Review Article

Channelopathies an Approach to Elevate Level of Cure- A Review

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ABSTRACT

Channelopathies is group of diseases which is concerned with changes occur in the structural unit i.e., cell and its subunits (channels). Particularly disturbances in equilibrium potential in cell membrane carry toward the major cause of disease. Study of channel physiology with its mechanism is essential methodology to establish the differential factor in between normal phenomenon and disorder. Specific channels permit movement of selected ions through cellular membranes and are of important importance during variety of physiological processes, particularly in excitable tissues. In this review channelopathies in diseases like Central nervous system, Cardiovascular system, Renal system with their mechanism of action of channel disruption and treatment approaches have been covered.

Keywords: Channel's physiology, Channel disruption, Channelopathies in diseases, Treatment approaches.

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INTRODUCTION

The Channelopathies an heterogeneous group of genetically and phenotypically relevant neurologic disorders that results from genetically determined defects in ion-channel located within the membranes of all cells and much of cellular organelles.

Channels are pores within the cell wall, through these pore ions flow across the membrane and depolarize or hyperpolarize the cell. Channels are often classified into 3 types: non-gated, directly gated and second messenger gated channels. Among the important directly gated channels are voltage gated (Na (+), K (+), Ca (2+), Cl (-)) and ligand gated (ACh, Glutamate, GABA, Glycine) channels.[1] Channels are macromolecular protein complexes within the lipid membrane. They are divided into distinct protein units called subunits. Each subunit features a specific function and is encoded by a special gene. Etiological changes in these channels result in various types of neurological [migraine, epilepsy, anxiety, dementia, depression, schizophrenia], cardiovascular [hypertension, torsade de point], cancer, asthma, multiple sclerosis, kidney stone etc. Genetical inheritance of channel also mutate the function of particular channel.[2]

Ion Channel Physiology

Voltage-gated ion channels are proteins essential for establishment of the resting membrane potential in muscle and the ability of these membranes to generate action potentials. Voltage-gated opening of sodium channels leads to the genesis of "all-or-none" action potentials. A simultaneous effect of depolarization of the membrane (albeit on a slower time scale) is that the opening of voltage-gated potassium channels. Along with the inactivation of the voltage-gated sodium channels, the movement of positive potassium ions out of the cell through voltage-gated potassium channels leads to a relatively rapid repolarization of the muscle membranes.[3] Chloride channels are responsible for a majority of the polarity of resting membranes. The voltage-gated L-type calcium channel in striated muscle, also referred to as the dihydropyridine receptor because dihydropyridines block this channel, allows conductance of calcium into the cell. Although ion channels are essential for the traditional function of all eukaryotic cells, they're particularly important within the systema nervosum for the generation, repression and propagation of action potentials. Ion channels are often highly selective for a specific ionic species, for instance, sodium, potassium or calcium. The opening of sodium channels results in depolarisation of neurons whereas potassium channel opening results in hyperpolarisation, as does the opening of chloride channels in adult neurons. The opening of calcium channels causes membrane depolarisation, but calcium ions even have more important roles as second messengers. Hence, loss of function mutations in potassium or chloride channels or gain of function mutations should cause disorders characterised by hyperexcitability, like epilepsy. However, the effect of a mutation depends on the precise neuronal circuitry

involved. For example, a mutation that causes a gain of function effect in inhibitory interneurons can decrease excitability. Given their importance in neuronal excitability and synaptic transmission through the central and peripheral nervous systems, it's not surprising that mutations in Ion channel genes can cause disease. Many of the mutations that are related to ion channel disorders are missense mutations that affect channel kinetics. However, inherited mutations and chromosomal rearrangements can affect any stage of ion channel biogenesis, including transcription, mRNA processing, splicing, translation, folding and trafficking, also as subunit assembly.[4]

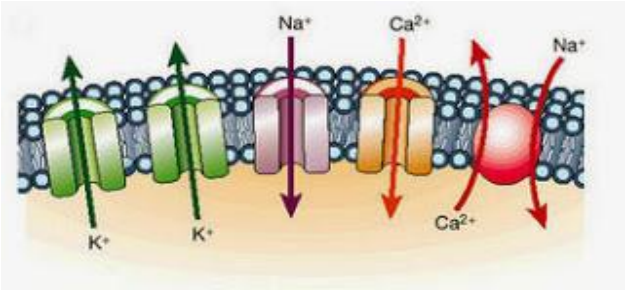


Figure 1: Illustration of Channels

Potassium channels are membrane-bound tetrameric protein complexes. Each subunit may be a polypeptide with six putative transmembrane segments (S1-6). Four identical subunits may associate to make a homomeric K channel. Alternatively, different subunits may assemble to make a heteromeric K channel. Mutagenesis studies have identified several critical functional domains in K channel. They constitute the foremost diverse class of ion channels and are expressed in both excitable and non-excitable tissues. More than 13 subfamilies of potassium channels are described in vertebrates. Of all the episodic disorders caused by defective ion channels, the long QT syndrome (LQTS) is the most severe. LQTS may be a genetically heterogeneous disorder that there are 6 loci. Three of these are associated with potassium channels; one with sodium channels (LQT3) and the last two have still to be completely identified.[4]

Sodium Channels are localised membrane depolarisation of excitable cells results from an increase in sodium conductance of the membrane. This localised phenomenon is amid further depolarisation and recruitment of adjacent sodium channels resulting in a more generalised membrane depolarisation. Spontaneous inactivation of the sodium channels then occurs rapidly and leads to subsequent repolarisation of the membrane.[3,4] Channelopathies refer to disorders resulting from defective ion channel functioning and include neurological, cardiovascular, and muscle disorders. Structure Composed of α, β subunits A subunit consist four homologous domains, each with 6 α helical trans membrane subunits an α subunit form core of the channel and function on its own B subunit displays altered voltage dependence and cellular localizations highly conserved S4 subunit act as a voltage sensors domain Consist inactivation gate selectivity filter.[5]

Structure of α subunit Mainly consist of 6 subunits in each homologous domain Ion conductions is administered mainly through pore which is selective in nature Pore domain is split into two portions i.e., external part and inner pore External portions is made by P-loops that connect S5-S6 subunits Inner pore is made by the combined S5-S6 subunits from each domain All subunits are linked to each other.

Structure of β subunit β1 is non-covalently bounded, has four cysteine in its extracellular domain that contribute Ig like fold Subunit β1 abundantly present in muscles, heart, and brain Subunit β2 is covalently bounded, has five extracellular cysteine and form a disulphide bond to the α subunit β2 forms a single intracellular carboxyl terminal domain and a large glycosylated extracellular domain Functioning of β subunits is to modulate the kinetics of activations.

Selective for sodium ion Selective filter is formed from charged aminoalkanoic acid residue, which magnetize only charged sodium ion rather than negative ions like chloride Pore size is about 0.5 nm, which is enough for passage of one sodium ion with water molecule.

Calcium Channels Specialised ion channels within the membrane of nerve cells mediate calcium influx along the electrochemical gradient. As with sodium channels, these calcium channels are activated by depolarisation of the membrane, but in contrast to sodium channels, inactivation of the channels is slower in order that membrane repolarisation is consequently delayed. There are eight different human genes that code for calcium channel proteins.[5] Calcium channels may be classified according to their inactivation properties; transient (T-type), or long lasting (L-type); or according to the tissues during which they're expressed; brain (B), nerve (N), Purkinje cell (P): or their toxin sensitivity e.g., toxin resistant (R). Of particular interest to anaesthesiologists are two distinct sorts of calcium channels that are expressed in striated muscle. These are the dihydropyridine receptor (DHPR) and therefore the ryanodine receptor (RYR1). They are situated respectively within the t-tubules and therefore the sarcoplasmic reticulum of striated muscle. RYR1 is responsible for the release of calcium ions from the sarcoplasmic reticulum or endoplasmic reticulum into the cytoplasm, an essential step for muscle contraction.

Chloride channels are found within the cell wall of cells involved in cell volume regulation, transepithelial transport, secretion of fluid from secretory glands, and stabilization of membrane potential. Cystic fibrosis may be a common inheritable disease related to chloride channel abnormalities. The clinical manifestations of this disease are thanks to a defect during a chloride channel protein called the CF transmembrane regulator (CFTR), situated at the apex of epithelial cells lining the ducts of organs like the pancreas, skin and therefore the lung. The mutant CFTR blocks the passage of chloride ions into the lumen.[6]

Table 1: Channels and associated

Diseases	Ion channels involved
Cystic fibrosis	Chloride
Episodic ataxia	Calcium
Spino-cerebellar degeneration	Calcium
Eaton Lambert syndrome	Calcium
Migraine	Calcium
X-linked congenital stationary night blindness	Calcium
Heritable hypertension (Liddle's syndrome)	Sodium
Familial persistent hyperinsulinemia hypoglycemia of infancy	Potassium
Hereditary nephrolithiasis (Dent's disease)	Chloride
Long QT syndrome	Potassium
LQT1	Potassium
LQT2	Sodium
LQT3	Chloride
Myopathies	Chloride
Becker's myotonia congenita	Sodium
Thomsen's myotonia congenita	Calcium
Para myotonia congenita	Sodium
Central core disease	Calcium
Hyperkalemic periodic paralysis	Calcium
Hypokalemic periodic paralysis	
Malignant hyperthermia (RYR1)	

Mechanisms of Channel Disruption

Started from production step which includes mutation in gene and its coding, that put forward towards the processing step in which specific proteins are recognized for the action. In conduction step particular mutated signal are conducted for the further processing disruption in signals, at end the gating is muted for the ion's selectivity.

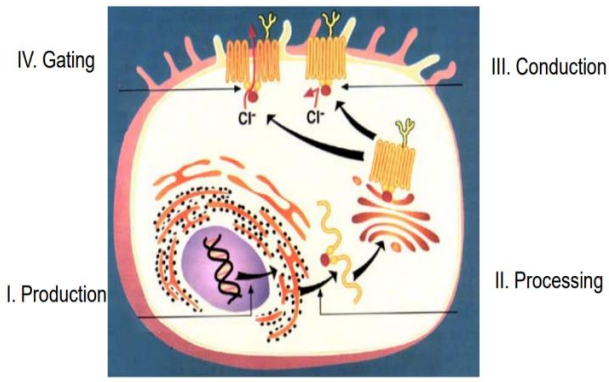


Figure 2: Illustration of mechanism of channel disruption

Consequences of Ion Channel Mutations

Mutation of ion channel can alter,

-Activation
-Inactivation
-Ion selectivity/Conduction

-Abnormal gain of function
- Loss of function

Channelopathies of The Central Nervous System

Epilepsy

Disease which relevant to major cause of neurological diseases, various types of epilepsy occur distinguished as per location of brain, verity infantile encephalopathies to relatively benign focal seizures. Monogenic channelopathies only account for a little fraction of the epilepsy seen in clinical practice.[7] Although most epilepsies aren't inherited, it's estimated that about 70% of an individual's risk of developing a disorder like epilepsy is accounted for by genetic risk factors.

Channelopathies associated with epilepsy

Early onset epileptic encephalopathies are generally severe epilepsy syndromes that always have a poor neurodevelopmental outcome. Severe myoclonic epilepsy of infancy, also referred to as Dravet syndrome, manifests as intractable seizures that begin within the first year of life related to developmental regression and cognitive impairment. Missense or nonsense mutations in the SCNA1 gene which encodes the pore-forming unit of the fast sodium channel, are present in over 80% of cases and are typically de novo, leading to haploinsufficiency. More rarely, mutations in other genes including SCN1B and SCN2A are found, also as mutations within the GABAA receptor subunit gene GABRG.[8]

For some time, it had been not understood how a mutation during a sodium channel leading to haploinsufficiency and reduced function could cause hyperexcitability. However, it had been subsequently found that Na channels have an important role in GABAergic inhibitory neurons, thus loss of function channels leads to hypo excitability of inhibitory networks and consequently hyperexcitability of neuronal networks and successively, epilepsy. SCN2A mutations have also been related to other infantile encephalopathies including infantile spasms, acute encephalitis with refractory repetitive partial seizures and recurrent encephalopathy. Recently, mutations of GABRA1, GABRB2 and GABRB3 related to infantile spasms and Lennox-Gastaut syndrome.

Generalised epilepsy syndromes

Generalised epilepsy with febrile seizures is a genetically and clinically heterogeneous familial epilepsy syndrome. It develops febrile seizures early in life that persist beyond the age of 6 years. Numerous different genes are implicated; namely the sodium channel genes SCN1A, SCN1B, SCN2A and thus the GABAA receptor subunit genes GABRG2 and GABRD.[9] Benign familial neonatal infantile seizures are an epilepsy syndrome characterised by sudden onset and subsequent remission of seizures in infancy. It is caused by missense mutations within the SCN2A gene. Benign familial neonatal convulsions (BFNC) a similar syndrome characterised by brief seizures, occurring on

the second or third day after birth that usually terminate within 6 weeks with normal neurological development. It is often caused by loss of function mutations in two potassium channel genes, KCNQ2 and KCNQ3, which code for the potassium channel subunits K.

Absence epilepsy

Absence epilepsy has been reported during association with mutations in a number of various genes that code for ion channels. Variants in CACNA1H which codes for the α1H pore-forming subunit of T-type calcium channels are reported, during a subset of patients with childhood absence epilepsy. Missense mutations of GABRA1, GABRA6, GABARB3 and GABARG2 which encode various GABAA receptor subunits have also been implicated in childhood absence epilepsy.[10]

Focal epilepsy syndromes: Autosomal dominant nocturnal lobe epilepsy (ADNFLE) may be a rare syndrome characterised by frequent short-lived motor seizures that typically occur during sleep or on waking. Mutations in three genes encoding subunits of the nicotinic acetylcholine receptor (AChR), CHRNA4, CHRNB2 CHRNA2.

Table 2: Channels and genes mutation associated syndrome

Channel	Gene	Channel	Epilepsy syndromes
Sodium	SCN1A	α subunit of Na	Severe myoclonic epilepsy of infancy (SMEI) Intractable epilepsy with generalized tonic-clonic seizures (IEGTC). Migrating partial seizures of infancy (MPSI) Generalized epilepsy with febrile seizures (GEFS+)
	SCN1B	β subunit of Na	SMEI GEFS+
	SCN1C	α2 subunit of Na	SMEI Ohtahara syndrome Benign familial neonatal infantile seizures (BFNIS) West syndrome Infantile spasms
	SCN3A	α3 of Na	Partial Epilepsy
Potassium	KCNQ2	K	Benign familial neonatal convulsions Infantile encephalopathy Myokymia associated with neonatal or early infantile epilepsy
	KCNQ3	K	Benign familial neonatal convulsions
Calcium	CACNA1 H CACNA1 A	α subunit of t-type calcium channels Ca channel α subunit	Childhood absence epilepsy Episodic ataxia and childhood absence epilepsy
Acetylcholine receptor (AChR)	CHRNA4, CHRNB2 CHRNA2	Subunits of nicotinic Ach receptor	Autosomal dominant familial nocturnal frontal lobe epilepsy
GABA	GABRA1	α subunit of GABA receptor	Childhood absence epilepsy Idiopathic generalized epilepsy (IGE) Juvenile myoclonic epilepsy (JME), Infantile spasms, Lennox-Gastaut Infantile spasms, Lennox-Gastaut
	GABRA2	B2 subunit of the GABA receptor	
	GABRA3	**β3 subunit of GABA receptor**	**Absence epilepsy Infantile spasms, Lennox-Gastaut**

Treatment approach of epileptic channelopathies

Increased understanding of channel dysfunction in various epilepsy syndromes can cause an individualised approach to treatment. For example, functional work on mutations in KCNQ2 have shown that the functional changes (decreased voltage sensitivity) are often restored by retigabine, a neuronal KV7 activator.[10] it's also been recognised for a few times that medications that block sodium channel function can worsen seizures in SMEI. With further research, there's potential for precision medicine during which drugs target specific channels or maybe target the mechanism by which a channel becomes dysfunctional.

Channelopathies in Migraine

Migraine, one of the diseases occurs in majority of population. Familial Hemiplegic Migraine (FHM) may be a subtype of severe migraine inherited in an autosomal dominant fashion. Patients have severe auras that include unilateral weakness, also as visual, somatosensory or dysphasic symptoms, typically followed or amid migraine's headaches. FHM is genetically heterogeneous and is

assessed into three types, FHM1 accounts for 75% of genetically confirmed cases and is caused by missense mutations in CACNA1A, an equivalent gene that is implicated in EA2 and SCA6.[11] Functional expression studies have shown that FHM mutations end in various gain of function effects, including increased Calcium current density in cerebellar neurons and enhanced neurotransmitter release. FHM2 is caused by loss of function mutations within the ATP1A2 gene. This gene encodes the α2 subunit of Na+/K+ pumps, which contribute to maintaining transmembrane ion gradients. FHM3 is related to heterozygous mutations within the sodium channel gene SCN1A.

Motor and sensory neuropathies Several inherited neuropathies that present mainly with motor dysfunction are known to flow from to ion channel dysfunction. Three allelic disorders, Charcot-Marie-Tooth disease type IIC (HSMNIIC), scapuloperoneal spinal muscular atrophy (SPSMA) and congenital distal spinal muscular atrophy (SMA) are caused by mutations in another class of TRP channel—the TRPV4 channels. HSMNIIC is an autosomal dominant axonal neuropathy characterised by progressive distal limb weakness and weakness of the diaphragm laryngeal muscles and vocal cords. SPSMA manifests as progressive weakness of scapular and peroneal muscles, laryngeal palsy and skeletal abnormalities.[12] Congenital distal SMA affects lower motor neurons with variable disease severity starting from congenital weakness restricted to the distal lower limbs to more severe forms with involvement of pelvis and trunk muscles and arthrogryposis. TRPV4 encodes a channel that's broadly permeable to cations including calcium, and may be activated by mechanical stimuli, heat and endogenous and artificial agonists. TRPV4 is widely expressed within the brain and medulla spinalis.

Channelopathies in Congenital myasthenic syndromes
Congenital myasthenic syndromes (CMS) are a heterogeneous group of genetic disorders that affect the myoneural junction. They are typically inherited during a recessive fashion and should be caused by mutations in proteins of the neuromuscular junction that are presynaptic, synaptic or postsynaptic. Mutations in over 15 different genes are identified so far.[12] the foremost common sort of CMS is caused by mutations in various genes encoding the subunits of muscle Ach receptors. Mutations in anybody of the adult subunits of the AChR channel may result in deficiency or kinetic abnormality of the AChR. Recessive mutations of CHRNA1, CHRNB1, CHRND and CHRNE, which code for α1, β1, δ and ε subunits, respectively, have all been implicated in primary AChR deficiency syndromes. Mutations within the ε (epsilon) subunit are most often encountered. Most patients with AChR deficiency syndromes present with feeding problems and ophthalmoplegia in early infancy.

Skeletal muscle channelopathies

The striated muscle channelopathies are disorders whose clinical manifestations range from nervous disorder to myotonia. They are divided into the non-dystrophic myotonias (NDMs) and therefore the periodic paralyses and are caused by mutations in striated muscle ion channels that affect muscle excitability. Non-dystrophic myotonias The NDMs are a gaggle of striated muscle channelopathies that present with myotonia (delayed muscle relaxation following voluntary contraction) without systemic features. This group of conditions includes Thomsen's disease (MC), Para Thomsen's disease (PMC) and therefore the sodium channel myotonias (SCMs), Neurogenetics Thomsen's disease. Myotonia congenita is that the most typical of the skeletal muscle channelopathies and should be inherited in an autosomal dominant (Thomsen disease) or recessive fashion (Becker disease).[13] It's characterised by muscle stiffness that predominantly affects the limbs. Patients often exhibit a warm-up phenomenon when muscle stiffness improves with repeated activity. Patients with recessive MC can also have transient weakness on the initiation of a movement. Myotonia Congenita is caused by mutations within the striated muscle chloride channel CLCN1, which encodes the channel ClC-1. ClC-1 underlies the bulk of the resting conductance of striated muscle. Functional expression studies show that pathogenic mutations can reduce the macroscopic chloride current, posing to muscle cell depolarisation and after-discharges. Typically, nonsense, missense and frame shift mutations that don't affect the functional properties for the wild-type subunits within the channel dimer are recessively inherited.[13] Missense mutations that shift the voltage dependence of activation out of the physiological range are often dominantly inherited. Recessive mutations generally end in more severe symptoms.

Hypokalaemic periodic paralysis

Hypokalaemic periodic paralysis is that the commonest sort of periodic paralysis and is characterised by episodes of flaccid muscle weakness that occur in association with a low serum potassium level. Attacks last hours to days and typically affect the limbs; respiratory involvement is rare. Precipitants include carbohydrate meals and rest after exercise. With time, the frequency of attacks may diminish and a hard and fast proximal weakness may develop.[14] Hypo PP is inherited in an autosomal dominant fashion but features a reduced penetrance in women, a feature seen in several muscle channelopathies. Causal mutations were first identified in CACNA1S, which encodes the α1S subunit of the skeletal muscle calcium channel CaV1.These account for about 80% of cases. Mutations within the sodium channel gene SCN4A, also related to the SCMs, account for about 10% of cases but up to 10–20% of cases remain genetically undefined.

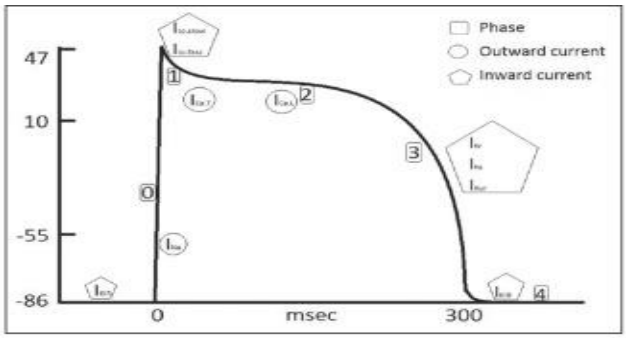
Channelopathies in cardiovascular diseases

Ion channels for sodium (Na+), potassium (K+), and calcium (Ca2+) in the myocardial cellular membrane are responsible for allowing this interplay across the membrane. When genetic abnormalities cause these channels to be dysfunctional, the resulting cardiac

channelopathies can predispose to life-threatening arrhythmias and other relevant conditions. The major cardiac channelopathies-long QT syndrome (LQTS), short QT syndrome (SQTS), Brugada syndrome (BS), and catecholaminergic polymorphic ventricular tachycardia (CPVT).

Cardiac Arrhythmia

Major disease in the CVS based on the imbalance in polarization and repolarization of the channels. The cardiac nerve impulse may be a measurement of the membrane potential waveform of the cardiac myocytes signifying the electrical activity of the cell during the contraction and relaxation of the guts. Specific ionic currents contribute to every phase of the cardiac nerve impulse. The current waveforms in action potential are those of inward/depolarizing currents (Na, CaL) and the sodium calcium exchanger [Na/Ca]), and the current waveforms below the action potential illustrate outward ionic (predominately K+ repolarizing) currents liable for repolarization of the nerve impulse.



Phase 0 Rapid depolarization	Phase 1 Early repolarization	Phase 2 Action potential plateau	Phase 3 Final rapid repolarization	Phase 4 Resting membrane depolarization and diastolic depolarization
Excitatory stimulus or pacemaker potential depolarizes cell membrane beyond −70 mV At −70 mV, Na^+ channels are activated and allow inward current I_{Na} (channel NaV1.5). This current is brief but enormous, peaking the membrane potential at +47 mV	The increase in potential from phase 0 results in opening of outward K^+ channels and inward Ca^{2+} channels. There is repolarization from +47 mV to +10 mV due to rapid closure of $I_{NaV1.5}$ and activation of transient outward K^+ current $I_{K(t),slow}$ (channel KV1.4) and $I_{K(t),fast}$ (channel KV4.2/4.3)	The membrane potential remains depolarized near 0 mV. Plateau phase is maintained by two inward Ca^{2+} currents $-I_{Ca,T}$ (channel CaVT.2) and $I_{Ca,L}$ (channel CaV1.2) and four outward K^+ currents described below	As the time dependent inward currents above inactivate, the outward K^+ currents dominate and cause rapid repolarization. These are rapid I_{Kr} (channel KHERG), ultrarapid I_{Kur} (channel KV1.5) and slow I_{Ks} (channel KLVQT1)	The outward K^+ channels in phase 3 deactivate, the membrane is repolarized to −40 mV. The inward rectifier current I_{Kir} (channel Kir2.1) continues to drive the membrane potential to −70 mV, and the voltage dependent Na^+ channel which causes phase 0 remains inactivated till this happens

Figure 3: phases in Action potential in Myocardial muscles

Long QT interval

LQTS one of the most common cardiac channelopathy. LQTS is estimated to occur in about 1 in 2500 persons. Initial classification of inheritable LQTS was as the autosomal dominant Romano-Ward syndrome, and the rarer autosomal recessive form associated with bilateral sensorineural deafness. There are currently 14 types of LQTS described based on the specific gene involved, location of a mutation along the gene, and associated noncardiac findings. Subtypes are associated with different triggering events such as exercise, swimming, or loud sounds such as alarms.

The first genes responsible for LQTS were elucidated in 1995. The majority of cases are ascribed to three major genes causing three major syndromes - KCNQ1 causing LQTS1 (35%), KCNH2 causing LQTS2 (30%) and SCN5A causing LQTS3 (10%). Mutations in KCNQ1 and KCNH2 result in loss of function mutations of K^+ repolarization currents, while SCN5A mutations result in gain of function mutations in the Na^+ channel. JLNS is thought to be a homozygous form of LQTS1.

Catecholaminergic polymorphic ventricular tachycardia

Individuals with CPVT generally have normal resting EKGs with a structurally and functionally normal heart. These patients are in danger for exercise-induced syncope or SD secondary to catecholamine dependent polymorphic ventricular tachycardia (often a bidirectional ventricular tachycardia). Cardiac events occur most ordinarily in children and adolescents, predominantly young males. It is a big explanation for SUD which is discussed below.

Autosomal dominant mutations in the RYR2 gene which encodes the ryanodine receptor/Ca2+ release channel, account for 50-65% of CPVT. This receptor regulates the discharge of Ca2+ from the sarcoplasmic reticulum during the plateau of the nerve impulse. Mutations end in uncontrolled release of Ca2+ during catecholaminergic stimulation. A rarer subtype, CPVT2 is caused by autosomal recessive mutations in CASQ2 which encodes calsequestrin, the main Ca2+ binding protein within the sarcoplasmic reticulum. This has more severe features and earlier onset. A third syndrome, CPVT3 occurs with mutations within the KCNJ2 K+ channel gene.

Brugada syndrome

BS accounts for 4-12% of Sudden Cardiac Death (SCD). BS appears associated with mutations affecting Na+ channels. There are currently quite 300 mutations described, mostly autosomal dominant, affecting the SCN5A gene, resulting in loss of Na+ channel function during a sort of ways (Interestingly, mutations in other parts of this gene cause LQTS3). Other genes affecting the Na+ channel is also implicated in BS.

Table 3: Channels associated with cardiac channelopathies

Disease	Affected channel	Gene	Protein
LQTS1	Potassium	KCNQ1	Kv7.1
LQTS2	Potassium	KCNH2	hERG Kv11.1
LQTS3	Sodium	SCN5A	Nav1.5
LQTS4	Calcium (related)	ANK2	Ank-B
LQTS5	Potassium	KCNE1	MinK
LQTS6	Potassium	KCNE2	MiRP1
LQTS7 (Anderson-Tawil syndrome)	Potassium	KCNJ2	Kv2.1 Kir2.1
LQTS8 (Timothy syndrome)	Calcium	CACNA1C	Cav1.2
LQTS9	Sodium (related)	CAV3	M-Caveolin
LQTS10	Sodium	SCN4B	Navβ4
LQTS11	Potassium (related)	AKAP9	Yotiao
LQTS12	Sodium (related)	SNTA1	Syntropin
LQTS13	Potassium	KCNJ5	Kv3.1 Kir3.4
LQTS14	Calcium	RYR2	Ryanodine receptor
CPVT1	Calcium	RYR2	Ryanodine receptor
CPVT2	Calcium	CASQ2	Calsequestrin
CPVT3	Potassium	KCNJ2	Kv2.1 Kir2.1
BS1	Sodium	SCN5A	Nav1.5
BS2	Sodium	GPD1-L	Glycerol-3-P-DH-1
BS3 (and SQTS4)	Calcium	CACNA1C	Cav1.2
BS4 (and SQTS5)	Calcium	CACNB2B	Voltage dependent β-2
BS5	Sodium	SCN1B	Navβ1
BS6	Potassium	KCNE3	MiRP2
BS7	Sodium	SCN3B	Navβ3
BS8	Potassium	KCNJ8	Kv6.1 Kir6.1
BS9	Potassium	HCN4	Hyperpolarisation cyclic nucleotide gated 4
BS10	Sodium (related)	MOG1	RAN-G-release factor
BS11	Potassium	KCNE5	Potassium voltage gated channel sub family E member1 like
BS12	Potassium	KCND3	Kv4.3 Kir4.3
BS13	Calcium	CACNA2D1	Voltage dependent α2/δ1
SQTS1	Potassium	KCNH2	hERG Kv11.1
SQTS2	Potassium	KCNQ1	Kv7.1
SQTS3	Potassium	KCNJ2	Kv2.1 Kir2.1
SQTS4 (and BS3)	Calcium	CACNA1C	Cav1.2
SQTS5 (and BS4)	Calcium	CACNB2B	Voltage dependent β-2

LQTS: Long QT syndrome, CPVT: Catecholaminergic polymorphic ventricular tachycardia, BS: Brugada syndrome, SQTS: Short QT syndrome

BS is typified by classical finding of coved ST-segment elevation in anterior precordial leads, as demonstrated in. Cardiac events secondary to ventricular tachycardia typically occurs in young adults but are described in children and infants. Individuals with BS develop a monomorphic ventricular tachycardia; often precipitated during sleep or rest, and particularly fever. It is thought that some SCN5A mutations alter the Na+ channel during a temperature dependent manner. Males have arrhythmic events more frequently, and there's thought to be a gender effect on ion channel expression.

Channelopathies In Renal Diseases

The renal channelopathies are not restricted to salt and water, however, different channelopathies have now been described affecting every nephron segment, from glomerulus to collecting duct. channelopathies described by anatomical location, and illustrate the molecular basis of normal physiology plus disease syndromes, with brief outlines of diagnosis and treatment. Other proteins implicated within the same disorders, but which don't function as ion channels – for instance NKCC2 in Bartter syndrome, any more channel associated disease condition related to renal and nephron can occur.

Glomerular disorders

Focal and segmental glomerulosclerosis (FSGS) is a common cause of the nephrotic syndrome in adults, presenting with significant proteinuria, hypoalbuminemia and peripheral oedema, and frequently resulting in progressive loss of renal function and ultimately end stage kidney failure (ESRF). The glomerular filtration barrier is made by the fenestrated capillary endothelium, the glomerular basement membrane (maintained by glomerular podocytes) and slit diaphragms between podocyte foot processes. The early hallmark of FSGS is loss of podocyte architecture, with disruption of the slit diaphragm and glomerular basement membrane, and consequent loss of normal glomerular permeability. Disease-causing mutations have thus far been described in several podocyte-expressed genes, including TRPC6, which encodes a member of the transient receptor potential (TRP) superfamily of cation channels.[9] TRP non-selective, voltage-independent, cation channels are widely expressed during a sort of tissues, including kidney, brain, lung and muscle, and are implicated in ion homeostasis, mechanosensation and signal transduction.TRPC6 contains six transmembrane spans and forms homotetramers or heterotetramers with other class members to make calcium-permeable cation channels, expressed both within the glomerulus and collecting duct.

Phospholipase C-1 (PLCE1, itself linked to childhood nephrotic syndrome) cleaves phosphatidylinositol-3,4-bisphosphate to make diacylglycerol (DAG), which activates TRPC6, resulting in an influx of calcium, rearrangement of the podocyte actin cytoskeleton and potential closure of the slit diaphragm.[10,15]

Additional TRPC6 mutations have now been described in over a dozen different families – in both paediatric- and adult-onset disease, and also in sporadic cases of FSGS. When studied in cell culture, the effect of most mutations is to extend calcium influx, potentially through increased cell surface expression of TRPC6; increased glomerular expression of TRPC6 has also been demonstrated during a series of biopsies from patients with FSGS.[12,15]

Increased expression of wild-type TRPC6 has also been found in other acquired protein uric renal diseases, such as membranous glomerulonephritis and minimal change disease, and overexpression of wild-type TRPC6 in mice induces proteinuria, adding further credence to the theory that excessive TRPC6-mediated calcium influx is pathogenic.[11,15] Recent work has demonstrated that tyrosine-phosphorylation of TRPC6 enables complex formation with phospholipase C (PLC)-g1, a prerequisite for cell surface expression of TRPC6. Nephron can interact with phosphorylated TRPC6 to prevent PLC-g1 binding; FSGS-causing nephron mutations reduce its interaction with TRPC6, thus leading to increased cell surface expression and channel activity.[16]

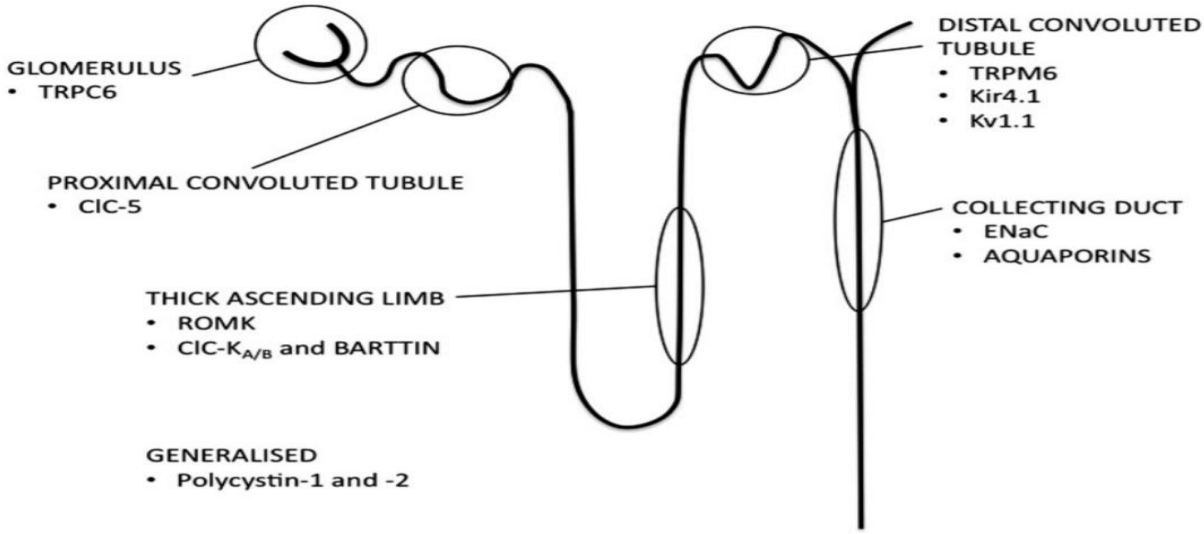


Figure 4: illustration of renal channelopathies with their location in nephron

TRPC6 activation results in calcium influx into the podocyte (foot process is shaded in grey), with downstream effects on the cytoskeleton and the calcineurin-NFAT pathway.

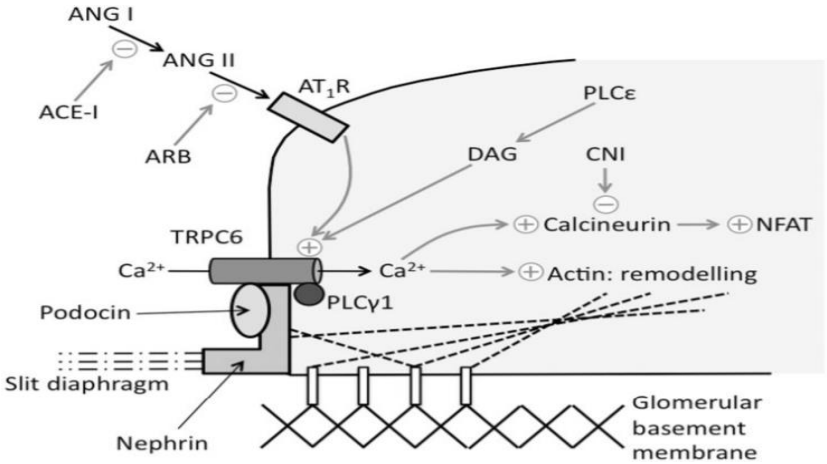


Figure 5: TRPC6 and the podocyte. PLC: phospholipase C; NFAT: nuclear factor of activated T-cells; DAG: diacylglycerol; AT1R: Angiotensin II receptor 1; ANG: angiotensin; ACE-I: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; CNI: calcineurin inhibitors (cyclosporin and tacrolimus).

Bartter syndrome

Bartter syndrome results from malfunction of one of the transport proteins of the Thick Ascending Limb epithelial cells. Within these cells, apical membrane NKCC2 (Na/K/2Cl- cotransporter – blocked by loop diuretics, e.g., furosemide) mediates sodium, potassium and chloride reuptake, primarily driven by the low intracellular sodium concentration consequent on the basolateral Na/K-ATPase. Recycling of potassium occurs via the apical

membrane channel Renal Outer-Medullary K channel (ROMK), providing for persistent NKCC2 function along the length of the TAL, and generating an intraluminal positive charge and the electrical driving force for the paracellular reuptake of sodium, calcium and magnesium (50% of sodium reuptake within the TAL is via cation-selective paracellular pathways, and 50% via NKCC2). Chloride exits the cells via basolateral membrane chloride channels ClC Kb and –Ka, which require the presence of a -subunit.[13,16]

Bartter syndrome is thus characterised by urinary losses of sodium and chloride, causing loss of extracellular volume, which combined with intact function results in a hypokalaemia alkalosis with low blood pressure.[17,18]

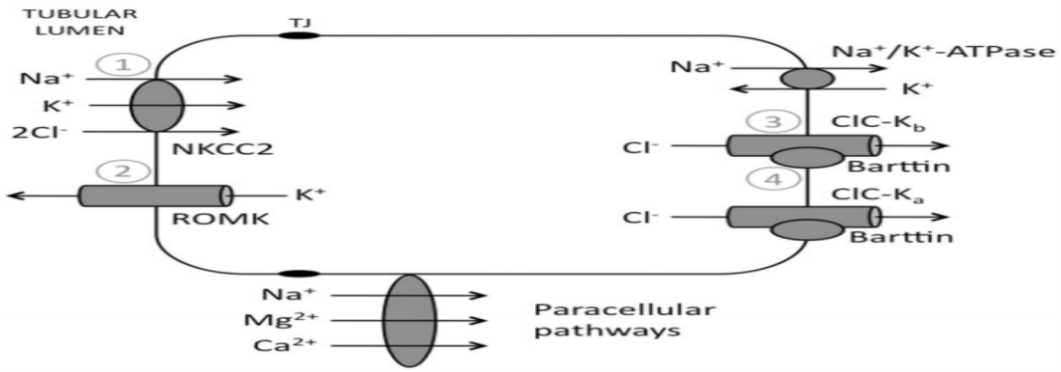


Figure 6: Transport proteins involved in Bartter syndrome. NKCC2: Na/K/2Cl co-transporter, ROMK: Renal Outer-Medullary K channel; ClC-Ka/b: chloride channel Ka/b; TJ: tight junction.

Nephrogenic diabetes insipidus

NDI results from a failure of the kidney to concentrate the urine in response to antidiuretic hormone (ADH, vasopressin) secreted by the posterior pituitary, and in the inherited form is a consequence of mutations in key proteins involved in water reabsorption.[19,24] Clinically, acquired disease predominates, caused by drugs (lithium [Lithium enters collecting duct principal cells via ENaC and causes downregulation of AQP2; amiloride are often wont to block this if lithium can't be discontinued. Lithium also causes a chronic tubulointerstitial nephritis, which will also contribute to a loss of urinary concentrating ability], amphotericin, tetracyclines), chronic kidney disease – particularly chronic tubulointerstitial nephritis, hypokalaemia and hypercalcaemia, ureteric obstruction and sickle cell disease.[23]

Autosomal dominant polycystic kidney disease

Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common monogenic disorders – with a prevalence of 1:400–1:1000 and the commonest inherited renal disease. Characterised by progressive renal cyst formation, clinical presentation may occur as a result of flank pain through bleeding into or infection of a cyst, haematuria, urinary tract infections, hypertension or renal insufficiency. Extrarenal manifestations also are common, including intracranial aneurysms, hepatic cyst formation and cardiac valvular abnormalities. ADPKD arises from mutations in two genes, PKD1 and PKD2.[18]

Disorders of the collecting duct

ENaC and sodium transport

Approximately 5% of filtered sodium is reabsorbed within the collecting duct, where there are three cell populations – the principal cell, liable for salt and water reabsorption, the intercalated cell, responsible for acid secretion and bicarbonate reabsorption, and its mirror image, the intercalated cell with a role in bicarbonate secretion. Na uptake from the tubular lumen occurs through apical epithelial sodium channels (ENaC), the gradient for Na reabsorption driven by basolateral Na/K-ATPase activity. Apical K excretion occurs through ROMK1 and Maxi-K channels, the latter activated by increased tubular flow.[20]

ENaC is a hetero multimeric channel, formed from a, and g subunits (encoded by SCNN1A, SCNN1B, and SCNN1G) – the exact stoichiometry remains unclear – which consist of cytoplasmic N and C terminal, and a large extracellular domain.[21] The C terminus of each subunit contains a PPPXY (PY) motif recognised by the WW domain of E3 ligases, these ubiquitinate ENaC and target it for internalisation and proteasomal degradation, thus regulating surface concentrations and hence activity. Hyperkalaemia and hypovolaemia increase aldosterone concentrations – this act via the cytosolic mineralocorticoid receptor in principal cells to promote transcriptional activation of ENaC.[21,22]

Analysis of the first kindred demonstrated linkage to the subunit gene (ENaC), containing a turn cation mutation with loss of the cytoplasmic C terminus. Mutations in other families are heterogeneous but all result in loss of the C-terminal PY domain in or g-ENaC; mutant channels are not targeted for internalisation and remain at the cell surface resulting in enhanced activity. A gain of function mutation has also been described in the extracellular domain of g-ENaC, but no mutations have yet been described in a-ENaC.1

Treatment Approches

- Increased understanding of channel dysfunction in various Diseases can lead to an individualised approach to treatment.

- With further research, there is potential for precision medicine in which drugs target specific channels or even target the mechanism by which a channel becomes dysfunctional.
- Determination of causative factor and recuring the status of disorder in earlier range.
- For increasing specificity toward channels, projecting for main mutated genes of particular channel and then rectifying the main factor of disorder related to that signal of channel.

CONCLUSION

In essence, the study of channelopathies reminds us to provide unique insights into both normal physiology and mechanisms of disease. It enables to precise diagnosis to be made in affected families and may lead to future advances in therapeutics. Use of channelopathies establishes linking in structural component changes to diseases. Ion channels are a beautiful target for investigation of those common diseases with polygenic inheritance. Channelopathies can be accurately diagnosed by careful clinical assessment and diagnosis.

REFERENCES

1. Blanckenberg Joanne M (2002) The channelopathies: an overview, Southern African Journal of Anaesthesia and Analgesia, 8: 1, 13-16, DOI: 10.1080/22201173.2002
2. Lehman-Horn F and Jurkat-Rott K Physiological Reviews October 1999; Volume 79, No. 4: pages 1317 - 1356.
3. Loudon KW, Fry AC, The renal channelopathies a review, Annals of Clinical Biochemistry 2014; Vol. 51(4): 441–458
4. Ashcroft Frances M Book of Ion and channels channelopathies, Academic press London 1999; 67-165
5. Behere Shashank P., Weindling Steven N., Inherited arrhythmias: The cardiac channelopathies, Ann Pediatr Cardiol 2015 Sep-Dec; 210–220.
6. Kass , The channelopathies: novel insights into molecular and genetic mechanisms of human disease, J Clin Invest. 2005; 1986-1989.
7. Kelly knupp, Amy R. Brooks-kayal, Swaimens pediatric neurology 2017; Pages 405-411.
8. Ptacek LJ, Johnson KJ & Griggs RC in NEJM 1993; 328: 482 – 489.
9. Towbin JA in NEJM 1995; 333: 384 – 385.
10. Shah M, Carter C Ann Pediatr Cardiol, Long QT syndrome: A therapeutic challenge 2008 Jan; 1(1): 18-26.
11. Tester DJ, Ackerman MJ Pediatr Cardiol. 2012 Mar; 33(3): 461-70.
12. Tester DJ, Ackerman MJ. The molecular autopsy: Should the evaluation continue after the funeral Pediatr Cardiol. 2012; 33: 461–70
13. Chockalingam P, Wilde A. The multifaceted cardiac sodium channel and its clinical implications Heart. 2012; 98: 1318–24.
14. Kitiyakara C, Eggers P and Kopp JB. Twenty-one-year trend in ESRD due to focal segmental glomerulosclerosis in the United States. Am J Kidney Dis 2004; 44: 815–825.
15. Weins A, Kenlan P, Herbert S, et al. Mutational and biological analysis of alpha-actinin-4 in focal segmental glomerulosclerosis. J Am Soc Nephrol 2005; 16: 3694–3701.
16. Dietrich A, Chubanov V and Gudermann T. Renal channelopathies. J Am Soc Nephrol 2010; 21: 736–744.
17. Seyberth HW. An improved terminology and classification of Bartter-like syndromes. Nat Clin Pract Nephrol 2008; 4: 560–567.
18. Nedvetsky PI, Tamma G, Beulshausen S, et al. Regulation of aquaporin-2 trafficking. Handbook Experiment Pharmacology 2009; 9(190): 133–157.
19. Chapin HC and Caplan MJ. The cell biology of polycystic kidney disease. J Cell Bio 2010; 191: 701–710.
20. Snyder PM. Minireview: regulation of epithelial Na channel trafficking. Endocrinology 2005; 146: 5079–5085. 95.
21. Mick VE, Itani OA, Loftus RW, et al. The alpha-subunit of the epithelial sodium channel is an aldosterone induced transcript in mammalian collecting ducts, and this transcriptional response is mediated via distinct cis elements in the 5'-flanking regions of the gene. Mol Endocrinol 2001; 15: 575–588.
22. Nedvetsky PI, Tamma G, Beulshausen S, et al. Regulation of aquaporin-2 trafficking. Handbook Exp Pharmacology 2009; 9(190): 133–157. 110.
23. Kawahara M, Iwai K, Ooeda T, et al. Three families with autosomal dominant nephrogenic diabetes insipidus caused by aquaporin-2 mutations in the C-terminus. Am J Hum Genet 2001; 69: 738–748.
24. Asai T, Kawahara M, Kurihara H, et al. Pathogenesis of nephrogenic diabetes insipidus by aquaporin-2 C-terminus mutations. Kidney Int 2003; 64: 2–10.

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