



Ion Channels as Drug Receptors

Dept. of Pharmacology, GMC
Amritsar

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Types of Receptors

- Ion Channels - Iontropic Receptors
- G-Protein Coupled Receptors-
Metabotropic Receptors
- Kinase Linked Receptors
- Nuclear Receptors

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Ion Channels

- Ion channels are present in virtually every living cell.
- They are proteins that exist within the membrane that surrounds each cell, acting as a 'doorway' through which ions – such as potassium (K^+), sodium (Na^+) and calcium (Ca^{2+}) can pass.
- Channels differ with respect to the ions they allow through, and to the way they regulate the flow of these ions.

Ion Channels

- Ions cannot penetrate the lipid bilayer of cell membranes.
- They are transported across cell membranes with the help of Ion Channels.
- Only after Erwin Neher and Bert Sakmann developed the “patch clamp technique” was the existence of ion channels proven.

Patch Clamp Technique

- The "patch" refers to the patch of membrane that interfaces with a recording electrode.
 - The flow of current / voltage into the patch is recorded.
- The "clamp" refers to holding the membrane at a fixed voltage / current and recording the resultant current / voltage.
- Microelectrodes are used to form a seal with the membrane and then break the seal by applying a negative pressure.
 - This results in the membrane forming a continuum with the microelectrode.
- The current / voltage of the membrane then is amplified by an amplifier; and the amplified signal analysed.

Role of Ion Channels

- Electrical impulse generation and conduction along nerves in the central and peripheral nervous system, the heart and other organs
- Fluid balance within cells and across cell membranes.
- Signal transduction within and among cells.

Features – Ion Channels

- Protein molecules form water filled pores that span the membrane
- Switch between open and closed states.
- Rate and Direction of movement depends on the electrochemical gradient of the ions

Characteristics

- Selectivity of the channel for a particular ion.
- Gating properties
- Molecular structure

Selectivity

- Ion channels are either Cation or Anion selective
 - Cations
 - Na^+ , Ca^{2+} or K^+
 - Anions – Cl^- .

- Membranes in a resting cell are relatively permeable to K^+ but impermeable to Na^+ and Ca^{2+} .
- Example : Drugs that open Potassium Channels reduce membrane excitability.

Gating

- Voltage gated channels
- Ligand gated channels
- Calcium release channels
- Store operated calcium channels

Voltage gated

- Open when cell membrane is depolarised
- They modulate excitability of membranes
 - Na⁺, K⁺, Ca²⁺ channels
- Channel opening – activation is initiated by membrane depolarisation
- Short lasting and followed by a slower Inactivation

Example : Calcium Channel

- 5 different subtypes of Voltage gated calcium channels.
- L, T, N, P and R
- L Channels- Cardiac and smooth muscle
- T Channels- CNS Neurons
- Calcium channel antagonists are powerful Direct antagonists
- Some drugs act indirectly through GPCRs.

Ligand Gated Channels

- Activated by binding of a chemical Ligand to the channel.
- Fast in activity
- Neurotransmitters glutamate, acetylcholine, GABA and ATP
- Intracellular signals activate some channels:
 - Calcium activated Potassium channels
 - ATP sensitive Potassium Channels
 - Vanilloid receptors

- Ligand gated channels activated by excitatory NT are non-selective and conduct Calcium as well as other ions.
- NMDA receptor is highly permeable to Ca activation can lead to excessive calcium entry resulting in cell death-**Excitotoxicity**.
- Important for neurodegenerative disorders Epilepsy, Parkinsonism, Alzheimer's disease.

Calcium release channels

- **Ryanodine receptors**
 - release calcium ions from the sarcoplasmic /endoplasmic reticulum into the cytosol
 - thereby convert extracellular stimuli into intracellular calcium signals or amplify and regulate the intracellular calcium concentration.

InsP3

- Inositol 1,4,5-trisphosphate gated Calcium channels
- Similar to Ryanodine receptors but have distinctly different properties.

Store operated Ca channels

- Activated when intracellular Ca stores are depleted.
- Allow calcium entry by a GPCR mediated mechanism.

Channelopathies

- Diseases caused by mutations in genes encoding ion channels.
- Other than genetic mutations, autoimmune, toxic, or iatrogenic mechanisms may be involved in the channelopathies.

Examples-Channelopathies

- Intermittent diseases in people who are otherwise healthy and active
 - epilepsy, migraine, arrhythmias
- Debilitating illnesses
 - muscular disorders,
 - deafness, blindness,
 - Rasmussen's encephalitis
- Rare disorders like periodic paralysis.

- Myotonia congenita (Thomson's disease)
- Periodic paralysis (hyper and hypokalaemia)
- Malignant hyperthermia
- Long QT syndrome
- Cystic fibrosis
- Heritable hypertension (Liddle's syndrome)
- Familial persistent hyperinsulinemic hypoglycemia of infancy
- Generalized Myotonia (Becker's disease)

As drug targets

- Small molecule compounds have been shown to both activate and inhibit ion channels.
- Ion channels are therapeutic targets because they play crucial roles in all functions and pathophysiological processes in the human body
- Ion channels represent an important class of drug targets for various diseases

Examples

- Calcium channel blockers
- Potassium channel blockers (oral hypoglycaemics)
- Diuretics (amiloride) - sodium channels
- Anticonvulsants (clonazepam; phenobarbitone) - chloride channels
- Anticonvulsants (carbamazepine; phenytoin; valproate, lamotrigine) - sodium channels

...Examples

- Antiarrhythmic drugs (amiodarone) - potassium channels
- Class I antiarrhythmics - sodium channels
- Local anaesthetics (lignocaine; bupivacaine) - sodium channels
- Antihypertensive drugs (diazoxide) - potassium channels
- Adenosine - potassium channels
- Benzodiazepine - chloride channels

Prospects

- In the search for new drugs, ion channels have become a favourite target since they provide the ability to regulate many physiological processes.
- They could potentially be used to treat a wide range of diseases
- Epilepsy, migraine, pain, allergy, asthma, glaucoma, stroke, irregular heart beat and cancer.