Voltage-Gated Ion Channels and the Action Potential

jdk3

Principles of Neural Science, chaps 8&9

• The Action Potential
  – Generation
  – Conduction
• Voltage-Gated Ion Channels
  – Diversity
  – Evolutionary Relationships

Electronically Generated Current Counterbalances the Na⁺ Membrane Current

\[ g = \frac{I}{V} \]

Equivalent Circuit of the Membrane Connected to the Voltage Clamp

For Large Depolarizations, Both \( I_{Na} \) and \( I_K \) Are Activated

\[ V_m \]

\[ I_m \]

\[ I_K \] is Isolated By Blocking \( I_{Na} \)

\[ V_m \]

\[ I_m \]

\[ 1 \text{ ms} \]
**INa is Isolated By Blocking IK**

- **Calculation of gNa**
  
  \[ \frac{V_m - E_{Na}}{g_{Na}} = I_{Na} \]
  
  where:
  - \( V_m \) is the Value of the Na Battery plus the Voltage Drop Across gNa
  - \( I_{Na} \) is the Current measured in presence of TEA
  - \( E_{Na} \) is the Sodium equilibrium potential

**gNa and gK Have Two Similarities and Two Differences**

**Voltage-Gated Na⁺ Channels Have Three States**

**Total I_{Na} is a Population Phenomenon**
Na⁺ Channels Open in an All-or-None Fashion

The Action Potential is Generated by Sequential Activation of $g_{Na}$ and $g_K$

Negative Feedback Cycle Underlies Falling Phase of the Action Potential

Local Circuit Flow of Current Contributes to Action Potential Propagation

Conduction Velocity Can be Increased by Increased Axon Diameter and by Myelination

Myelin Speeds Up Action Potential Conduction
Voltage-Gated Ion Channels and the Action Potential

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Opening of Na⁺ and K⁺ Channels is Sufficient to Generate the Action Potential

Rising Phase

Falling Phase

However, a Typical Neuron Has Several Types of Voltage-Gated Ion Channels

Functional Properties of Voltage-Gated Ion Channels Vary Widely

• Selective permeability
• Kinetics of activation
• Voltage range of activation
• Physiological modulators

Voltage-Gated Ion Channels Differ in their Selective Permeability Properties

<table>
<thead>
<tr>
<th>Cation Permeable</th>
<th>Anion Permeable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺, Ca⁺⁺, K⁺</td>
<td>Cl⁻</td>
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Functional properties of Voltage-Gated Ion Channels Vary Widely

• Selective permeability
• Kinetics of activation
• Voltage range of activation
• Physiological modulators
Voltage-Gated K⁺ Channels Differ Widely in Their Kinetics of Activation and Inactivation

![Graph of Voltage-Gated K⁺ Channels](image)

Functional properties of Voltage-Gated Ion Channels Vary Widely

- Selective permeability
- Kinetics of activation
- Voltage range of activation
- Physiological modulators:
  - e.g., phosphorylation, binding of intracellular Ca²⁺ or cyclic nucleotides, etc.

Voltage-Gated Ca⁺⁺ Channels Differ in Their Voltage Ranges of Activation

![Graph of Voltage-Gated Ca⁺⁺ Channels](image)

The Inward Rectifier K⁺ Channels and HCN Channels Are Activated by Hyperpolarization

![Graph of Inward Rectifier K⁺ Channels](image)

Physiological Modulation

![Diagram of Physiological Modulation](image)
HCN Channels That Are Opened by Hyperpolarization Are Also Modulated by cAMP

Voltage-Gated Ion Channels Belong to Two Major Gene Superfamilies

I. Cation Permeant

II. Anion Permeant

Voltage-Gated Ion Channel Gene Superfamilies

I) Channels With Quatameric Structure Related to Voltage-Gated, Cation-Permeant Channels:
   A) Voltage-gated:
      • K⁺ permeant
      • Na⁺ permeant
      • Ca²⁺ permeant
      • Cation non-specific permeant

Structurally related to:

B) Cyclic Nucleotide-Gated (Cation non-specific permeant)

C) K⁺-permeant leakage channels

D) TRP Family (cation non-specific); Gated by various stimuli, such as osmolarity, pH, mechanical force, ligand binding and temperature

The α-Subunits of Voltage-Gated Channels Have Been Cloned

Voltage-Gated Cation-Permeant Channels Have a Basic Common Structural Motif That is Repeated Four-fold
Four-Fold Symmetry of Voltage-Gated Channels Arises in Two Ways

K⁺ Channels, HCN Channels → Na⁺ or Ca²⁺ Channels

Leakage K⁺ Channels Are Dimers of Subunits With Two P-Loops Each

P-Loops Form the Selectivity Filter of Voltage-Gated Cation-Permeant Channels

Voltage-Gated Ion Channel Gene Superfamilies

II) “CLC” Family of Cl⁻-Permeant Channels
(dimeric structure):
- Gated by:
  - Voltage - particularly important in skeletal muscle
  - Cell Swelling
  - pH

Voltage-Gated Cl⁻ Channels Differ in Sequence and Structure from Cation-Permeant Channels
Voltage-Gated Cl\(^-\) Channels are Dimers

\[ x2 \]