

Lecture 3 -- Neuroexcitability I -- Koester

General Review of Ion Channels

Ion Channels

I. Introduction to Ion Channels

A. Why needed? - Ions, because of their polar nature, cannot diffuse through the hydrophobic (non-polar) lipid bilayer of the membrane

B. Ion channels have a wide range of functions throughout the body

C. Some of diseases that are caused by defects in ion channels:

1. Cystic fibrosis
2. Myasthenic syndrome
3. Hyperkalemic periodic paralysis
4. Myasthenia gravis
5. Paramyotonia congenita
6. Hyperekplexia
7. Episodic ataxia/myokymia
8. Rasmussen's encephalitis
9. Long Q-T syndrome
10. Nocturnal frontal lobe epilepsy
11. Generalized epilepsy
12. Liddle's syndrome
13. Pseudohypoaldosteronism type-1
14. Retinitis pigmentosa
15. Dent's disease
16. Bartter's syndrome
17. Familial hemiplegic migraine
18. Charcot-Marie-Tooth Disease
19. Non-syndromic deafness
20. Nephrolithiasis (kidney stones)

II. Structure of ion channels

A. Water-filled central pores

B. Glycoproteins

C. Pore, formed from α -subunit(s), is made of multiple subunits or pseudosubunits

D. Minor subunits (β , γ or δ) modify functional properties of α -subunits

III. Three types of functional properties

A. Conduct

1. Up to 2×10^8 ions /sec – much faster than pumps or transporters
2. Acts like a catalyst for increasing *rate* of transmembrane ion flux (current)
3. Current, which is determined by driving force, varies with membrane potential and concentration

B. Select

1. Two basic flavors
 - a. Cation selective (Na^+ K^+ , Ca^{++} , or cation non-specific)
 - b. Anion selective (Cl^-)
2. **Selectivity filter** selects between ions with the same charge on the basis of:
 - a. Size (molecular sieve)
 - b. Chemical interaction (polar groups substitute for waters of hydration)

C. Gate

1. Kinetics
 - a. All-or-none
 - b. 0.1-10 msec open time most prevalent; but opening and closing transitions appear to be instantaneous
2. Two ways to open & close
 - a. Constriction
 - (1) Global
 - (2) Local (can result in drugs being trapped inside the channel)
 - b. Stopper
 - (1) Intrinsic to channel (ball and chain)
 - (2) Free in cytoplasm or in extracellular fluid (e.g. Mg^{++} or polyamines)
3. Five types of control
 - a. Ligand binding
 - b. Phosphorylation
 - c. Mechanical force

d. Membrane potential

e. Temperature

D. Modulation of channel function

1. Open channel block

a. Analogous to blocking the catalytic site of an enzyme

b. Can be voltage-sensitive if blocker is an ion and the binding site is inside the channel

2. Modulation of gating

a. Extracellular ligands that bind directly to the channel

b. Pore blockers

c. Allosteric regulators

IV. Evolutionary relationships between ion channels

A. Ion channels are grouped into five major superfamilies on the basis of similarities in amino acid sequences and 2°, 3° and 4° structure of their alpha subunits.

B. Evolution is a conservative process

V. Ion channel diversity

A. Various factors contribute to ion channel diversity

1. Different genes encode different isoforms of α -subunits

2. Homologous or heterologous combination of α -subunits

3. α -subunits combine with different β , δ , or γ subunits

4. Alternative splicing of pre-mRNA molecules

5. Post-transcriptional mRNA editing

Resting Potential and Passive Membrane Properties

I. The electrical signals carried by a neuron can be understood by representing the neuron by an electrical **equivalent circuit model**, consisting of:

A. Capacitors

B. Conductances

C. Batteries

II. The **lipid bilayer** acts as a capacitor-

- A. It consists of a lipid insulator that separates two conductors (ECF and cytoplasm).
- B. It can store excess + and - charge (Q), although bulk electroneutrality is maintained (except for the region immediately adjacent to the membrane).
- C. Separation of + and - charges on either side of the membrane gives rise to an electrical potential difference, the membrane potential ($V_m = Q/C$).
- D. C is directly proportional to membrane area (because the lipid membrane is uniform in composition and thickness).
- E. In order for membrane potential to change, Q must change, so capacitance acts to slow the rate of change of V_m in response to current flow across the membrane.

III. **Ion channels** endow the membrane with two additional electrical properties:

- A. **Conductance** (g)
 - 1. Virtually all current flow across the membrane is through ion channels
 - 2. $g = 1/R$
- B. **Electromotive force** (EMF) (acts as a battery)
 - 1. Because of:
 - a. Selective conductance
 - b. Unequal ion distributions
 - 2. Battery value is determined by Nernst equilibrium potential

IV. The **resting membrane** consists of channels that are permeable to K^+ , Na^+ , and Cl^- , in parallel with the membrane capacitance and ion pumps and carriers:

- A. $V_m = (g_K \cdot E_K + g_{Cl} \cdot E_{Cl} + g_{Na} \cdot E_{Na}) / (g_K + g_{Cl} + g_{Na})$
- B. g_K (and therefore E_K) predominate at rest
- C. Active pumping of Na^+ and K^+ keeps the ionic batteries from running down

V. The membrane **time constant**:

- A. Membrane capacitance slows the rate of change of membrane potential
- B. Time constant (τ) = $R_m \times C_m$
- C. Capacitance slows the time course of synaptic potentials and action potential conduction

VI. The membrane **length constant**

- A. The combination of membrane leakage channels and axial resistance causes membrane potential changes to decrement with distance
- B. Length constant (λ) = $\sqrt{(r_m/r_a)}$
- C. Affects the decay with distance of synaptic potentials

Relevant reading: chapters 6-8 in “Principles”