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Ion Channels Association with Diseases and their Role as Therapeutic Targets in Drug Discovery

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ABSTRACT

Ion channels as potential drug targets has been widely designated in pharmaceutical industries for treatment of life threatening diseases .This targeting is a challenging area in drug development and discovery because of availability of extensive knowledge of structures and functions about ion channels such as sodium and calcium voltage-gated ion channels found in mammals. This knowledge mostly obtained on the basis of 3-D crystallographic studies along with their computational analysis. Analysis and modulation of Ion channels provide us with understanding of various properties, such as channel opening, pore function, voltage sensing and ion selectivity. Any disruption and deregulation in the mentioned functions leads to pathological states thus supporting the idea of their choice as valid targets in drug discovery projetcs. In this paper we focused on importance of ion channels in drug discovery and reviewed their structures and functions and their role in disease and drug discovery and their modulation technologies in drug discovery for their targeting purpose.

Keywords: Ion Channel, Target, Drug Discovery, Pathology. Modulation of Ion Channels

I. INTRODUCTION

Ion channels are membrane proteins which form potential drug targets. Therapeutic drugs with ion channels as their targets has been formed the third bestselling prescribed drugs so far. In this paper we survey information on various types of ion channels that play an important role in pathophysiological conditions, providing designation of target specific drugs that either cause direct block of channel or modulation of ion channel functions. Attempts are required for exploration of new drug gable ion channel targets with a strong focus on the following aspects: Exploration of technology of channel discovery at the molecular level using high-throughput screening (HTS), Identification of the disorders accompanied with ion channel dysregulation, Exploration of therapeutic scope for ion channel modulation and Identification of strategies for ion channel modulators.[1,2].Although ion channels with high therapeutic potential has taken a great place in drug discovery but only 7% of them have been commercially exploited as drug targets. However, only, ligand or voltage –gated channels in excitable tissues has been targeted so far and non-voltage-gated cation channels present in non-excitable tissues like inflammatory cells have been remained unexplored and commercially unexploited as drug target. In the history of ion channels targeting drugs, Sulphonylureas were used as blockers of the L type voltage –gated calcium channels (L-VOCCs) for treatment of cardiovascular diseases .These drugs were strongly investigated on observation in human patients and animal models. The molecular targets for sulphonylureas were, however, detected as the K ATP channels in B cells of pancreases. Later on after identification of K ATP channels molecular compositions of these channels was worked out ,and since then ion channels became more attractive targets in pharmacological industries .With the appearance of patch-clamp instrumentation technology, which facilitate investigation of opening , closing and ion conduction, voltage –gated ion channel research area has become a promising filed in drug target discovery projects . Non-voltage gated ion channels also show attractive interest in development of novel drugs for

CBS diseases due to their potential role. During 19880s, ion channels research area was expanded and a large number of ligand-gated ion channels were investigated and categorized. Among these, the prominent ones are 5HT3 receptors and nAChRs along with their appropriate ligands identified .For identification of blockers antagonists of 5HT3 channels, animal models were used to treat certain neuronal diseases such as migraine and anxiety which were not so much successful. In case of other receptors (nAChR) blockers as muscle relaxant have been discovered that were quite effective. The difficulties are present in ion channel discovery, in spite of wide availability of technologies, are lack of appropriate high –throughput assay technologies and pharmacological tools for assessment of their physiological roles , their role in development of pathophysiological conditions and verification of them as targets .[1,2,3,4]

II. METHODS AND MATERIAL

A. Molecular Structures and Properties of Ion Channels

Ion channels are membrane proteins which are pore forming and their functions are such as establishment of resting membrane potential, configuration of action potential, conduction of electrical signals by gating the ions flow across the cell membrane, regulation of cell volume and controlling ion flow across secretory and epithelial cells. Ion channels are classified into four divisions such as:

Voltage gated : These type of channels opens while changing membrane potential of the channel. Examples are K^+,Na^+ and Ca^+ channels distributed in cardiac muscles

Ligand –gated: includes three types :
External ligand-gated these type of channels opens due to their induction by a specific extracellular ligand molecule.

Internal ligand-gated these type of channels open or close when an intracellular molecule like ATP or cyclic nucleotide stimulate them.

Mechanically –gated. These open by exertion of some mechanical pressure (there is no involvement of membrane potential)

Voltage gated channels consist of two transmembrane helices which form the basic building block and separated by a loop which is called as P-loop and form a inverted pore. In voltage –gated cation channels, more transmembrane helices form a basic block which contains six transmembrane helices and the P-loop. For a functional voltage –gated channel, four basic blocks are required. The location of amino and carboxyl terminals of the six alpha helical transmembrane proteins is in the cytoplasm. The transmembrane domains contain intracellular and extracellular loops. In calcium and sodium channels, these blocks are associated with one large polypeptide, forming the alpha-1 subunit in calcium channels and alpha subunit in sodium channels .Except to these subunits which form central pore forming subunits, sodium channels contain two auxiliary beta subunits , and calcium channels consist of large complexes of alph1,alpha2 subunits. Formation of actual pores in channels is done by subunits apposition. The pore forming subunits are named the alpha subunits, while the complementary subunits are symbolized as α β γ δ and so on. While some ion channels allow the passage of ions based on their carrying charge, the archetypal pore is only one or two atoms wide at its narrowest point. It transports specific ions like NA+ or K+ and transfer them through the membrane. Passage process through the membrane in some ion channels is regulated by "gate" which is opened and closed by external factors such as temperature, chemicals, electrical signals and mechanical forces, depending on the channel variety. Channels are gated because they open transiently and theses opening and closing of gates precisely controlled. [2, 5, 6].Voltage gated channels are mainly consisting of four types such as:

Ca^{++} channel: It is calcium channel which shows selective permeability to calcium ions. It consist of five types : L-type which is mostly distributed in Skeletal muscle, smooth muscle, bone (osteoblasts), dendrites and dendritic spines of cortical neurons and ventricular myocytes, P/Q type present in Purkinje neurons in the cerebellum / Cerebellar granule cells, N type distributed throughout the brain and peripheral nervous system, R type found in Cerebella granule cells, other neurons and T type found in neurons, cells that have pacemaker activity, bone (osteocytes), thalamus (thalamus).

K^+ channel these are potassium channels that are found most widely in all living organism. They consist of potassium pores which are selective to potassium. They consist of following classes: Calcium-activated potassium channel ,Tandem pore domain potassium channel , Voltage-gated potassium channel and Inwardly rectifying potassium channel.

Na^+ channel are another type of integral membrane proteins that transporting sodium through plasma membrane they are grouped into voltage-change ("Voltage-gated", "voltage-sensitive and voltage-dependent" sodium channel.
CL^- channel are another type of ion channels which consist of 13 members.[2]

B. Role of Ion Channels in Diseases and Drug Discovery

As the importance and role of every molecule in drug discovery and its targeting is understood by analysis its participation in emergence of diseases and its linkage with pathophysiological states. Here we focus on diseases associated with ion channels to provide extensive knowledge to support their role as attractive target in drug discovery. Ion channels are various types and distributed in variety of tissues and they have several functions which have vital role in physiology of the body. Any mutation in the genes encoding them can cause specific diseases. Ion channels functions are regulated by several factors and any dysregulation of their function leads to pathophysiological state. A number of human diseases have been detected that are caused by ion channels gene mutation. As these diseases are due to mutation of their genes so they are inherited and known as channelopathies. Some specific types of channelopathies are mentioned below: [2]**.**Sodium –channel diseases: some specific diseases are associated to dysfunction of sodium channel which is due to its gene mutation. These diseases are such as certain types of muscle spasms, Liddle's syndrome which is due to inadequate sodium transport out of the kidney. Other diseases which is result of defection and disruption in function of sodium channels are Blockage of hERG, Showing prolonged QT interval in ECG, Hyperkalemia, periodic paralysis of skeletal muscles, Long QT syndromes and Familial generalized epilepsy. [2,8,9].Potassium channel diseases: The most inheritable life threatening disorders in the heartbeats are caused by defection in K+channels. Other important diseases associated to this ion channel are Episodic ataxia type 1 and Benign infantile epilepsy [10-14].Chloride –channel diseases : Dysregulation of Cl^- channels caused cystic fibrosis and this defect is a inheritable disorders and causes kidney stones . Other disorders related to this ion channel are Osteoporosis, Epilepsia, Myotonic congenital[1,2]. Calcium channel diseases: The main disease caused by dysfunction of calcium channels are Migraine,Spinocerebellar ataxia type6,Congentital night blindness, central core disease and Hypokalemic paralysis of skeletal muscles .[1,2] .Due to distribution of ion channels in different body cells ,tissues and organs ,several diseases caused because of dysfunction and dysregulation of these distributed ion channels .These diseases mainly are Hypertension due to dysregulation of voltage gated Ca^{++} channels in cardiovascular system. Epilepsis due to dysregulation of voltage gated Na+ channels in central nervous system. Stroke and inflammatory bowel syndrome due to dysregulation of voltage gated Ca+ channels in nervous system .Neuropathic pain due to dysregulation in voltage gated Na^+ channel in nervous system. Cystic fibrosis and Myotonia congentita due to dysregulation in CL^- channels in lungs, pancreas and cardiac muscles respectively and Paralysis due to dysregulation in voltage gated K^+ channels in skeletal muscles. [2, 15] Association of ion channels with mentioned diseases has demonstrated their significance in drug discovery as drug targets. Studies on ion channels regulation and expression helped us in understanding their properties such as voltage sensing, channel opening and closing, pore function and ion selectively. Any dysregulation of these functions result in development of pathological states thus support their role as novel drug targets. The ion channels consist of several interaction sites that can be investigated and studied for development of potential drugs. Expression and regulation of ion channels's function are complicated phenomena. In addition to transmembrane proteins, some complementary regulatory proteins are also involved in their functioning and this point adds another aspect to modulation strategy of ion channels. Highly excitable ion channels found in nerve and muscle cells can be stimulated by passing a current, so specific channel can be targeted by appropriate drugs. Their excitability can either be increased or decreased for better study and analysis. Ion channel modulation has been a fortunate area for drug discovery. [2,16-18]Modulation of ion channels helps in development of novel therapeutic drugs without extensive knowledge of their structures. This challenging area of ion modulation provides new opportunities for discovery of new drugs and designation of drugs for targeting specific ion channels is done by mechanisms of direct channel block or ion channel modulation for functional expression. [19,20].In drug discovery process via ion channel modulation following methods is used:

Voltage –dependent block. This direct blocking method of channel. In this method ion channel is blocked by a charged drug molecule.

Tonic-block. It is also called state –independent block and in this strategy, no current change is experienced by the channel and the channel may be in inactive or active state. In this strategy a tonic blocker or the drugs is bounded to the channel whether it is open or close .In this strategy, several pulses fail to unblock the channels, thus result in state –independent block.

State –dependent block .In this strategy the channel can be in three states namely resting, activated and inactivated states. During resting state ,the channel remains open and blocked by high affinity drug molecules towards the channel. This is called open-state block strategy. During inactivated state , binding of a drug molecule to the channel without alternation the channels open time occur as result of decreasing the ion flow .This strategy called inactivated –state block.

Phasic block. In this strategy , Irrespective of channel's states such as open, activated, inactivated, a drug molecule with high affinity towards the channel is applied and repetitive pulses enhance the block .[2,15-17]

Role of accessory proteins in the expression of ion channel is notable .Some drugs functioning as blockers which inhibit specific accessory proteins to regulate ion channel functioning .Most channels are studied and analyzed as drug target so far belong to voltage-gated and ligand gated classes found in excitable tissues where blockers are detected for clinical purposes .However , discovery of ion channels in non –excitable cell types are basically unexplored . $5HT_3$ and nicotinic acetylcholine recerptors are the best known examples of ligand –gated channels and their blockers have been identified that treat effectively many neural diseases . These studies mainly involved animal models.[2,19,20] The technologies for modulation of ion channels play essential role in their modulation. Different types of assay technologies are available for researchers to modulate ion channels . Although due to lack of high throughput technology, drug discovery process of ion channel is very slow but still using available technologies and their combination with other related technology is helpful for modulation of ion channels. The most known technologies are fluorescent technology, Non fluorescent technology and electrophysiology.

Fluorescent technology is used for determination ion concentration with the help of florescent indicators .This technology has been successfully used for studying Ca++ and P2X channels and Fluo-3 and 4 ,Fura and Indo-1 used as indicators .

*Non –fluorescent tech*nology is a direct method of measurement of ion flux through a channel with radiotracers such as 86Rb+ for potassium channels and $^{22}Na^{+/14}C$ for sodium channels or by using atomic absorption spectrophotometer .

Electrophysiology. This technology is a high throughput technology and used for screening ion channel function and also enables investigation of opening, closing and ion transfer of channels. It demonstrated that a single assay technology may not be sufficient to address all the problems regarding ion channels function and a combination of these technologies may be useful and more effective to achieve the desirable results.[2]

III. CONCLUSION

Ion channels as significance attractive targets for treatment of various types of life –threatening diseases such as Hyperkalemia periodic paralysis of skeletal muscles ,Long QT syndromes and Familial generalized epilepsy, disorders in the heartbeats ,Episodic ataxia type 1 and Benign infantile epilepsy ,Migraine, Spinocerebellar ataxia type6,Congentital night blindness, central core disease and Hypokalemic paralysis of skeletal muscles ,cystic fibrosis ,Osteoporosis,Epilepsia and Myotonic congenital, has been attracted drug discovery attention .Studies of regulation and expression of ion channels provided scientists with extensive knowledge about ion channels and their role in drug discovery , these knowledge widely are about opening and closing of the pore, orientation of pore, structure of pore, voltage sensing, gating process, ion selectivity and pore function. These basic and essential knowledge have been supported the idea of choice of ion channels as therapeutic targets .By studying of above mentioned functions and structures , scientist enable to identify associate pathological states which emerged as result of dysregulation of these functions. In drug discovery, one of the most challenging areas for targeting ion channel is their modulation. Modulation of ion channels has advantage of not requirement of extensive knowledge of the molecular structure of ion channels, their subtypes and their full regulation of their expression. Most of the drugs developed by modulation methods marketed are without extensive knowledge of above mentioned characters and they are therapeutically effective. Generally development of ion channel drug is very slow due to inadequate availability of high-throughput technologies. Electrophysiological measurement technologies have not achieved successful results because of their disadvantages such as low speed, time consuming and deficiency in sensitivity .However, exploration and synthesis of novel drug molecules as ion channel's ligands has been possible via advances in patch clamp instrumentation technology. Now days due

to advancement in *in silico* drug designing methods used in bioinformatics projects, several companies undergo such methods for benefitting ligand discovery. Although ion channels has been started for analysis and new discovery but as compared with some important clinical drugs, as a class, they are poorly explored and underexploited in drug discovery projects. This review considered ion channels as attractive drug targets in challenging area with high potential ability of being targets, and encourage scientists to focus on this challenging area with promising results for development of high desirable drugs and more successful treatment of life threatening disease.

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