Medical Neuroscience | Tutorial Notes

Molecular Mechanisms of Action Potential Generation

MAP TO NEUROSCIENCE CORE CONCEPTS[1]

NCC2. Neurons communicate using both electrical and chemical signals.

LEARNING OBJECTIVES

After study of the assigned learning materials, the learner will:

1. Describe the molecular properties of sodium and potassium channels that explain the voltage- and time-dependent permeability changes underlying action potential generation.
2. Describe the molecular mechanisms for establishing chemical gradients for sodium and potassium across the neuronal plasma membrane.

TUTORIAL OUTLINE

I. Introduction: review the Hodgkin-Huxley model of the action potential (see **Figures 3.8** & **3.9**[2])

- *A.* *THE ACTION POTENTIAL IS EXPLAINED BY VOLTAGE-DEPENDENT AND TIME- DEPENDENT CHANGES IN THE PERMEABILITY OF THE NEURONAL MEMBRANE TO Na^+ AND K^+*
- B. this model explains the *threshold* for the generation of an action potential (see **Box 3B**) and the *all-or-none* (regenerative) character of the action potential (see **Figure 3.9**)
- C. review the ionic basis of the action potential by viewing an online animation that accompanies *Neuroscience, 5th. Ed.*, Chapter 2: **Animation 2.3 The Action Potential** [click here]

II. Functional and molecular models of Na^+ and K^+ channels

- A. functional model (see **Figure 4.3**)
  1. Na^+ channels: Closed ⇔ open ⇔ inactivated ⇔ closed
  2. K^+ channels: Closed ⇔ open ⇔ closed
- B. molecular model (see **Figures 4.6** & **4.8**)
  - **1. integral membrane proteins**
    - a. a series of membrane-spanning domains

[1] Visit **BrainFacts.org** for *Neuroscience Core Concepts* (©2012 Society for Neuroscience) that offer fundamental principles about the brain and nervous system, the most complex living structure known in the universe.
[2] Figure references to Purves et al., *Neuroscience, 5th Ed.*, Sinauer Assoc., Inc., 2012. [click here]

i. "**pore loop**" that forms the channel for the selective passage of a certain ionic species

ii. "**voltage-sensor**" comprised of a segment of positively charged amino acid residues in an helical structure that changes its conformation in response to changes in membrane potential (see **Figure 4.8**)

iii. segment that allows for the aggregation of subunits (or the folding of a single subunit) into a functional three-dimensional channel structure

b. extracellular domain

i. may include a segment that binds certain toxins

c. intracellular domain

i. may include a segment of amino acids that "plugs" the pore during sustained depolarization (inactivation)

C. some channels are comprised of a single protein sequence (Na^+), others require the aggregation of multiple subunits (K^+)

D. CLINICAL APPLICATION: several skeletal and cardiac muscle disorders appear to be the consequences of faulty ion channels, produced by mutations in the genes that encode channel proteins (see **Box 4D**)

IV. Ion pumps

A. pumps, exchangers and transporters establish concentration gradients that are discharged when ions flow through channels (see **Figure 4.9**)

B. Na^+/K^+ ATPase

1. experiments demonstrated that Na^+ efflux is linked to K^+ influx and the supply of intracellular ATP (see **Figure 4.10A**)

2. stoichiometry of ionic fluxes

a. *THREE* Na^+ ions are transported out of cell for every *TWO* K^+ ions transported into cell

b. therefore, the pump is **electrogenic**: since there is a net loss of one positive charge for each cycle, pump activity can hyperpolarize the plasma membrane

3. model of pump activity (see **Figure 4.10B**)

a. integral membrane protein

b. intracellular domain with sites for ATP binding and hydrolysis

c. phosphorylation/dephosphorylation cycle of the pump induces a series of conformational changes that allow for the translocation of Na^+ and K^+ across the plasma membrane

d. view an online animation that accompanies *Neuroscience, 5th. Ed.*, Chapter 4: **Animation 4.2 the Sodium-Potassium Pump** [click here]

C. there are other important pumps and ion exchangers for maintenance of Ca^{++}, Cl^{-} and H^{+} homeostasis (see **Figure 4.9**)