

Voltage-Gated Ion Channels in Health and Disease

jdk3

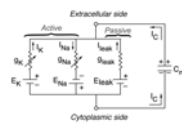
Principles of Neural Science, chapter 9

Voltage-Gated Ion Channels in Health and Disease

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

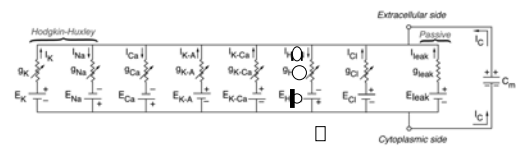
Squid Giant Axon According to Hodgkin & Huxley

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



But...

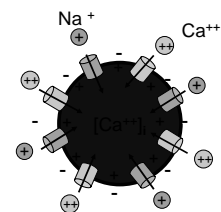
Mammalian Neurons Have Several Types of Voltage-Gated Ion Channels



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

I. Ca^{++} as a Second Messenger

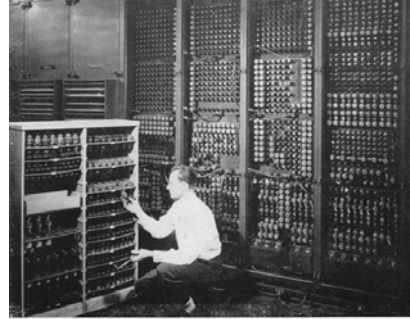
$[\text{Ca}^{++}]_i$ Can Act as a Regulator of Various Biochemical Processes



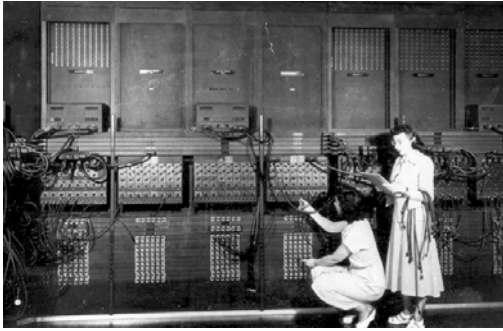
e.g., modulation of enzyme activity, gene expression, and channel gating; initiation of transmitter release

II. Fine Control of Membrane Excitability

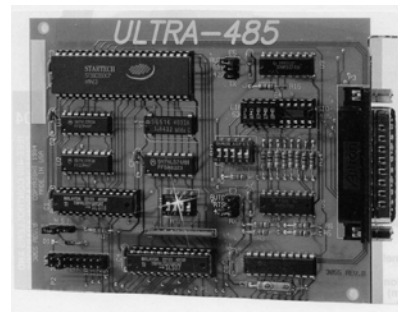
Early Computers Were Made of Thousands of Identical Electronic Components



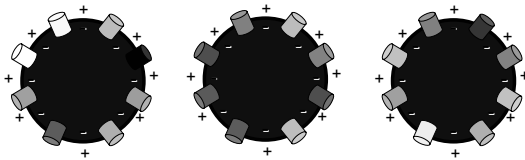
ENIAC's Computational Power Relied on the Specificity of Connections Between Different Identical Elements



Electronic Devices Are Made of a Variety of Specialized Elements With Specialized Functional Properties

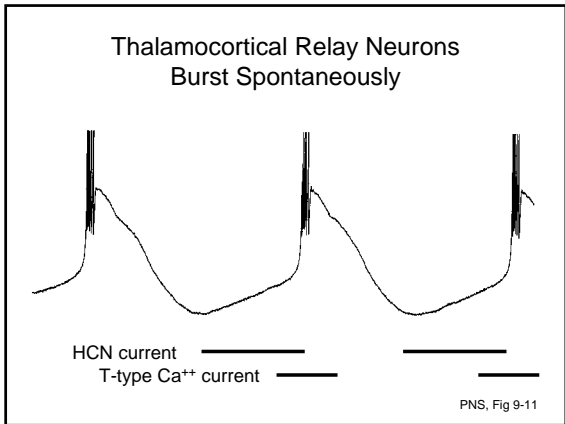
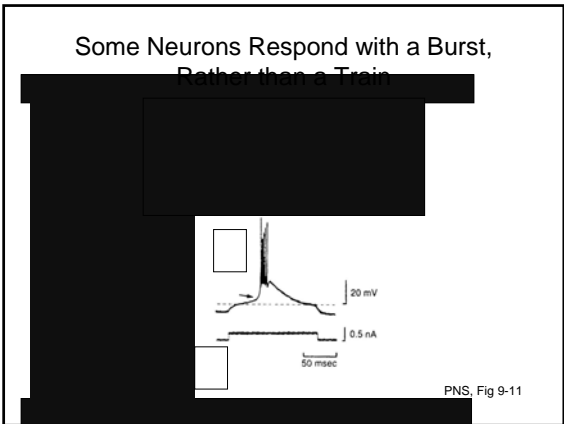
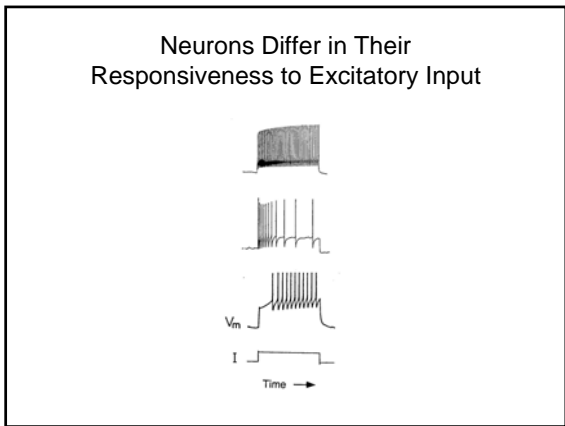
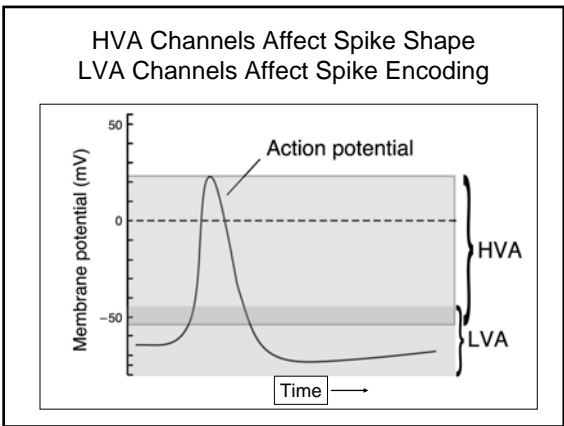
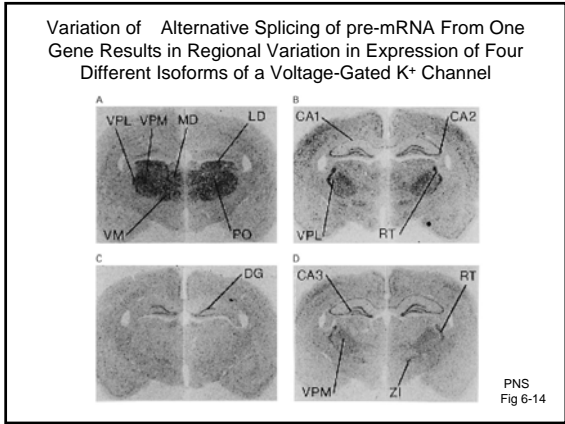
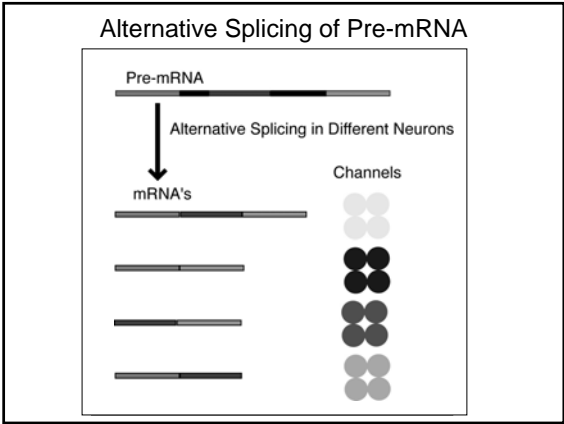


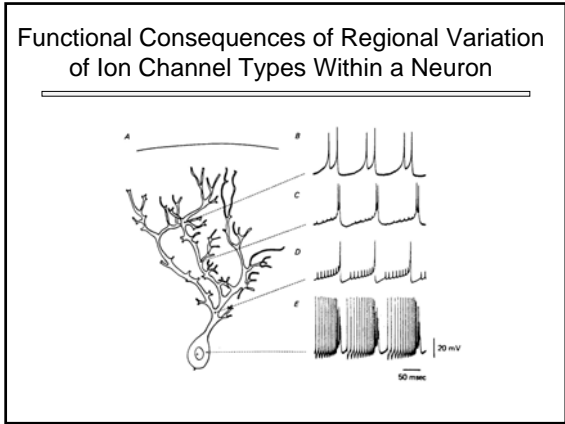
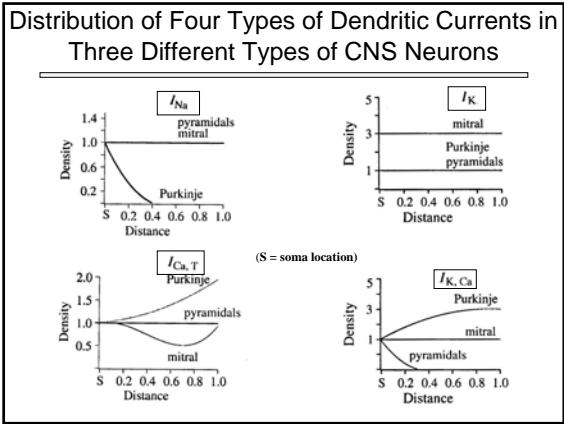
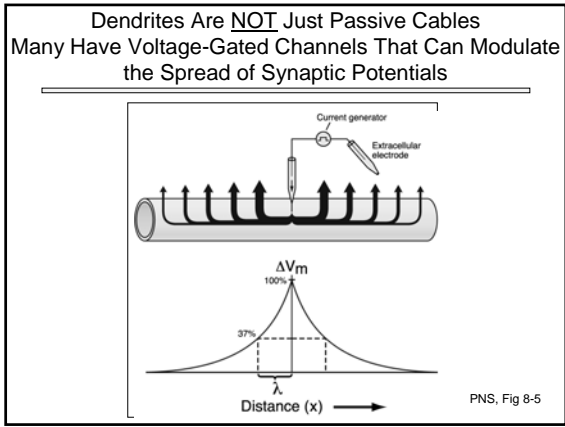
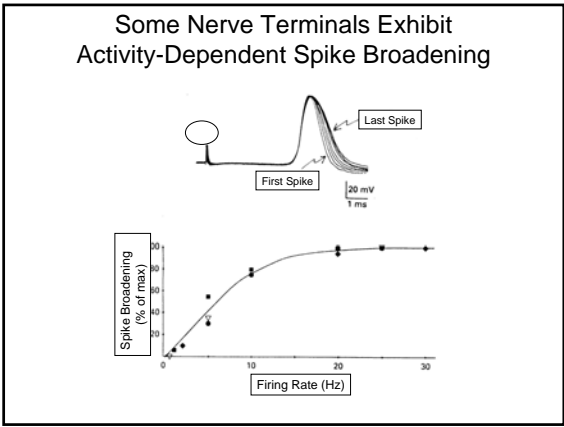
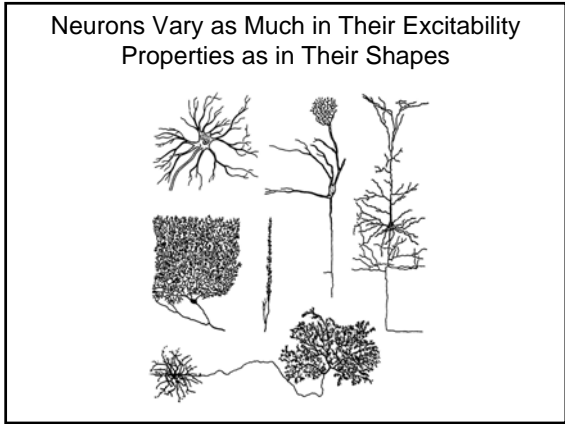
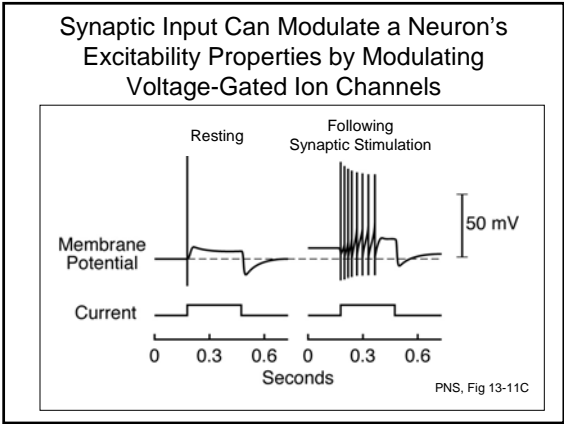
Each Class of Neuron Expresses a Subset of the Many Different Types of Voltage-Gated Ion Channels, Resulting in a Unique Set of Excitability Properties



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





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

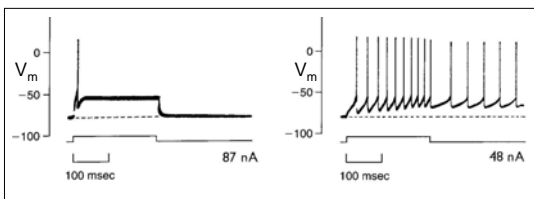
$\text{Na}^+, \text{K}^+, \text{Ca}^{++}, \text{Cl}^-$

How Voltage-Gated Ion Channels Go Bad

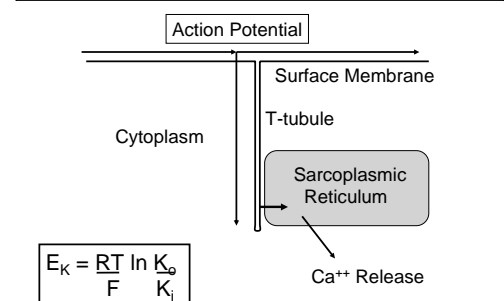
- Mutations
- Autoimmune diseases
- *Defects in transcription of normal genes*
- *Mislocation within the cell*

I. Mutations in Different Genes Can Lead to Similar Symptoms

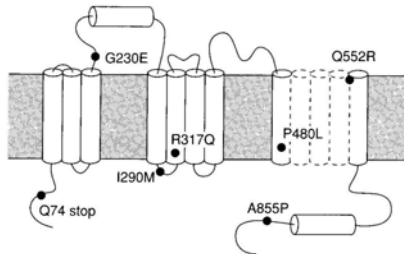
Myotonic Muscle is Hyperexcitable



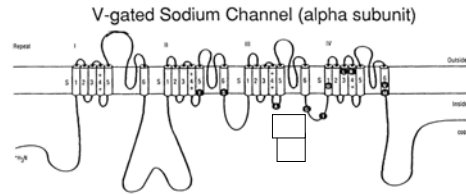
Build-up of K^+ Ions in the T-Tubules Following an Action Potential Can Depolarize the Muscle Cell



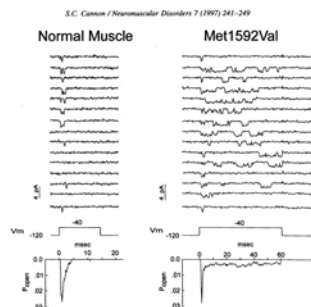
Mutations in Voltage-Gated Cl⁻ Channels in Skeletal Muscle Can Result in Myotonia



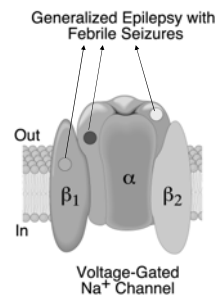
Mutations in Voltage-Gated Na⁺ Channels in Skeletal Muscle Can Also Result in Myotonia



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

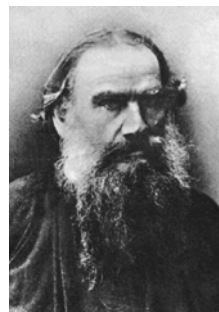


Mutations in Either α or β-Subunits Can Lead to Similar Symptoms



II. Different Mutations in the Same Gene Can Lead to Different Symptoms

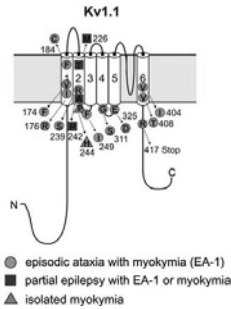
“Happy families are all alike.
Every unhappy family is unhappy in its own way.”



Tolstoy, p.1,
Anna Karenina

Different Point Mutations in the Same α -Subunit Lead to Three Different Classes of Symptoms

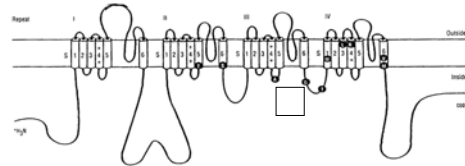
Voltage-gated K^+ channel



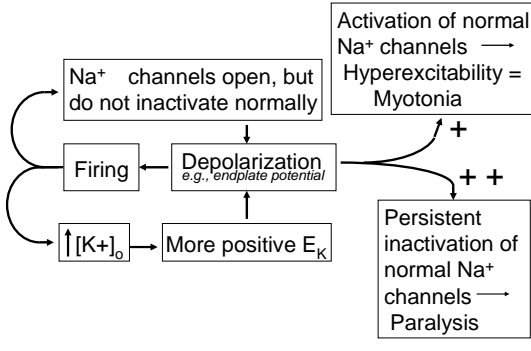
Voltage-Gated Na^+ Channels in Skeletal Muscle Can Have Point Mutations That Lead to:

Potassium Aggravated Myotonia, Paramyotonia Congenita, or Hyperkalemic Periodic Paralysis

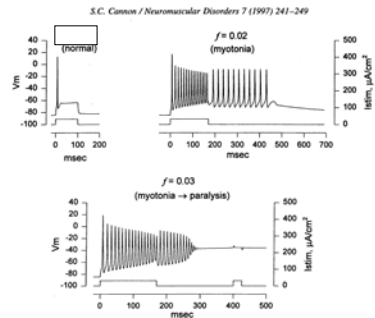
V-gated Sodium Channel (alpha subunit)



Degree of Na^+ Inactivation Deficit Determines Whether Paralysis or Hyperexcitability Occurs



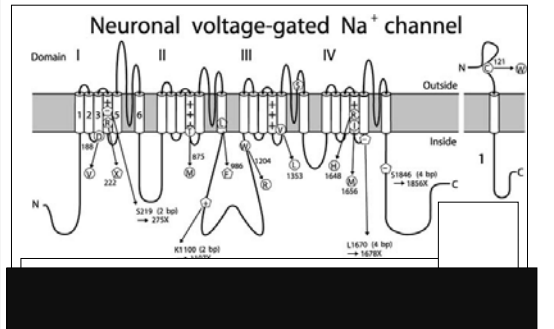
Increasing Degree of Persistent Activation Can Switch the Muscle Fiber from Hyperexcitable to Inexcitable



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

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



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

