Voltage-Gated Ion Channels in Health and Disease

Principles of Neural Science, chapter 9

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

Ca++ as a Second Messenger

Mammalian Neurons Have Several Types of Voltage-Gated Ion Channels

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

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

e.g., modulation of enzyme activity, gene expression, and channel gating; initiation of transmitter release
II. Fine 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 Class of Neuron Expresses a Subset of the Many Different Types of Voltage-Gated Ion Channels, Resulting in a Unique Set of Excitability Properties

Each Class of Voltage-Gated Ion Channel Has a Unique Distribution Within the Nervous System

e.g., consider a single gene that encodes voltage-gated K⁺ channels
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 Ca²⁺ current
Synaptic Input Can Modulate a Neuron’s Excitability Properties by Modulating Voltage-Gated Ion Channels.

Membrane Potential

Resting Following Synaptic Stimulation

50 mV

Current

0 0.3 0.6 0 0.3 0.6

Seconds

PNS, Fig 13-1C

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

Some Nerve Terminals Exhibit Activity-Dependent Spike Broadening.

Firing Rate (Hz)

First Spike

Last Spike

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

Dendrites Are NOT Just Passive Cables Many Have Voltage-Gated Channels That Can Modulate the Spread of Synaptic Potentials.

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

Na⁺, K⁺, Ca²⁺, Cl⁻

How Voltage-Gated Ion Channels Go Bad

- Mutations
- Autoimmune diseases
- Defects in transcription of normal genes
- Mislocation within the cell

I. Mutations in Different Genes Can Lead to Similar Symptoms

Myotonic Muscle is Hyperexcitable

Build-up of K⁺ Ions in the T-Tubules Following an Action Potential Can Depolarize the Muscle Cell

\[ E_K = \frac{RT \ln K_o}{F K_i} \]
Mutations in Voltage-Gated Cl⁻ Channels in Skeletal Muscle Can Result in Myotonia

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

Mutations in Either α or β-Subunits Can Lead to Similar Symptoms

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

II. Different Mutations in the Same Gene Can Lead to Different Symptoms
Different Point Mutations in the Same α-Subunit Lead to Three Different Classes of Symptoms

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

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

III. Regional Differences in Gene Expression Account for Much of the Specificity of Ion Channel Diseases

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