

Lecture 5

Neuroexcitability III:

Voltage-Gated Ion Channels in Normal Neuronal Function and in Disease

- I. Two major functional implications stem from the fact that there are several dozen types of voltage-gated ion channels found in vertebrate neurons, as opposed to just two types that are found in squid axon:
 - A. Calcium ions entering through voltage-gated ion channels can serve as second messengers that:
 1. Modulate:
 - a. enzyme activity
 - b. channel gating
 - c. gene expression
 2. Trigger transmitter release
 - B. Various unique combinations of the several dozen types of voltage-gated ion channels are found in different neurons:
 1. They can be roughly categorized into two major classes:
 - a. Low-voltage-activated: affect mainly action potential- encoding (converting input into a train of action potentials)
 - b. High voltage-activated: affect mainly spike shape, which in turn can affect Ca^{++} influx
 2. Because different types of voltage-gated channels are mixed in widely differing combinations in different types of neurons, neurons differ in their excitability properties in various ways:
 - a. Response to synaptic input
 - b. Spontaneous activity
 - c. Ability to have their excitability properties modulated by synaptic input
 - d. Action potential shape, and its ability to be modulated by activity
 - e. Variations of excitability properties between the different functional regions within a neuron (dendrites and soma, initial segment, axon and axon terminals).
- II. Various neurological diseases are caused by malfunction of voltage-gated ion channels:
 - A. How ion channels go bad:

1. Mutations
2. Autoimmune processes
3. Defects in transcription
4. Mislocation within the cell

B. Principles that apply to “channelopathies:

1. Mutations in different genes can lead to similar phenotypes; e.g., mutations in genes encoding either voltage-gated Na^+ or Cl^- channels expressed in skeletal muscle can lead to excessive muscle excitability (myotonia).
2. Differences in gene expression account for much of the specificity of ion channel diseases:
 - a. e.g., voltage-gated Na^+ channels found in the CNS and in skeletal muscle are encoded by different genes
 - b. defects in the CNS channels lead to epilepsy (excessive neuronal excitability), while defects in muscle Na^+ channels can lead to myotonia.
3. Different point mutations in the same channel-gene can lead to different phenotypes, depending on how each mutation alters the function of the channel (e.g., mutations in genes encoding voltage-gated Na^+ channels can lead to either myotonia or to paralysis).
4. The subunit structure of ion channels can be important for understanding how hereditary ion channel diseases are inherited.