Ion Channel Diseases
‘Channelopathies’

Dr. Aslı AYKAÇ
NEU Faculty of Medicine
Dep of Biophysics
A rapidly growing group of diseases caused by ion channel dysfunction is classified as “channelopathies”
Ion channels are involved in various cellular functions

• Generation of electrical currents
• Transepithelial transport
• Regulation cellular volume and pH
• Acidification of intracellular organelles
• Chemical signalling
What kind of tissue, organ or cell is subjected to a channel disorder?

• Virtually every organ, tissue, cell and even subcellular organelles.
Table 1. Known ion channel diseases

<table>
<thead>
<tr>
<th>Channel</th>
<th>Gene</th>
<th>Channel-forming unit(ligand)</th>
<th>OMIM</th>
<th>Disease</th>
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<tbody>
<tr>
<td>Cation channels:</td>
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<td>CHERNA1/ACHRA</td>
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<td>α, ACh</td>
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<td>Myasthenia gravis</td>
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<td>Polycystin-2</td>
<td>PKD1</td>
<td>α</td>
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<td>CNGA3</td>
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<td>α, cGMP</td>
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<td>Sodium channels:</td>
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<td>Na1.1</td>
<td>SCN1A</td>
<td>α</td>
<td>182389</td>
<td>Generalized epilepsy with febrile seizures (GEFS+)</td>
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<td>Na1.5</td>
<td>SCN5A</td>
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<td>Long QT syndrome, progressive familial heart block type I, Brugada syndrome (idiopathic ventricular arrhythmia)</td>
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<td>SCN1B</td>
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<td>β</td>
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<td>ENaCβ</td>
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<td>Pseudohypoaldosteronism type I (PHAI)</td>
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<td>Kc1.1</td>
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<td>KCNQ1/KCNE1/KCNE2</td>
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<td>KCNQ2</td>
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<td>DFNA2 (dominant hearing loss)</td>
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<td>HERG1/KCNH2</td>
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<td>ABCC7</td>
<td>α</td>
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Channelopathies

Congenital Chpt.
- Genetic factors

Acquired Chpt.
- Transcriptional Chpt.
  - Nerve injury
  - Inflammation
- Autoimmune or toxic Chpt.
  - Chemicals
  - Venoms
  - Antibodies

Genetic factors
Mutated genes → Abnormal or absent channel proteins → Altered function → Genetic channelopathies

Antibodies, toxins → Binding to channels → Altered function → Autoimmune and toxic channelopathies

Abnormal transcription of normal genes → Aberrant expression of normal proteins → Altered function → Transcriptional channelopathies
General properties of channelopathies

• A change in the channel
  • Structure
  • Expression
  • Localization

• A change in the function of the cell
  • “Gain off function”
  • “Loss of function”
Genetic channelopathies

• Mutation in ion channel genes is the cause.
• “Loss of function” mutations often lead to recessive inheritance of the disease.
  – CFTR mutation “Cystic Fibrosis”
  – CLCNKB mutation “Bartter Syndrome”
• (homozygous) Patients with recessive mutations are worse than (heterozygous) patients with dominant mutations
• For example dominant-negative mutation of KCNQ1 $K^+$ channel leads to severe cardiac arrhythmia while homozygous recessive mutation leads to deafness in addition.
Genetic channelopathies

• Observation of the disease is also dependent on expression level of the current

• KCNQ2 and KCNQ3 mutation which is not dominant-negative, cause dominant neonatal convulsions since 20-30 % reduction of the current can not be tolerated

• “Gain of function” mutations are most often associated with dominant inheritance of the disease

• Mutations in various isoforms of sodium channels cause para-myotonia, cardiac arrhythmia and epilepsy as result of the additional late sodium current due to insufficient inactivation.
Genetic channelopathies

Bartter syndrome

- Bartter syndrome is a group of hereditary tubulopathies
  - Salt wasting
  - Hypokalemic metabolic alkalosis
  - Hyperreninemic hyperaldosteronism
  - Normal blood pressure
- Autosomal recessive inheritance
- Occurs in infancy or early childhood
- Impaired transepithelial transport in the thick ascending limb of the loop of Henle is the cause
**Genetic channelopathies**

**Deafness**

- Fluid surrounding of the upper part of hair cells, endolymph, has elevated $[K^+]$ and low $[Na^+]$.
- $K^+$ entering the cell through the mechanosensitive channel leaves the cell through the KCNQ4 channel at the basolateral side.
- Mutated KCNQ4 leads to autosomal dominant progressive hearing loss.
- $K^+$ removed by the Deiter cells through a $K$-$Cl$ co-transporter KCC4.
- $K^+$ diffuses through the gap junctions to the adjacent cell.
- At least three connexin genes GJB2, GJB3, GJB6 are involved in deafness.
Genetic channelopathies

Deafness

- In stria vascularis Na-K/ATPase and Na-K-2Cl transporter NKCC1 is taken into the marginal cells.
- To increase the efficiency the Cl- has to recycle across the basolateral membrane.
- This is achieved by CIC-Ka/barttin and CIC-Kb/barttin Cl- channels.
- Mutations in barttin leads to deafness in addition to renal symptoms in Bartter type 4.
- K is secreted into endolymph through KCNQ1 and KCNE1 potassium channels.
- Homozygous loss of both channel leads to Jervel-Lange-Nielsen syndrome characterized by cardiac arrhythmia and congenital hearing loss.
**Genetic channelopathies**

**Liddle Syndrome**

- In principle cells of distal collecting duct Na\(^+\) enters the cell passively through the apical ENaC channels
- Na\(^+\) accumulates in the body if ENaC channel is over expressed and decreases if ENaC channels are down regulated
- Na\(^+\) absorption is accompanied by water retention
- PathophysiologicaL volume expansion leads to hypertension while the opposite induces hypotension
- In Liddle syndrome internalization of the ENaC channels are impaired “gain of function”, leads to a salt sensitive hypertension
Genetic channelopathies

Dent’s Disease

• X-linked Hypercalciuric nephrolithiasis
• CLCN5 encodes a chloride channel CIC-5
• Mutations leads to failure in acidification of renal endosome and internalization small proteins. Apical endocytosis of parathyroid hormone and vitamin-D impaired
• Disturbances of renal phosphate and calcium handling leads to Kidney stones
Genetic channelopathies

Bone Diseases

- Mutations in Cl⁻ channel gene CLCN/ are associated with severe autosomal recessive osteopetrosis.
- CIC7 is colocalized with H⁺-ATPase on part of osteoclastic membrane facing the bone resorption lacuna.
- In osteopetrosis number of osteoclasts are normal but they fail to acidify the lacuna.
Genetic channelopathies
Persistent Hyperinsulinemic Hypoglycemia
Genetic channelopathies
Persistent Hyperinsulinemic Hypoglycemia

- K-ATP channel is consisted of 4 pore forming units, Kir6.2 (encoded by KCNJ11).
- SUR1 transmembrane protein is necessary for expression of the channel on surface membrane.
- Mutations in either part results in autosomal recessive disorder PHH manifests at birth or early in the first year of life.
Genetic channelopathies

Best Disease

FIGURE 1. The retina in health and disease
A: diagram of retina (redrawn from an illustration available at http://webvision.med.utah.edu). B: ophthalmoscopic images of retinas. The optic nerve is the yellowish spot on the right of each retina. Normal retina, Best vitelliform macular dystrophy (vitelliform stage), and age-related macular degeneration are shown from left to right. (Images are from http://webvision.med.utah.edu/ and are reprinted with permission.)
Genetic channelopathies

Best Disease

• Best disease is an age related macular degeneration

• Several bestropins have been identified. There are compelling evidences that bestropins are Cl- channels

• Cl- channels are involved in
  – Regulation of fluid environment
  – Cell volume regulation
  – Intracellular Cl channels
  – Calcium regulation
Genetic channelopathies  
Neurological Disorders

• Ion channels have key function in nervous system.
  – Generation
  – Repression
  – Propagation of action potentials
• Na\(^+\) channel depolarizes the neurons
• K\(^+\) channels causes hyperpolarization
• Cl\(^-\) channel may induce hyperpolarization
• Ca\(^{++}\) channel depolarizes the neuron, however Ca\(^{++}\) is more important as second messenger.
• Thus, loss of function mutations in K\(^+\) and Cl\(^-\) channel and gain of function mutations in Na\(^+\) channels may induce hyperexcitability and perhaps epilepsy.
Genetic channelopathies

Epilepsy

• **KCNQ2** and **KCNQ3** underlie benign familial neonatal convulsions (BNFC)

• **M currents** is a noninactivating potassium current involved in regulating the subthreshold excitability of neurons.

• **In BNFC the M current reduced 25%**. This amount suffice to evoke convulsions since it has very important critical role in neuronal excitability.

• **Homozygous knockout of KCNQ2 is lethal in mice**
D  Spike accommodation

\[50 \text{ mV}\]

\[2 \text{ nA}\]
Genetic channelopathies

Epilepsy

• Some mutations in sodium channel gene SCN1A and SCN2A leads to a sodium channel population with impaired inactivation properties
• Those causes generalized febrile and afebrile seizures respectively
• Mutation in calcium channel gene CACNA1A can cause ataxia
• Mutation in GABRA1 gene encoding GABAa receptor is associated with autosomal dominant juvenile myoclonus epilepsy
• Mutation of glycine receptor cause startle disease
• There has been no reports indicating an association of epilepsy with the major excitatory neurotransmitter glutamate receptors.
Erythromelalgia

- Characterized by an severe burning pain in extremities in response to warm stimuli or moderate exercise.
- Autosomal dominant inheritance.
- Mutation in Nav1.7 sodium channels present in dorsal root ganglion neurons is the cause.
- This channel is not expressed in CNS.
Genetic channelopathies

Cardiac Arrhythmias

• Each heartbeat initiated by a depolarization in pacemaker cells spreads through the heart.
• Cardiac action potential is much longer than neuronal one due to long lasting opening of the calcium channels.
Genetic channelopathies
Cardiac Arrhythmias

- The fast initial depolarization is achieved by Nav 1.5 sodium channel coded in SCN5A gene
- Mutations leads to sodium channel with incomplete inactivation.
- Several different types of potassium channels also contribute repolarization of the cardiac action potentials
- KCNQ1/KCNE1 mutation results in long-QT syndrome.
A Simulated ΔK7Q mutation of SCN5A Na+ channel gene ("Long Q-T Syndrome mutation")

Wild-type Na+ channel

Cycle length = 400 ms

Cycle length = 600 ms

B Guinea pig ventricular cell model

Membrane potential, mV

Membrane potential, mV

Current, µA

Current, pA

Time, ms

Time, ms
Genetic channelopathies

Cardiac Arrhythmias Brugada Syndrome

- This is an idiopathic cardiac arrhythmia which can lead to a ventricular fibrillation and sudden death
- Typical ECG pattern helps diagnosis
- Biophysically sodium currents are smaller
- 20 different genetic mutations have been associated with Brugada syndrome
- Recently it was identified that ankyrin-G which anchors Nav1.5 sodium channel
- Mutations in ankyrin-G result in loss of binding to sodium channel and results in Brugada syndrome
Genetic channelopathies

Disturbances of Skeletal Muscle

- Depolarization at the motor end plate activates extrasynaptic sodium channels, resulting in action potential and calcium release.
- A defect in sodium channel inactivation may cause myotonia as in:
  - Pramyotonia congenita
  - Hyperkalemic and hypokalemic paralyis
- Cl- conductance plays a major role in repolarizing part of the action potential. Mutations in CLCN1 gene encoding CIC-1 channel cause:
  - Myotonia congenita
- Mutations in RYR1 gene which encodes intracellular calcium release channel cause:
  - Malignant hyperthermia
Acquired Channelopathies

• When peripheral nerve is cut within some days a new family of sodium channel is expressed in the neuronal soma. Neuron becomes more excitable.
• Snake, scorpion, anemone, bee, frog, fish venom mediates the toxic effect by severely altering functional properties of various ionic channels.
• Inflammation is another factor affecting ion channels.
Neuromuscular Junction

Diagram showing the neuromuscular junction, including motor neuron, muscle fiber, myelin, Schwann cell sheath, and presynaptic terminal boutons. Details include mitochondria, synaptic vesicles (ACh), presynaptic membrane, active zone, synaptic cleft, postsynaptic membrane, Ca²⁺ channel, basement membrane, junctional fold, voltage gated Na⁺ channel, and ACh receptors.

Graphs showing A. Normal and B. With curare, with parameters Vₘ (mV) and time (ms).
Myasthenia gravis
A Normal muscle

B Myasthenic muscle

1. Amplitude of end-plate potential (mV)
   - Safety factor of transmission
   - Threshold

2. Muscle action potential
   - Time (s)
Lambert Eaton Syndrome

• Mostly observed in patients with Small cell lung cancer
• Progressive weakness is the major symptom
• Antibodies against to the presynaptic voltage gated calcium channels in the motor end plate is detected in the blood samples
• Morphology of the presynaptic site is altered regular alignment of the VGCC is lost
Rasmussen Encephalitis

• Rasmussen encephalitis is a rare disease observed in children under the age of 10
• Seizures, loss of motor functions, hemiparesis, inflammation of the brain are the observed
• Autoantibodies bind to glutamate receptor are the cause of the disease
Transcriptional Channelopathies

• Results from expression of nonmutated channels
• Dysregulated production of normal channel proteins as a result of changes in transcription may perturb the cellular function
Sodium channels are diverse

• 10 sodium channel genes has been identified in human genome and 9 has been shown to code distinct sodium channels.

• They have different voltage-dependence and kinetic properties.

• Selective expression of the channels endow the cells with different functional properties.
**Sodium channels are diverse**

- Nav1.1, Nav1.2, Nav1.3 rise during the course of development
- NGF and GDNF upregulate Nav1.8 and Nav1.9 and downregulate Nav1.3 sodium channels
- Further, electrical activity may modulate expression of sodium channels
Sodium channels are diverse

- Magnocellular neurosecretory neurons of hypothalamic supraoptic nucleus are silent at normal conditions.
- When osmotic pressure increases they fire at a high frequency bursts of action potentials and trigger release of vasopressin.
- It was shown that after salt loding conditions expression of Nav1.2 and Nav1.6 increased in association with the transition to bursting state.
- Nav1.6 can be activated by small depolarizations.
Peripheral nerve injury

Neuropathic pain and paraesthesiae

- Neuropathic pain
- Burning or electrical type of pain developing in response to injury of a nerve
- Paraesthesiae
- Spontaneously developing pain described as pins or needles, probably due to damage to sensory fibres in spinal cord
Neuropathic pain and paraesthesiae
Peripheral nerve injury

Neuropathic pain and paraesthesiae

• Prolonged duration of opening indicates persistent activation of a sodium channel

• However, it was not possible to conclude if it is different mode of the same pre-existing channel or expression of a new type of channel
Neuropathic pain and paraesthesiae
Neuropathic pain and paraesthesiae
Peripheral nerve injury

Neuropathic pain and paraesthesiae

• The factors triggering changes in sodium channel expression are not fully understood

• NGF and GDNF are responsible for expression of Nav1.8 and Nav1.9

• Loss of access to peripheral sources of neurotrophic factors is the most probable cause
Multiple Sclerosis

- Demyelination is the hallmark of MS
- Axonal degeneration is also present
- Recently a change in sodium channel expression is also observed
- In paranodal region sodium channels are present at a low density
- Following demyelination Nav1.8 expression increases
Multiple sclerosis
Multiple sclerosis
Ca^{2+} sparks parameters in diabetic cardiomyocytes

Yaras et al., Diabetes, 2005
Voltage Sensitive Ion Channels and Cancer
Voltage sensitive ion channels and cancer
# Voltage sensitive ion channels and cancer

<table>
<thead>
<tr>
<th>Channel group</th>
<th>Expression level associated with cancer</th>
<th>Evaluation parameter</th>
<th>Cancer</th>
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<td>K_v</td>
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<td>Colon</td>
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<td>RT-PCR</td>
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<td>Oral squamous cell</td>
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<td>Breast</td>
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Voltage sensitive ion channels and cancer

- Ion channels are involved in malignant progression of cancer
- There are evidences indicating control of cell proliferation and migration by ion channels
- Cell specific differentiation???
- Current efforts to create new drugs to ion channels is promising to halt the progression of cancer by either cytostatic or cytotoxic mechanisms
Inflammation induced channelopathy in the GIS

- Inflammation markedly alters the motility of the GIS system.
- Orderly passage of food from osephagus to colon is achieved by the coordinated movement of the muscle layers under the influence of
  - Neuronal
  - Hormonal
  - Myogenic factors
- Each of those factors, which is dependent on ion channels, alters the excitability of the muscle cells.
Contractile Patterns

- Phasic contractions
  - APs superimposed on slow wave generated by ICC, involved in local mixing and distal propagation of luminal content.

- Tone
  - Basal level of tone in smooth muscle cells is maintained by intracellular calcium concentration.

- Migrating motor complexes
  - Cyclic contractions due to periodic firing of enteric neuronal network.

- Giant migrating contractions
  - Contraction with large amplitude, happening two or three times daily, involved in defecation and under neuronal control.
Changes in contractile patterns in inflammation

• Phasic contractions
  – Suppressed due to a damage to the ICC cells.

• Tone
  – Suppressed.

• Migrating motor complexes
  – Frequency may not change but amplitude reduced.

• Giant migrating contractions
  – Increased in frequency  DIARRHEA??.
Changes in contractile patterns in inflammation

- Circular muscles
  - Suppression of contractions.

- Longitudinal muscles
  - Contractions either unchanged or enhanced.
Changes in electrical excitability of the smooth muscle cells

- Smooth muscle cells depolarized
- ICC damaged
- Calcium currents reduced 70 %
- At least in some models of inflammation calcium channel protein expression is not decreased.
- Steady state of activation shifted to more negative potentials.
- Responses to Ca\(^{++}\) channel agonist attenuated.
Changes in calcium channels in intestinal smooth muscle cells.

- In smooth muscle cells two isoforms of calcium channels are present (alternative splicing of Cav.12).
- Each isoform is regulated by different promoters.
- Loss of calcium current is restored by Nuclear factor (NF-kB) inhibitor.
- NF-kB is inactive complexed to inhibitor IkBalpha.
- NF-kB is increased in inflammatory bowel diseases.
- NFAT is another transcriptional factor expressed in intestine.
- Activation of NFAT requires Ca/calmodulin dependent protein phosphatase “calcineurin”.
- Ca channels are substrate to non receptor tyrosine kinase c-src, which looses its affinity to the channel protein.
Changes in ionic channels are selective.

- Ca$^{++}$ current decreases in inflammation
- Transient potassium channels do not change
- K-ATP channel, coupling cell metabolism to membrane excitability, increased 20 folds
- Thus, upregulation of some potassium channels together with the depression of the calcium channels may account for the decreased motility of smooth muscle after inflammation
Changes in muscarinic receptor coupling in inflammation

• Muscarinic agonists increase opening of a non-selective cation channel by a combined action of M2 and M3 receptors.

• Inflammation results in 30% reduction in muscarinic receptor density.

• This may account for the reduction in the GIS motility observed in inflammation.
Inflammation induced changes in GIS

• Are not related to a defect in genes.
  – 1. Calcium current reduced
  – 2. Muscarinic activity (mediated via the cation channel) is reduced
  – 3. K-ATP channel is upregulated

• Changes are related to conditional modulation of the ionic channels and receptor signalling pathways.

• Thus, this is a typical example of “transcriptional channelopathies”
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