Voltage-Gated Ion Channels in Health and Disease

jdk3

Principles of Neural Science, chapter 9

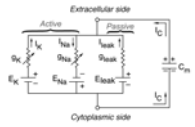
Voltage-Gated Ion Channels in Health and Disease

I. Multiple functions of voltage-gated ion channels

II. Neurological diseases involving voltage-gated ion channels

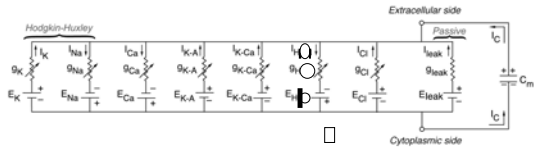
Squid Giant Axon According to Hodgkin & Huxley

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



But....

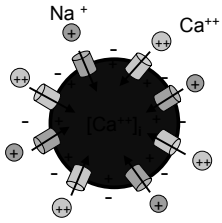
Mammalian Neurons Have Several Types of Voltage-Gated Ion Channels



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

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

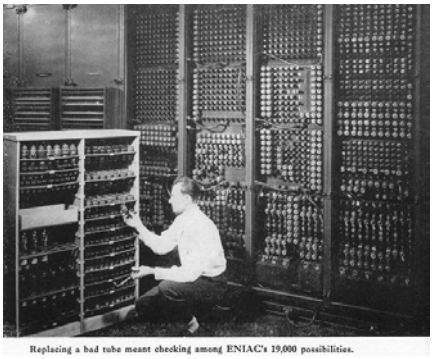
$[Ca^{++}]_i$ Can Act as a Regulator of Various Biochemical Processes



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

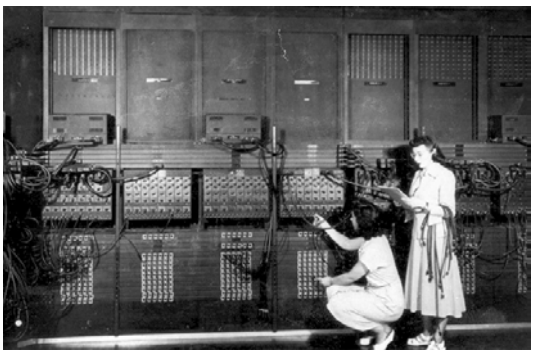
II. Control of Membrane Excitability

Early Computers Were Made of Thousands of Identical Electronic Components



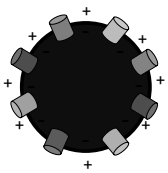
Replacing a bad tube meant checking among ENIAC's 19,000 possibilities.

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

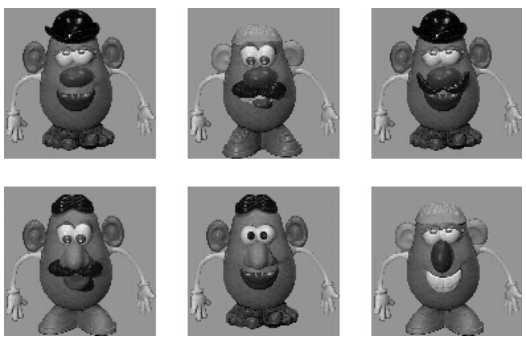


Electronic Devices Are Made of a Variety of Specialized Elements With Specialized Functional Properties

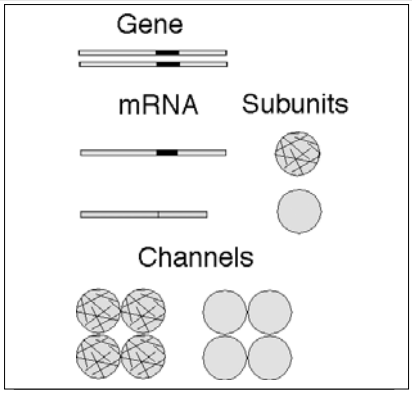
Each Neuron Expresses a Subset of the Many Different Types of Voltage-Gated Ion Channels



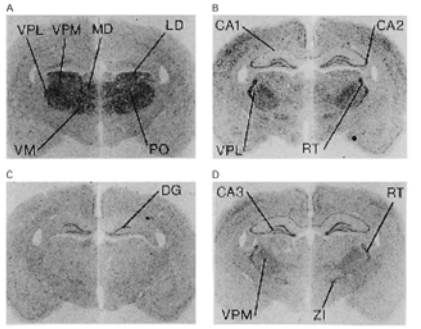
Each Class of Neurons Expresses a Unique Set of Voltage-Gated Ion Channels, Which Endows it with a Specific Excitability Property



Alternative Splicing of Pre-mRNA

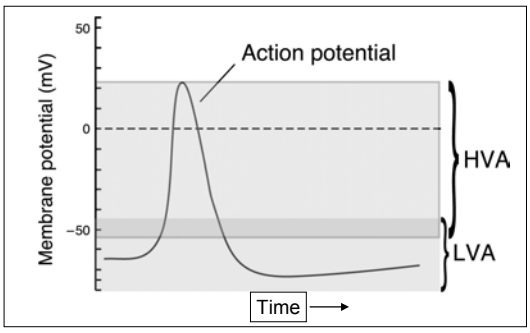


Variation of Alternative Splicing of pre-mRNA From One Gene Results in Regional Variation in Expression of Four Different Isoforms of a Voltage-Gated K^+ Channel

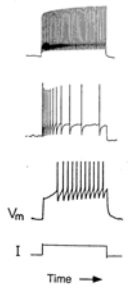


PNS
Fig 6-14

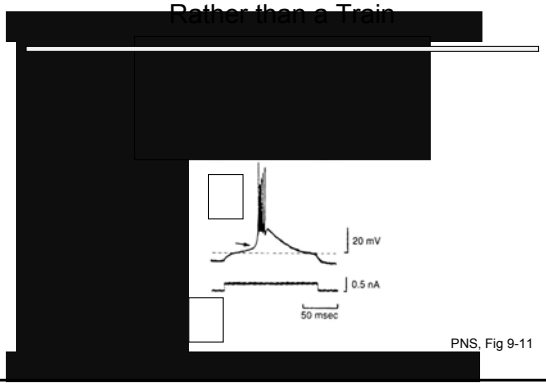
HVA Channels Affect Spike Shape
LVA Channels Affect Spike Encoding



Neurons Differ in Their Responsiveness to Excitatory Input

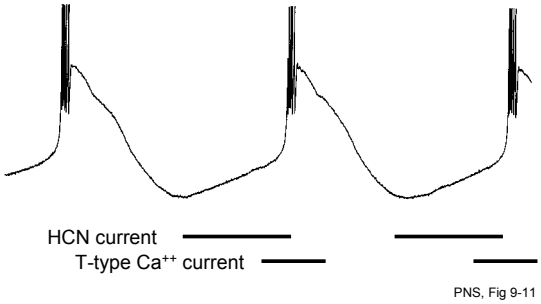


Some Neurons Respond with a Burst, Rather than a Train



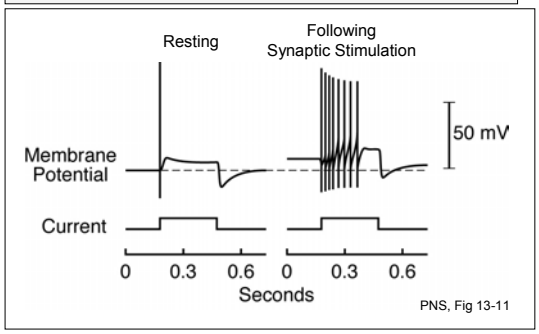
PNS, Fig 9-11

Thalamocortical Relay Neurons Burst Spontaneously



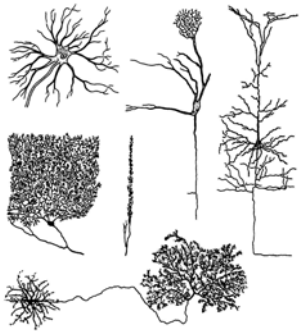
PNS, Fig 9-11

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

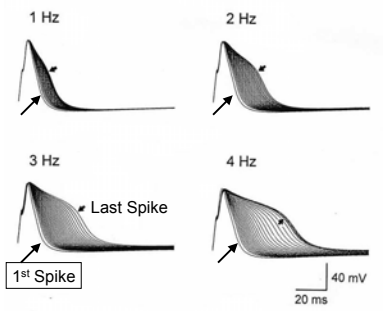


PNS, Fig 13-11

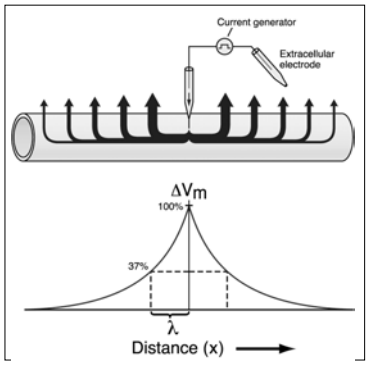
Neurons Vary as Much in Their Excitability Properties as in Their Shapes



Activity-Dependent Action Potential Broadening

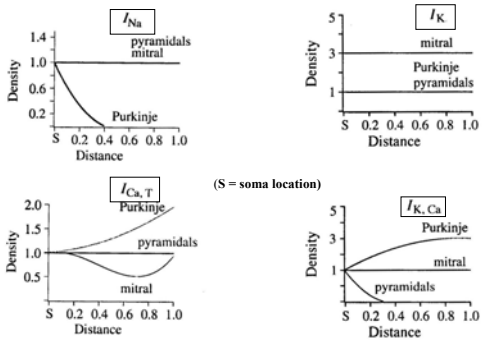


Length Constant $\lambda = \sqrt{r_m/r_a}$

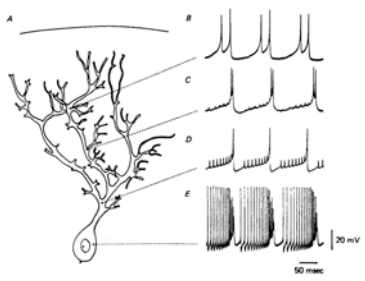


PNS, Fig 8-5

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

I. Multiple functions of voltage-gated ion channels

II. Neurological diseases involving voltage-gated ion channels

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

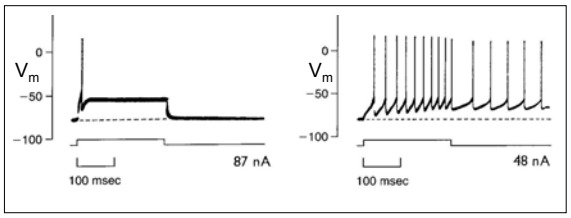
Na^+, K^+, Ca^{++}, Cl^-

How Voltage-Gated Ion Channels Go Bad

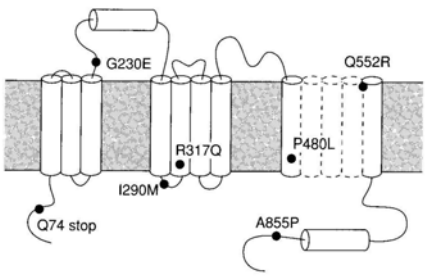
- Mutations
- Autoimmune diseases
- *Defects in transcription*
- *Mislocation within the cell*

I. Mutations in Different Genes Can Lead to Similar Symptoms

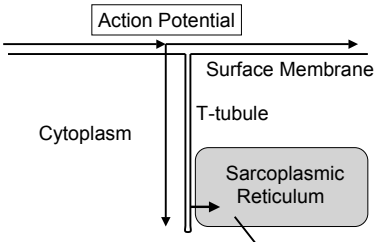
Myotonic Muscle is Hyperexcitable



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

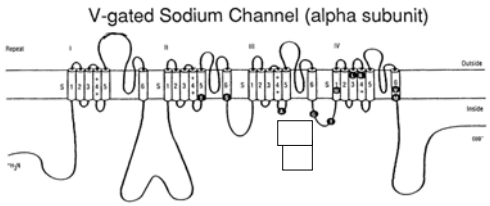


Build-up of K^+ Ions in the T-Tubules Following an Action Potential Can Depolarize the Muscle Cell

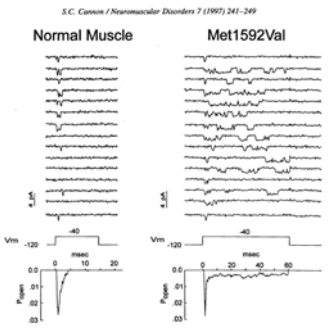


$$E_K = \frac{RT}{F} \ln \frac{K_o}{K_i}$$

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



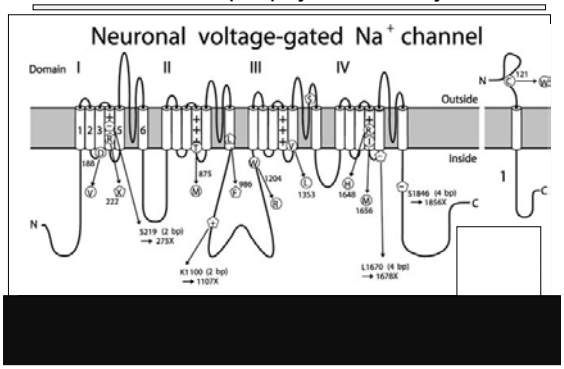
Many of These Point Mutations Affect Kinetics or Voltage-Range of Inactivation



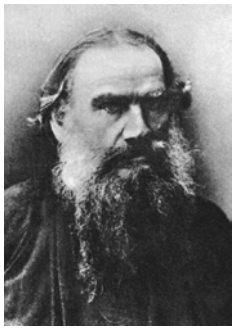
II. Regional Differences in Gene Expression Account for Much of the Specificity of Ion Channel Diseases

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



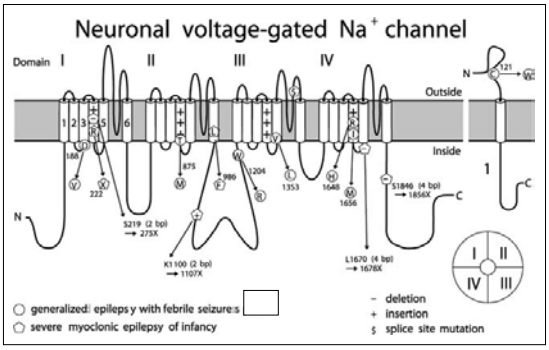
"Happy families are all alike. Every unhappy family is unhappy in its own way."



Tolstoy, p.1,
Anna Karenina

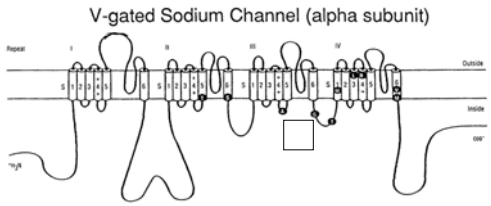
III. Different Mutations in the Same Gene Can Lead to <u>Different</u> Symptoms

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

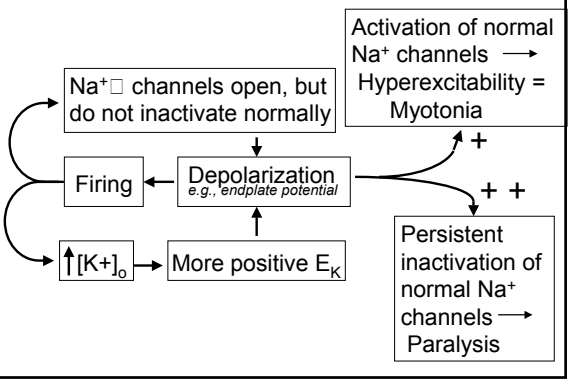


Voltage-Gated Na^+ Channels in Skeletal Muscle Can Have Point Mutations That Lead to:

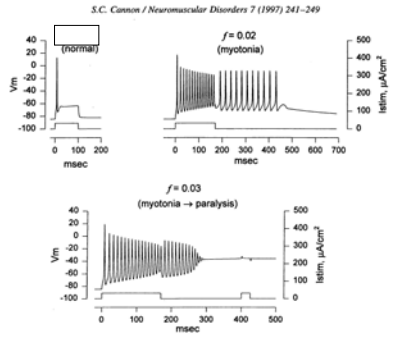
Potassium Aggravated Myotonia,
Paramyotonia Congenita, or
Hyperkalemic Periodic Paralysis



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



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