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

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, 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
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

Thalamocortical Relay Neurons Burst Spontaneously

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
Ion Channel Distributions Differ Not Only Between Neurons, but also Between Different Regions of an Individual Neuron

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

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How Voltage-Gated Ion Channels Go Bad

- Mutations
- Autoimmune diseases
- Defects in transcription
- Mislocation within the cell
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

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

Phenotypic Variability
Mutations in the Same Gene Lead to Different Symptoms

Genetic Variability
Mutations in Different Genes Lead to Similar Symptoms

Different Point Mutations in the Same $\alpha$-Subunit Lead to Three Different Classes of Symptoms

Mutations in Either $\alpha$ or $\beta$-Subunits Can Lead to Similar Symptoms

Myotonic Muscle is Hyperexcitable
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

Mutations Often Affect Gating Functions

Many of These Point Mutations Affect Kinetics or Voltage-Range of Inactivation

Increasing Degree of Persistent Inactivation Can Move the Muscle Fiber from Hyperexcitable to Inexcitable

Voltage-Gated Na⁺ Channels in Skeletal Muscle Can Have Point Mutations That Lead to:
- Potassium Aggravated Myotonia
- Paramyotonia Congenita
- Hyperkalemic Periodic Paralysis
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

Understanding Ion Channel Subunit Structure Helps to Explain Aspects of Heritability of Disease

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

- 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