Lecture 5 -- Neuroexcitability III – Koester

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. 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).

3. Regional 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.
4. The subunit structure of ion channels can be important for understanding how hereditary ion channel diseases are inherited.