

## 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 found in different neurons determine their membrane excitability characteristics
    1. These channels 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  $\text{Ca}^{++}$  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. 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. **Phenotypic Variability:** 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  $\text{Na}^+$  channels can lead to either myotonia or to paralysis).

2. **Genotypic Variability:** Mutations in different genes can lead to similar phenotypes; e.g., mutations in genes encoding either voltage-gated Na<sup>+</sup> or Cl<sup>-</sup> channels expressed in skeletal muscle can lead to excessive muscle excitability (myotonia).
3. **Gating** (rather than selectivity or conductance) is typically modified by mutations that modify ion channel function.
4. **Regional specificity of ion channel diseases** is largely accounted for by regional differences in gene expression:
  - a. *e.g.*, voltage-gated Na<sup>+</sup> 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<sup>+</sup> channels can lead to myotonia (excessive muscle excitability).
5. **Inheritance patterns of ion channel diseases** are often affected by the subunit structure of ion channels.

**Relevant reading: chapter 9 in “Principles”**