Voltage-Gated Ion Channels in Health and Disease

jdk3

Principles of Neural Science, chapter 9

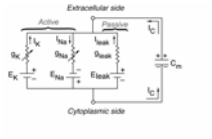
Voltage-Gated Ion Channels in Health and Disease

I. Multiple functions of voltage-gated ion channels

II. Neurological diseases involving voltage-gated ion channels

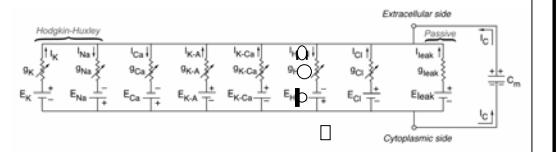
Squid Giant Axon According to Hodgkin & Huxley

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



But....

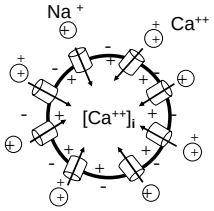
Mammalian Neurons Have Several Types of Voltage-Gated Ion Channels



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

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

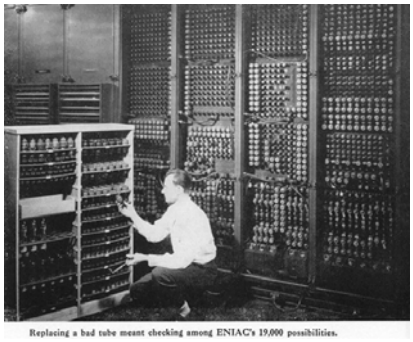
$[Ca^{++}]_i$ Can Act as a Regulator of Various Biochemical Processes



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

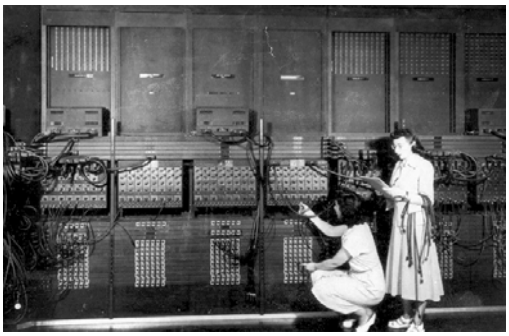
II. Fine Control of Membrane Excitability

Early Computers Were Made of Thousands of Identical Electronic Components

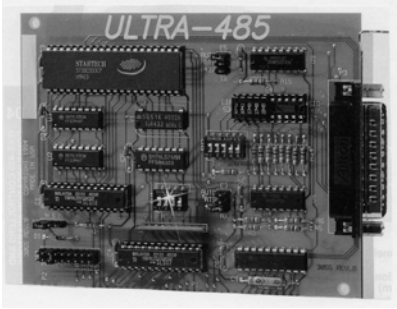


Replacing a bad tube meant checking among ENIAC's 19,000 possibilities.

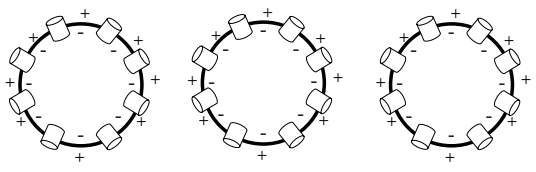
ENIAC's Computational Power Relied on the Specificity of Connections Between Different Identical Elements



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



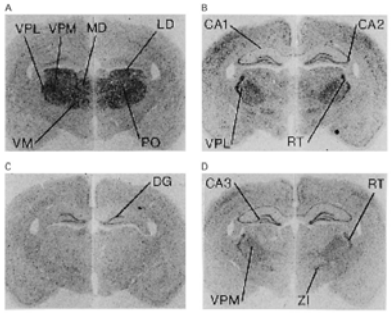
Each Class of Neuron Expresses a Subset of the Many Different Types of Voltage-Gated Ion Channels, Resulting in a Unique Set of Excitability Properties



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

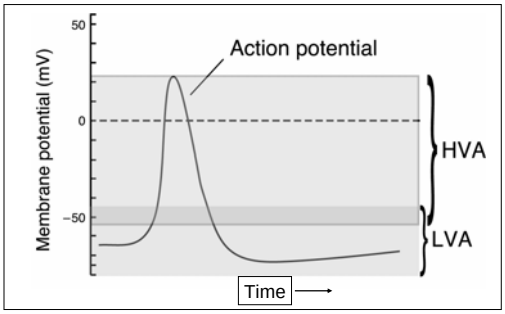
e.g., consider a single gene that encodes voltage-gated K^+ channels

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

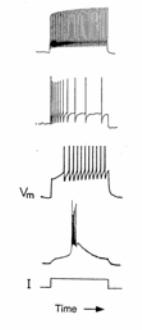


PNS
Fig 6-14

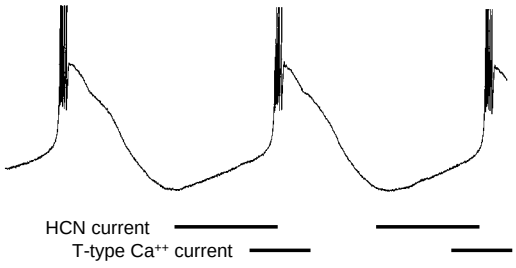
HVA Channels Affect Spike-Shape
LVA Channels Affect Spike-Encoding



Neurons Differ in Their Responsiveness to Excitatory Input

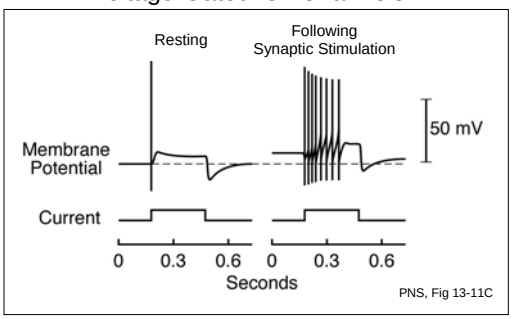


Thalamocortical Relay Neurons
Burst Spontaneously



PNS, Fig 9-11

Synaptic Input Can Modulate a Neuron's Excitability Properties by Modulating Voltage-Gated Ion Channels

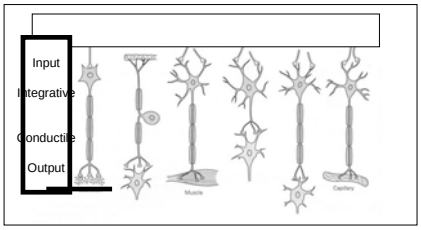


PNS, Fig 13-11C

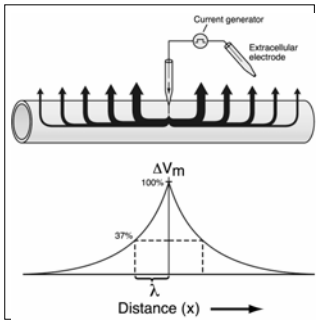
Neurons Vary as Much in Their Excitability Properties as in Their Shapes

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

Each Functional Zone of the Neuron Has a Special Complement of Voltage-Gated Ion Channels

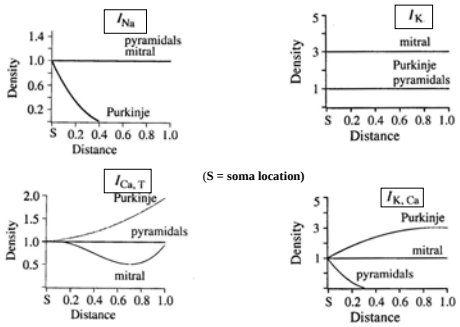


Dendrites Are NOT Just Passive Cables
Many Have Voltage-Gated Channels That Can Modulate the Spread of Synaptic Potentials



PNS, Fig 8-5

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



Voltage-Gated Ion Channels in Health and Disease

I. Multiple functions of voltage-gated ion channels

II. Neurological diseases involving voltage-gated ion channels

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

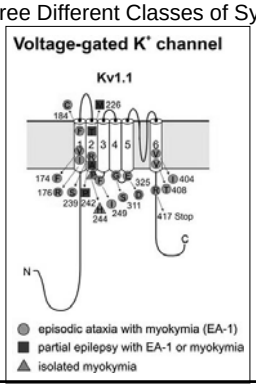
- Acquired neuromyotonia
- Andersen's syndrome
- Becker's myotonia
- Episodic ataxia with myokymia
- Familial hemiplegic migraine
- Generalized epilepsy with febrile seizures
- Hyperkalemic periodic paralysis
- Malignant hyperthermia
- Myasthenic syndrome
- Paramyotonia congenita
- Spinocerebellar ataxia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

Na^+, K^+, Ca^{++}, Cl^-

Phenotypic Variability

Mutations in the Same Gene
Lead to Different Symptoms

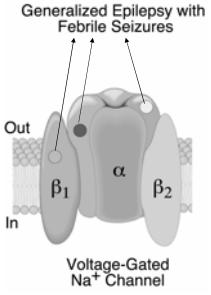
Different Point Mutations in the Same α-Subunit Lead to Three Different Classes of Symptoms



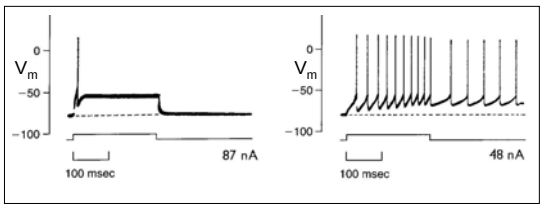
Genetic Variability

Mutations in Different Genes
Lead to Similar Symptoms

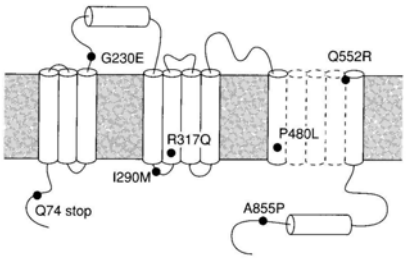
Mutations in Either α or β-Subunits Can Lead to Similar Symptoms



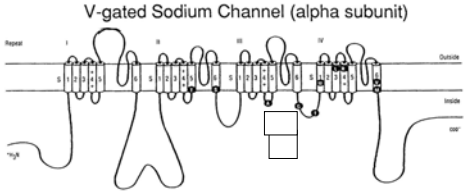
Myotonic Muscle is Hyperexcitable



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

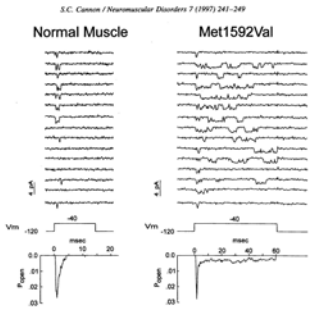


Mutations in Voltage-Gated Na^+ Channels in Skeletal Muscle Can Also Result in Myotonia

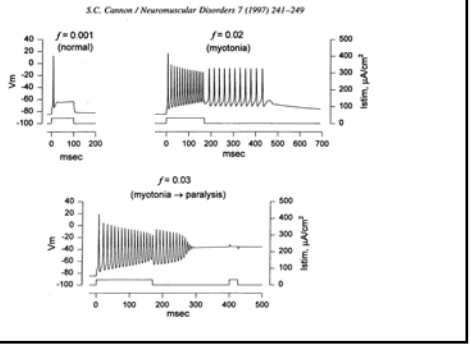


Mutations Often Affect Gating Functions

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

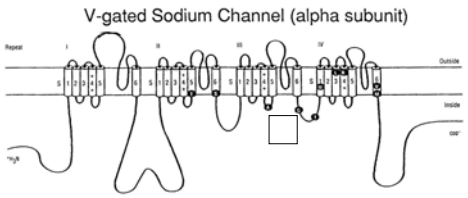


Increasing Degree of Persistent Inactivation Can Move the Muscle Fiber from Hyperexcitable to Inexcitable



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

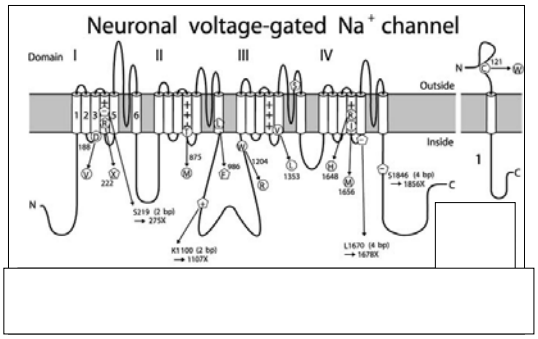
Potassium Aggravated Myotonia
Paramyotonia Congenita
Hyperkalemic Periodic Paralysis



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

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



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

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