Voltage-Gated Ion Channels in Health and Disease

I. Multiple functions of voltage-gated ion channels
II. Neurological diseases involving voltage-gated ion channels

Squid Giant Axon According to Hodgkin & Huxley

Only Two Types of Voltage-Gated Ion Channels are Required to Generate the Action Potential

But...
Mammalian Neurons Have Several Types of Voltage-Gated Ion Channels

Why do neurons need so many types of voltage-gated ion channels?

I. Ca++ as a Second Messenger

[Ca++] Can Act as a Regulator of Various Biochemical Processes

e.g., modulation of enzyme activity, gene expression, or channel gating; or initiation of transmitter release
II. Control of Membrane Excitability

Early Computers Were Made of Thousands of Identical Electronic Components

ENIAC’s Computational Power Relied on the Specificity of Connections Between Different Identical Elements
Electronic Devices Are Made of a Variety of Specialized Elements With Specialized Functional Properties

Each Neuron Expresses a Subset of the Many Different Types of Voltage-Gated Ion Channels

Each Class of Neurons Expresses a Unique Set of Voltage-Gated Ion Channels, Which Endows it with a Specific Excitability Property
Alternative Splicing of Pre-mRNA

Variation of Alternative Splicing of pre-mRNA From One Gene Results in Regional Variation in Expression of Four Different Isoforms of a Voltage-Gated K⁺ Channel

HVA Channels Affect Spike Shape
LVA Channels Affect Spike Encoding
Neurons Differ in Their Responsiveness to Excitatory Input

Some Neurons Respond with a Burst, Rather than a Train

Thalamocortical Relay Neurons Burst Spontaneously

HCN current
T-type Ca^{++} current
Synaptic Input Can Modulate a Neuron’s Excitability Properties by Modulating Voltage-Gated Ion Channels

Neurons Vary as Much in Their Excitability Properties as in Their Shapes

Activity-Dependent Action Potential Broadening
Length Constant $\lambda = \sqrt{\frac{r_m}{r_a}}$

Distribution of Four Types of Dendritic Currents in Three Different Types of CNS Neurons

Functional Consequences of Regional Variation of Ion Channel Types Within a Neuron
Voltage-Gated Ion Channels in Health and Disease

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Various Neurological Diseases Are Caused by Malfunctioning Voltage-Gated Ion Channels

- Acquired neuromyotonia
- Andersen’s syndrome
- Becker’s myotonia
- Episodic ataxia with myokymia
- Familial hemiplegic migraine
- Generalized epilepsy with febrile seizures
- Hyperkalemic periodic paralysis
- Malignant hyperthermia
- Myasthenic syndrome
- Paramyotonia congenita
- Spinocerebellar ataxia
- Thompson’s myotonia

$\text{Na}^+, \text{K}^+, \text{Ca}^{++}, \text{Cl}^-$

How Voltage-Gated Ion Channels Go Bad

- Mutations
- Autoimmune diseases
- Defects in transcription
- Mislocation within the cell
I. Mutations in Different Genes Can Lead to Similar Symptoms

Myotonic Muscle is Hyperexcitable

![Graph showing voltage (V_m) vs. time (ms) with two different traces for current (I) at 87 nA and 48 nA.]  

Mutations in Voltage-Gated Cl⁻ Channels in Skeletal Muscle Can Result in Myotonia

![Diagram of Cl⁻ channel with mutations highlighted at various amino acid positions: G230E, R117Q, I290M, Q552R, P485L, and A855P.]
Build-up of $K^+$ Ions in the T-Tubules Following an Action Potential Can Depolarize the Muscle Cell

$E_K = RT \ln \frac{K_o}{F \cdot K_i}$

Mutations in Voltage-Gated Na$^+$ Channels in Skeletal Muscle Can Also Result in Myotonia

Many of These Point Mutations Affect Kinetics or Voltage-Range of Inactivation
II. Regional Differences in Gene Expression Account for Much of the Specificity of Ion Channel Diseases

e.g., Voltage-Gated Na⁺ Channels Found in the CNS And Those Found in Skeletal Muscle Are Encoded by Different Genes

Mutations in Na⁺ Channels in the CNS Give Rise to Epilepsy - Not to Myotonia

"Happy families are all alike. Every unhappy family is unhappy in its own way."

Tolstoy, p. 1, Anna Karenina
III. Different Mutations in the Same Gene Can Lead to Different Symptoms

Different Mutations in Na⁺ Channels in the CNS Give Rise to Different Types of Epilepsy

Voltage-Gated Na⁺ Channels in Skeletal Muscle Can Have Point Mutations That Lead to:
- Potassium Aggravated Myotonia,
- Paramyotonia Congenita, or
- Hyperkalemic Periodic Paralysis
Degree of Na+ Inactivation Deficit Determines Whether Paralysis or Hyperexcitability Occurs

- Na+ channels open, but do not inactivate normally
- Firing
- [K+]o More positive E_K

Activation of normal Na+ channels → Hyperexcitability = Myotonia

Depolarization e.g., endplate potential → Persistent inactivation of normal Na+ channels → Paralysis

Increasing Degree of Persistent Activation Can Switch the Muscle Fiber from Hyperexcitable to Inexcitable

IV. Subunit Structure of Ion Channels Can Influence Inheritance Patterns of Hereditary Ion Channel Diseases
Paradox

• Pharmacological block of 50% of Cl⁻ channels produces no symptoms.

• Heterozygotes with 50% normal Cl⁻ channel gene product are symptomatic (autosomal dominant myotonia congenita).

Because Cl⁻ Channels are Dimers, Only 25% of Heterozygotic Channels are Normal

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<th>Genes</th>
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