disorder. Since then, the list of human diseases known to be associated with defects in ion channels has grown considerably. Ion channels being essential for a wide range of physiological functions, their dysfunctioning can cause diseases in numerous tissues. Most of the ion channel disorders are inherited (channelopathies), however, some are autoimmune in nature (in which the body produces antibodies to its own channel molecules).[33]

Channelopathies: The advancement in knowledge of human genome has significantly increased our understanding of ion channels regulating proteins. Defects in genes regulating expression of ion channel proteins lead to the discovery of a variety of genetic disorders known as "channelopathies".[33] They range in severity from mild (or self-limiting) to life-threatening conditions. Mutations or over expression of ion channel proteins alter the biological functioning of ion channels. Mutations in ion channel genes may cause either a loss or a gain of channel function. Examples of some of the channelopathies are described below

- **Muscle disorders**

Mutations in voltage gated sodium channel and voltage gated calcium channel cause skeletal muscle disorders like periodic paralysis and myotonia. In congenital myasthenia, mutations in

the muscle nicotinic acetylcholine receptors channel results inmuscle weakness, rapid fatigue and progressive muscle atrophy.[33]

- **Cardiac disorders**

In long QT syndrome, prolonged QT interval in ECG is associated with defects in functioning of voltage-gated potassium and sodium channels. Dysfunctioning of voltage gated sodium channels is implicated in Brugada syndrome (idiopathic ventricular fibrillation).[33]

- **Neuronal diseases**

Malfunctioning of various subunits of voltage gated sodium channels are held responsible for epilepsy syndromes like generalized epilepsy with febrile seizures, benign neonatal epilepsy, juvenile myoclonic epilepsy, familial hemiplegic migraine and ataxias like episodic ataxia and spinocerebellar ataxia.[33]

- **Malignant hyperthermia**

In this inherited autosomal disorder, anaesthetized patient develops sudden high grade fever and muscle rigidity. Use of general anesthetic agents or some skeletal muscle relaxants could provoke such episodes. The genetic defect insarcoplasmic calcium release channel (Ryanodine receptor), voltage dependent calcium channel and voltage dependent sodium channel are thought to be involved.[33]

- **Renal disorders**

Mutation in gene coding for inwardly rectifying potassium channel leads to loss of functionof channel protein resulting in Barter's syndrome. Barter's syndrome is associated with renal salt-wasting leading to severe intravascular volume depletion, metabolic disturbances and progressive renal failure. In another disorder, mutation in kidney specific voltage gated chloride channel results in X-linked nephrolithiasis.[33]

- **Autoimmune disorders**

Lambert-Eaton myasthenic syndrome is caused by antibodies to voltage gated calcium channels at the nerve terminal on which acetylcholine release depends. This results in a decrease in the amount of acetylcholine released by the nerve impulse.[33]

CONCLUSION

Ion channels are targets of many therapeutically useful agents. Many disorders are currently treated by drugs acting on ion channels. Epilepsy (Na^+ channel and $GABA_A$ receptors), anxiety ($GABA_A$ receptors), cardiac arrhythmias (Na^+ channel, K^+ channel and Ca^+ channels), diabetes (K^+ channel), hypertension (Ca^+ channels and K^+ channel), local (Na^+ channel) and general anaesthetic agents ($GABA_A$ receptors, K^+ channel), anti-emetics (5-HT3 receptors), muscle relaxing agents (nicotinic ACh receptors) and agents to help reduce smoking (nicotinic ACh receptors) are few of the examples. According to the recent updates, worldwide sales of ion channel-targeted drugs are estimated to be approximately US$12 billion.

Genetic disorders of channel proteins (i.e. channelopathies) can give rise to disease states like episodic ataxias, epilepsy, diabetes, cardiac arrhythmias andcystic fibrosis. Recent advances in drug discovery technologies have triggered the research for novel targets acting upon ion channels.This proactive research related with ion channels could lead to future therapeutic interventions against disease states like cancer, immune disorders, neuropathic pain, cystic fibrosis, drug addiction and neurodegenerative disorders. Experimental evidence also suggests the potential role of ion channel modulators in preventing tumour growth, metastasis and conquering resistance of tumour cells to chemotherapeutic agents.

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