Ion Channels and Channelopathies

J Clin Invest. 2005;115(8) review series

Frances M. Ashcroft 2005

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MSB C-506; 973-972-2411
May 11, 2015
Outline

Part I: Ion Channels
- Introduction
- Classification
- Structure
- Function

Part II: Channelopathies
- Long QT syndromes Type 1 and 2: LQT1 and LQT2: delayed K\(^+\) channel
- Long QT syndrome type 3: LQT3: Na\(^+\) channel
- Epilepsy: Voltage-gated Ca\(^{2+}\) channel
- Diabetes Mellitus: ATP-sensitive K\(^+\) channel
- Cystic fibrosis: CFTR, Cl\(^-\) channel
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What are Ion Channels?

- **Ion channels - structure**
  - are proteins that span (or traverse) the membrane
  - have water-filled ‘channel’ that runs through the protein
  - ions move through channel, and so through membrane

- **Ion channel - properties**
  - Selectivity: Each specific ion crosses through specific channels
  - Gating: transition between states (closed ↔ open ↔Inactivation)
    - Voltage-gated; Ligand-gated
  - Channels mediate ion movement down electrochemical gradients.
  - Activation of channel permeable to ion $X$ shifts membrane potential towards to its Equilibrium Potential, $E_X$
**Equilibrium Potential or Nernst Potential**

The voltage at which there is zero net flux of a given ion (Electrical gradient = a chemical concentration gradient)

For $K^+$: $\sim -90$ mV

$$E_K = \frac{RT}{ZF} \ln \frac{[K^+]_o}{[K^+]_i}$$

- $R$ = gas constant
- $F$ = Faraday constant
- $T$ = temperature (K)
- $Z$ = valence (charge) of ion

$K$ current ($I_{K1}$) is the major contributor for RMP
Four Milestones in Ion Channel Research

1. Ionic conductance
   Noble 1963 (Physiol/Medicine)
   - Alan L. Hodgkin
   - Andrew F. Huxley

2. Patch clamp methodology
   Noble 1991 (Physiol/Medicine)
   - Erwin Neher
   - Bert Sakmann

3. Channel cloning sequencing
   (Ach receptor, Na, Ca channels)
   - Shosaku Numa (沼 正作)
   - Japan Academy Prize 1985

4. K channel structure
   Noble 2003 (Chemistry)
   - Rod MacKinnon
Hodgkin-Huxley Model Predicted the Existence of Ion Channels

\[ C \frac{dV}{dt} = g_{Na} \bar{m}^3 h (V_{Na} - V) + g_K n^4 (V_K - V) + g_L (V_L - V) + I_{ext} \]

- \( C \) is the capacitance.
- \( V \) is the membrane potential.
- \( m, n, h \) are gating variables for Na, K, and Na channels, respectively.
- \( g_{Na}, g_K, g_L \) are conductances of Na, K, and leakage channels, respectively.
- \( \bar{m}, \bar{n} \) are average conductances.

The Giant Axon of Squid

1963 noble Prize
Patch-Clamp Techniques

1991 Nobel Prize

Erwin Neher & Bert Sakmann
Nobel prize for medicine in 1991
for the development of the patch-clamp technique making possible
the characterization of single ion channels
Cloning and sequence analysis of calf cDNA and human genomic DNA encoding α-subunit precursor of muscle acetylcholine receptor

Masaharu Noda, Yasuji Furutani, Hideo Takahashi, Mitsuyoshi Toyosato, Tsutomu Tanabe, Shin Shimizu, Sho Kikyotani, Toshiaki Kayano, Tadashi Hirose*, Seiichi Inayama* & Shosaku Numa

Department of Medical Chemistry, Kyoto University Faculty of Medicine, Kyoto 606, Japan

* Pharmaceutical Institute, Keio University School of Medicine, Tokyo 160, Japan

Fig. 3  Proximal neurons of the brown ganglion (top row) and the cell cDNA (bottom row) encoding the AC3α precursor cDNA. The electrodes (upper) were applied to the muscle fibers. The interneurons were stimulated by a supramaximal pulse. The current intensity was held constant at 100 μA. The cell cDNA was isolated from the AC3α-deficient mice. The DNA was isolated from the cell cDNA and inserted into the plasmid vector. The resulting plasmid was transfected into the AC3α-deficient mice. The AC3α precursor cDNA was isolated and sequenced. The sequence was compared with the sequence of the AC3α-deficient mice. The results were consistent with the sequence of the AC3α-deficient mice. The sequence was compared with the sequence of the AC3α-deficient mice.
Nobel Prize for Chemistry 2003

Protein x-ray crystallography

1) Purification
2) Crystallization
3) X-Ray Diffraction

Crystal structure of ion channel

The Nobel Prize in Chemistry 2003
Peter Agre, Roderick MacKinnon
Classification of Ion Channels

1) Based on ion selectivity:
   K⁺, Na⁺, Ca²⁺, Cl⁻ channels

2) Based on gating:
   Voltage-gated: ions
   Ligand-gated: Glutamate, GABA, ACh, ATP, cAMP

3) Based on rectification:
   Inwardly or outwardly rectifying
Structure of $K_{CSA}$ Channels: Selectivity Filter and Gating

(A) Selectivity filter and gating

(B) Side view of selectivity filter and gating

Inner helices form “inverted teepee” structure

Doyle et al. Science 1998;
Open-Close Gating

Bacterial K channel
selective filter: P-loop; **Gating: intracellular side of the pore bundle crossing**

Bacterial Na channel pore in the closed and “open” conformation

Doyle et al. Science 1998;
Ligand-Gated Channels

- Open when a signal molecule (ligand) binds to an extracellular receptor region of the channel protein.
- This binding changes the structural arrangements of the channel protein, which then causes the channels to open or close in response to the binding of a ligand such as a neurotransmitter.
- This ligand-gated ion channel, allows specific ions (Na+, K+, Ca2+, or Cl-) to flow in and out of the membrane.

ACh receptor channel

ATP-sensitive K channel

\[
\text{ACh} \quad \text{Neurotransmitter binds} \quad \text{Channel opens} \quad \text{Ions flow across membrane}
\]

\[
\text{Out} \quad \text{Inside cell}
\]

\[
\text{C} \quad \text{ATP-sensitive K channel} \quad \text{O}
\]

\[
\text{C} \quad \text{ATP} \quad \text{O}
\]

\[
\text{Also a weak inward rectifier}
\]
the S4 segment is responsible for detecting voltage changes.
The movement of positively-charged S4 segments within the membrane electric field
Transition between Close, Open, and Inactivation States

**C**

**Voltage-gated Na⁺ Channels**

*Closed* At the resting potential, the channel is closed.

**O**

*Open* In response to a nerve impulse, the gate opens and Na⁺ enters the cell.

**I**

*Inactivated* For a brief period following activation, the channel does not open in response to a new signal.
A positively charged inactivation particle (ball) has to pass through one of the lateral windows and bind in the hydrophobic binding pocket of the pore's central cavity. This blocks the flow of potassium ions through the pore. There are four balls and chains to each channel, but only one is needed for inactivation.
A: a subunit containing six transmembrane-spanning motifs. S5 and S6 and the pore loop are responsible for ion conduction (channel pore). S4 is the the *voltage sensor*, which bears positively charged amino acids (Arg) that relocate upon changes in the membrane electric field. N-terminal ball-and-chain is responsible for inactivation

B: four such subunits assembled to form a potassium channel.
Channel Function: Single Channel and Whole-cell Current

- Ion channels are not open continuously but open and close in a stochastic or random fashion.

- Ion channel function may be decreased by
  - decreasing the open time (O),
  - increasing the closed time (C),
  - decreasing the single channel current amplitude (i)
  - or decreasing the number of channels (n).

\[
I = n \cdot P_o \cdot i \quad P_o = \frac{\tau_o}{\tau_o + \tau_c}
\]
Channel Function: Single Channel and Whole-cell Current

Depolarizing voltage pulses result in brief openings in the seven successive recordings of membrane current.

Close correlation between the time courses of microscopic and macroscopic Na+ currents.
Physiological Function of Ion Channels

- **Maintain cell resting membrane potential:** inward rectifier K and Cl channels.
- **Action potential and Conduction of electrical signal:** Na, K, and Ca channels of nerve axons and muscles
- **Excitation-contraction (E-C) coupling:** Ca channels of skeletal and heart muscles
- **Synaptic transmission at nerve terminals:** glutamate, Ach receptor channels
- **Intracellular transfer of ion, metabolite, propagation:** gap junctions
- **Cell volume regulation:** Cl channel, aquaporins
- **Sensory perception:** cyclic nucleotide gated channels of rods, cones
- **Oscillators:** pacemaker channels of the heart and central neurons
- **Stimulation-secretion coupling:** release of insulin from pancreas (ATP sensitive K channel)
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Channelopathies?

1. **Definition:** Disorders of ion channels or ion channel disease
   Diseases that result from defects in ion channel function. Mostly caused by mutations of ion channels.

2. **Channelopathies can be inherited or acquired:**
   a. Inherited channelopathies result from mutations in genes encoding channel proteins (major)
   b. Acquired channelopathies result from *de novo mutations*, actions of drugs/toxins, or autoimmune attack of ion channels
      • Drug/Toxin - *e.g.* *Drugs that cause long QT syndrome*

3. **Increasingly recognized as important cause of disease (>30 diseases).**

4. **Numerous mutation sites may cause similar channelopathy**
   *e.g.* cystic fibrosis where >1000 different mutations of CFTR described
Molecular Mechanisms of Channel Disruption

I. Production

II. Processing

III. Conduction

IV. Gating
Consequences of Ion Channel Mutations

- Mutation of ion channel can alter
  - Activation
  - Inactivation
  - Ion selectivity/Conduction
- Abnormal gain of function
- Loss of function
Cardiac Channelopathies

• Long QT Syndrome (types 1-12, various genes)
• Short QT Syndrome (Kir2.1, L-type Ca\textsuperscript{2+} channel)
• Burgada Syndrome (I\textsubscript{to}, Na\textsuperscript{+}, Ca\textsuperscript{2+} channels)
• Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) (RyR2, SR Ca release)
ECG and QT interval

Bazett's Formula:

$QT_C = \frac{QT \text{ interval}}{\sqrt{R-R \text{ interval}}}$
FYI: ECG Recording 120 Years Ago

First recorded in 1887

In order to conduct the weak current of the heart’s electrical activity, Einthoven used electrolyte (saline-filled) tubs [“E” in photo] as electrode contacts to each of three limbs, the right arm, the left arm, and the left foot, respectively. He chose two of these limb electrodes to monitor each lead, making one electrode positive and the other electrode negative to record each of his three classic bipolar limb leads. He named these bipolar limb leads Lead I (left arm positive, right arm negative), Lead II (left foot positive, right arm negative), and Lead III (left foot positive, left arm negative). Note that the original string galvanometer consisted of massive equipment that filled a room.
FYI: ECG Recording 120 Years Ago

And Now!
AP Correlation to ECG Waveform

- **P wave**: Electrical activation (depolarization) of the atrial myocardium.

- **PR segment**: This is a time of electrical quiescence during which the wave of electrical excitation (depolarization) passes through mainly the AV node.

- **QRS wave**: Depolarization of the ventricular myocardium.

- **T wave**: Ending of ventricular myocardium repolarization

- **ST segment**: Ventricular repolarization
LQTS-facts

- Normal QT interval: 360-440 ms

- Delayed repolarization of the myocardium, QT prolongation (>450 in man; > 470 in women).

- Increased risk for syncope, seizures, and SCD in the setting of a structurally normal heart

- 1/2500 persons.

- Usually asymptomatic, certain triggers leads to potentially life-threatening arrhythmias, such as Torsades de Pointes (TdP)
### QT interval ranges

<table>
<thead>
<tr>
<th></th>
<th>Age 1 to 15</th>
<th>Adult man</th>
<th>Adult woman</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Less than 0.44 second</td>
<td>Less than 0.43</td>
<td>Less than 0.45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>second</td>
<td>second</td>
</tr>
<tr>
<td>Borderline</td>
<td>0.44 to 0.46 second</td>
<td>0.43 to 0.45</td>
<td>0.45 to 0.47</td>
</tr>
<tr>
<td></td>
<td></td>
<td>second</td>
<td>second</td>
</tr>
<tr>
<td>Prolonged</td>
<td>Greater than 0.46</td>
<td>Greater than 0.45</td>
<td>Greater than 0.47</td>
</tr>
<tr>
<td></td>
<td>second</td>
<td>second</td>
<td>second</td>
</tr>
</tbody>
</table>

# FYI: Genetic Basis for LQT syndromes

<table>
<thead>
<tr>
<th>Type</th>
<th>Locus</th>
<th>Gene</th>
<th>Protein</th>
<th>Function</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQT1</td>
<td>11p15.5</td>
<td>KCNQ1</td>
<td>KV7.1 α</td>
<td>$I_{Ks}$ ↓</td>
<td>30%-35%</td>
</tr>
<tr>
<td>LQT2</td>
<td>7q35</td>
<td>KCNH2</td>
<td>KV11.1 α</td>
<td>$I_{Kr}$ ↓</td>
<td>25%-30%</td>
</tr>
<tr>
<td>LQT3</td>
<td>3p21</td>
<td>SCN5A</td>
<td>NaV1.5 α</td>
<td>$I_{Na}$ ↑</td>
<td>5%-10%</td>
</tr>
<tr>
<td>LQT4</td>
<td>4q25</td>
<td>ANK2</td>
<td>Ankyrin-B</td>
<td>$I_{Na,K}$ ↓</td>
<td>1%-2%</td>
</tr>
<tr>
<td>LQT5</td>
<td>21q22.1</td>
<td>KCNE1</td>
<td>minK β</td>
<td>$I_{Ks}$ ↓</td>
<td>1%</td>
</tr>
<tr>
<td>LQT6</td>
<td>21q22.1</td>
<td>KCNE2</td>
<td>MiRP1 β</td>
<td>$I_{Kr}$ ↓</td>
<td>Rare</td>
</tr>
<tr>
<td>LQT7*</td>
<td>17q23</td>
<td>KCNJ2</td>
<td>Kir2.1 α</td>
<td>$I_{K1}$ ↓</td>
<td>Rare</td>
</tr>
<tr>
<td>LQT8†</td>
<td>12p13.3</td>
<td>CACNA1C</td>
<td>CaV 1.2 α1c</td>
<td>$I_{Ca,L}$ ↑</td>
<td>Rare</td>
</tr>
<tr>
<td>LQT9</td>
<td>3p25</td>
<td>CAV3</td>
<td>Caveolin-3</td>
<td>$I_{Na}$ ↑</td>
<td>Rare</td>
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<tr>
<td>LQT10</td>
<td>11q23</td>
<td>SCN4B</td>
<td>NaV1.5 β4</td>
<td>$I_{Na}$ ↑</td>
<td>Rare</td>
</tr>
<tr>
<td>LQT11</td>
<td>7q21</td>
<td>AKAP9</td>
<td>Yotiao</td>
<td>$I_{Ks}$ ↓</td>
<td>Rare</td>
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<tr>
<td>LQT12</td>
<td>20q11.2</td>
<td>SNTA1</td>
<td>A1-syntrophin</td>
<td>$I_{Na}$ ↑</td>
<td>Rare</td>
</tr>
</tbody>
</table>
Cardiac action potential

- **Phase 0.** Influx of Na⁺ (I_{Na}). Induces membrane depolarization

- **Phase 1.** Efflux of K⁺ (I_{K0}). Limits the Na⁺ spike

- **Phase 2.** Influx of Ca²⁺ (I_{Ca}). Activation of I_{K}. Balance between Ca²⁺ influx and K⁺ efflux. Ca²⁺ enters the cell to trigger the Ca²⁺-induced Ca²⁺ release.

- **Phase 3.** Efflux of K⁺ (I_{K}) increases. Repolarization starts

- **Phase 4.** Restoration of the resting potential: equilibrium potential of K via I_{K1}. and Na⁺ / K⁺ pump, Na⁺ / Ca²⁺ pump.
Pathophysiology of LQT (1, 2, 3)

TdP triggers in congenital LQTS
- **LQTS1**: Emotional stress or exercise, especially swimming or diving
- **LQTS2**: Extreme emotions or surprises, such as harsh, sudden noises
- **LQTS3**: Slow heart rate while sleeping

LQT syndromes: proarrhythmic mechanisms

- Upregulation of inward currents
  Or
- Downregulation of outward currents

- EADs → triggers
- Dispersion of APDs → substrates → reentry
Example 1:

LQT1 and LQT2

Downregulation of delayed K\(^+\) channel, \(I_{Ks}\) and \(I_{Kr}\)
LQT1: KCNQ1 (KvLQT1) mutations

IKs: Slow component of the delayed rectifier potassium current
LQT2: KCNH2(HERG) MUTATIONS

KCNH2 (HERG)

IKr: Rapid component of the delayed rectifier potassium current
LQT 1 and 2: $I_{K_s}$ and $I_{Kr}$ downregulation

KCNQ1 or KCNE2 gene mutations

$\text{KCNQ1 or KCNE2 gene mutations}$

$\left(I_{Ks}\right)$  $\left(I_{Kr}\right)$
Example 2:

LQT3

Inactivation of $\text{Na}^+$ channel
LQT3: Increased persistent Na Current

SCN5A

WT: normal inactivation

ΔKPQ:

Impaired inactivation

20 ms

50 ms

WT
Functional mechanisms in LQT3

LQT3

- Long QT

- Persistent $I_{Na}$

- $I_{Na}$

WT

- 40 mV

ΔKPQ

- EAD

- Action Potential

- $Na^+$ current
Example 3: Epilepsy - a CNS Channelopathies

Epileptic seizure

Epilepsy is a disorder marked by disturbed electrical rhythms in the central nervous system.
**FYI: Ion Channels Implicated in Epilepsy**

<table>
<thead>
<tr>
<th>Channel</th>
<th>Protein</th>
<th>Gene</th>
<th>Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Voltage-gated Sodium channel</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type I $\alpha_1$ subunit</td>
<td>SCN1A</td>
<td></td>
<td>Generalized epilepsy with febrile seizures plus syndrome (GEFS++)</td>
</tr>
<tr>
<td>Type I $\beta_1$ subunit</td>
<td>SCN1B</td>
<td></td>
<td>Generalized epilepsy with febrile seizures plus syndrome (GEFS++)</td>
</tr>
<tr>
<td>Type I $\alpha_1$ subunit</td>
<td>SCN1A</td>
<td></td>
<td>Severe myoclonic epilepsy of infancy (SMEI)</td>
</tr>
<tr>
<td>Type I $\alpha_1$ subunit</td>
<td>SCN1A</td>
<td></td>
<td>Intractable childhood epilepsy with generalized tonic-clonic seizures (ICGTCS)</td>
</tr>
<tr>
<td>Type I $\alpha_1$ subunit</td>
<td>SCN1A</td>
<td></td>
<td>Infantile spasms (IS)</td>
</tr>
<tr>
<td>Type II $\alpha_1$ subunit</td>
<td>SCN2A</td>
<td></td>
<td>Benign familial neonatal-infantile seizures (BFNIS)</td>
</tr>
<tr>
<td><strong>Calcium channel</strong></td>
<td></td>
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<tr>
<td>P/Q-type $\alpha_1$ subunit</td>
<td>CACNA1A</td>
<td></td>
<td>Episodic ataxia type 2 (EA2)</td>
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<tr>
<td>T-type $\alpha_1$ subunit</td>
<td>CACNB4</td>
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<td>Familial hemiplegic migraine (FHM)</td>
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<td></td>
<td>CACN1A/H</td>
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<td>Spinocerebellar ataxia type 6 (SCA 6)</td>
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<td>Episodic ataxia type 2 (EA2)</td>
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<td>Childhood absence epilepsy (CAE)*</td>
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<tr>
<td><strong>Potassium channel</strong></td>
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<tr>
<td>$K_V 1.1$ subunit</td>
<td>KCNA1</td>
<td></td>
<td>Episodic ataxia type 1 (EA1)</td>
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<tr>
<td>M-channel</td>
<td>KCNQ2</td>
<td></td>
<td>Benign familial neonatal convulsions (BFNC)</td>
</tr>
<tr>
<td>M-channel</td>
<td>KCNQ3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BK channel</td>
<td>KCNMA1</td>
<td></td>
<td>Generalized epilepsy with paroxysmal dyskinesia (GEPD)</td>
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<tr>
<td><strong>Chloride channel</strong></td>
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<tr>
<td>CLC-2</td>
<td>CLCN2</td>
<td></td>
<td>Juvenile myoclonic epilepsy (JME)</td>
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<td></td>
<td>Juvenile absence epilepsy (JAE)</td>
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<tr>
<td></td>
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<td></td>
<td>Epilepsy with grand mal seizures on awakening (EGMA)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CAE</td>
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<tr>
<td><strong>Ligand-gated</strong></td>
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<tr>
<td>Acetylcholine receptor</td>
<td>$\beta_2$ subunit</td>
<td>CHRNB2</td>
<td>Autosomal dominant frontal lobe epilepsy (ADNFLE)</td>
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<tr>
<td></td>
<td>$\alpha_4$ subunit</td>
<td>CHRNA4</td>
<td></td>
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<tr>
<td>GABA receptor</td>
<td>$\gamma_2$ subunit</td>
<td>GABRG2</td>
<td>GEFS+, CAE, SMEI</td>
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<tr>
<td></td>
<td>$\alpha_1$ subunit</td>
<td>GABRA1</td>
<td>JME</td>
</tr>
<tr>
<td></td>
<td>$\beta$ subunit</td>
<td>GABRD</td>
<td>JME*</td>
</tr>
</tbody>
</table>
Voltage-gated Ca Channels: Subunit Assembly and Subtypes

Ancillary subunits
- $\beta_1, \beta_2, \beta_3, \beta_4$
- $\gamma_1$ through $\gamma_8$
- $\alpha_{2-\delta_1}$ through $\alpha_{2-\delta_4}$

Neuronal $\alpha_1$ subunits

**HVA**
- $\text{Ca}_v 1.2$
- $\text{Ca}_v 1.3$
- $\text{Ca}_v 1.4$
- L-type

**Ca\_v 2.1**
- P/Q-type
- Ca\_v 2.2
- N-type
- Ca\_v 2.3
- R-type

**LVA**
- Ca\_v 3.1
- T-type
- Ca\_v 3.2
- Ca\_v 3.3
Epilepsy: Voltage-gated Ca\textsuperscript{2+} Channel

**A**
- **α2/δ2**
- **Ca\textsubscript{2,1}**
- **tg**
- **wb**
- **stg whirl**

**B**
- **extracellular**
- **intracellular**
- **α\textsubscript{1}**
- **II-III linker**
- **COOH**

*Legend:*
- ○ Episodic ataxia type 2
- □ Progressive ataxia
- □ Episodic/progressive ataxia with absence epilepsy
- ▪ Familial hemiplegic migraine
- □ Progressive ataxia with hemiplegic migraine
- □ Spino cerebellar ataxia type 6

*Annotations:*
- tottering:
- leaner:
- rolling Nagoya:
- tg-rol
- rocker:
- lethargic:
- ducky:
- entia:
- stargazer:
- wagglar:
- wobbly:
- du, du2↓ent
Enhancement of T-type Ca current in thalamocortical networks produces spike wave absence epilepsy
Epilepsy: Pathology and Symptom

In mice

Calcium Channelopathy and Absence Epilepsy

In human

Electroencephalogram (EEG)
disturbed electrical rhythms
Example 4:

ATP-Sensitive K⁺ Channel and Diabetes
Discovery of $K_{ATP}$ Channel

**Abstract**
An outward current of unknown nature increases significantly when cardiac cells are treated with cyanide or subjected to hypoxia, and decreases on intracellular injection of ATP. We report here that application of the patch-clamp technique to CN-treated mammalian heart cells reveals specific K+ channels which are depressed by intracellular ATP (ATPi) at levels greater than 1 mM. For these channels, conductance in the outward direction is much larger than the inward rectifier K+ channel which is insensitive to ATP. AMP had no effect on the ATP-sensitive K+ channel, and ADP was less effective than ATP. Thus, the ATP-sensitive K+ channel seems to be important for regulation of cellular energy metabolism in the control of membrane excitability.

Acetylcholine activation of single muscarinic K+ channels in isolated pacemaker cells of the mammalian heart.

**Abstract**
Acetylcholine (ACh) released on vagal stimulation reduces the heart rate by increasing K+ conductance of pacemaker cells in the sinoatrial (S-A) node. Fluctuation analysis of ACh-activated currents in pacemaker tissue showed this to be due to opening of a separate class of K+ channels.
ATP-Sensitive Potassium Channel

Is composed of Kir6.x and sulfonylurea receptors (SURs)

- Inhibited by ATP
- Inhibited by sulfonylurea via SURs
ATP-Sensitive K channel
Inhibited by ATP
Role of the $K_{\text{ATP}}$ Channel in Insulin Secretion in Pancreatic $\beta$ Cell

- Glucose enters the cell via the GLUT2 transporter
- Glycolytic and mitochondrial metabolism leads to an increase in ATP
- This results in $K_{\text{ATP}}$ channel closure, membrane depolarization,
- Opening of voltage-gated $\text{Ca}^{2+}$ channels, $\text{Ca}^{2+}$ influx,
- Exocytosis of insulin granules (insulin secretion).
K$_{ATP}$ Channel Mutations Causing Lower ATP Sensitivity and Diabetes
The $K_{ATP}$ Channel Couples Glucose Metabolism to Insulin Secretion
Example 5:

Cystic Fibrosis: Cl⁻ Channel Disease
Cystic Fibrosis: Facts

- Cystic fibrosis (CF) is autosomal recessive disease
- CF is a chronic, progressive, life threatening genetic disorder of pediatrics.
- It affects white population (1 in 3200 live births) but is uncommon among Asian and African population
- It affects exocrine glands (mainly sweat glands) and mucus gland present on the epithelial lining of lungs, pancreas, intestine, and reproductive system.
- CF is a defect in epithelial chloride channel protein, causes membrane to become impermeable to Chloride ion.
CF occurs due to the deletion of 3 nucleotides which code for the phenylalanine from the CFTR (cystic fibrosis transmembrane conductance regulator) gene located on chromosome no. 7 at position 508. This mutation is known as ΔF 508.
Structure of the CFTR protein

CFTR protein is a cAMP induced Channel made up of five domains:

Two membrane-spanning domain (MSD1 & MSD2) that form Cl⁻ ion channel.

Two nucleotide binding domains (NBD1 & NBD2) that bind and hydrolyze ATP.

A regulatory R domain.
CFTR mutation: Loss of Cl⁻ Channel Function

A normal-functioning CFTR channel moves chloride ions to the outside of the cell while a mutant CFTR channel does not, causing sticky mucus to build up on the outside of the cell.
Pathology of Cystic Fibrosis - 1

In sweat glands:

CFTR is responsible for re-absorption of Cl\(^-\) along with Na\(^+\) through epithelial Na channel (ENaC).

Impaired function of CFTR cause the production of hypertonic salty sweat, and ultimately dehydration.
In lung mucus glands:

- Loss of CFTR function to secrete chloride ion →
- Loss or reduction of Cl⁻ ion in luminal secretion →
- Followed by active luminal Na⁺ absorption through ENaC →
- Increases passive water absorption from the lumen →
- Impaired mucociliary action, accumulation of thick, viscous, dehydrated mucus
- Obstruction of air passage and recurrent pulmonary infections
Channelopathies: Summary

• Channel mutations are an increasingly recognized cause of disease.

• Many channelopathies are episodic despite persistently abnormal channel.

• Abnormalities in same channel may present with different disease states

• Mutations/ abnormalities in different channels may lead to same disease e.g. periodic paralysis or epilepsy

• Disease mechanism often unclear despite identification of mutation.
Thank you!
### FYI: Human Channelopathies

<table>
<thead>
<tr>
<th>Protein</th>
<th>Gene</th>
<th>Disease</th>
<th>Functional defect</th>
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<tbody>
<tr>
<td>Na\textsubscript{1.1}</td>
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<td>Generalized epilepsy with febrile seizures plus (GEFS+)</td>
<td>Hyperexcitability</td>
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**and MORE...**

*J Clin Invest. 2005;115(8)*