Introduction to Neurobiology

BIOL3833

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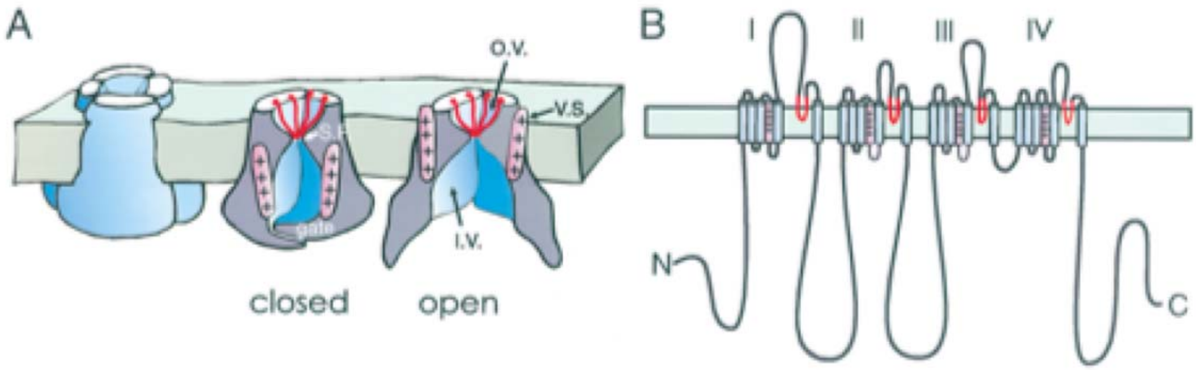
Module 3: Ion Channels Part 1

This document includes materials adapted from Nace Golding's lab manual for Neurobiology Laboratory at the University of Texas.

Module 2: Ion channels Part 1

<u>Voltage-gated ion channels determine the membrane conductance for each type of ion</u>

Ion channels provide the path for ionic movement across the membrane. That is, they give rise to ionic conductances. Open ion channels increase conductance for that ion, while closed ion channels reduce conductance. The hallmark of an ion channel is the channel pore which is selective for a particular ion species or a particular combination of ion species. For our purposes here, we will consider only ion channels that are selective for only one type of ion.



<u>Figure 1. Generalized structure of ion channels</u>

Ion channels generally share a set of common structural features (Figure 5) that confer specific functional properties.

1. *Pore selectivity filter*: Part of the basis for the ability of both voltage and ligand-gated ion channels to conduct ions of is simply due to the nature of the pore forming part of the channel, which can select for ions on the basis of size and charge.

2. *Voltage sensor*: In order for ion channel proteins to be voltage gated, the protein must have residues that sense voltage. The voltage-sensing region of most voltage-gated ion channels is thought to be on the 4th transmembrane segment, consisting of a series of positively charged amino acids. These residues would thus move during a voltage change, and provide the necessary energy for a conformational change in the protein.

3. *Inactivation 'gate'*: Some (but not all) ion channels posess an inactivation gate that blocks the channel pore soon after the channel activates. There is a good body of evidence supporting that the inactivation gate is located on the C-terminus on the intracellular face of the channel. Channel inactivation is thought to occur due to binding of this intracellular, tethered part of the protein to binding sites on the inside of the channel pore.

Voltage-gated ion channels and passive membrane properties

It is extremely important to realize that the action potential is an “active” process. The voltage changes during both the upstroke and repolarization of the action potential occur at rates faster than that of passive voltage changes. Action potentials depolarize in less than a millisecond, whereas passive voltage changes, reflected by tau, the membrane time constant, are on the order of many milliseconds. This is possible because the action potential is dominated by the kinetics of the underlying voltage-gated channels (the speed at which they activate, inactivate, and deactivate). *In general, below action potential threshold, changes in membrane voltage are dominated by the passive resistive and capacitive properties of the membrane. Above action potential voltage threshold, voltage-gated channels dominate voltage changes with (in general) faster kinetics.*

Diversity of ion channels in neurons

The simplified account of action potential generation is that the action potential begins with the activation of sodium channels which depolarize the membrane and end when sodium channels close and potassium channels repolarize the membrane. This account is accurate only in a general sense. All neurons in the brain possess many more types of voltage-gated channels which in turn display a staggering variety of properties. This diversity confers different signaling characteristics (threshold for action potential initiation, firing frequency, spike pattern, etc.). In some sense one can regard each neuron type as having an electrical “signature”. At this early stage in the course, we will not consider all types of voltage-gated channels. We will focus only on the two ion channels first identified by Hodgkin and Huxley as being necessary for the action potential in the squid giant axon. Later in the course we will examine a larger subset of ion channels that are important for determining information processing and transmission in neurons. We can capture the essential functional properties of ion channels in many ways, and some of the most important are:

1. *Voltage dependence of activation*: The primary determinant of an ion channel’s function is its voltage dependence of activation. This relationship describes what proportion of ion channels is open at each particular membrane voltatge.

2. *Rate of activation*: In addition to knowing how voltage affects the probability of channel opening, it is important to know how quickly a population of channels activate. Activation rates cover a broad range. Some channel types activate within a millisecond, while other channel types can take tens of milliseconds to activate. The activation rate determines how quickly the conductance through that channel type can contribute to changes in membrane potential.

3. *Rate of deactivation*. When a change in membrane voltage causes channels to open, once the membrane voltage returns to a potential where the channels are not activate, it can take some time for all of the channels to close. This process is known as deactivation.

4. Rate of inactivation. After activation, some types of channels will stop conducting ions after a period of time, even when the membrane voltage remains within the channels activation range. This process is known as inactivation and it occurs through a mechanism that is different from deactivation. Inactivation usually involves the movement of part of the channel protein into the channel pore, thus blocking ionic movement through the pore. Sodium channels commonly display inactivation of this type.

5. Recovery from inactivation. Once a channel has inactivated, the only thing that will relieve the inactivation is repolarization of the membrane to a potential low enough to allow recovery from inactivation. Once the membrane reaches a potential that allows recovery, the process of recovery from inactivation takes time to complete. The inactivation and delay associated with recovery from inactivation in sodium channels gives rise to the refractory period following the action potential.

Below is a description of only some of the ion channel types that are expressed by hippocampal neurons, along with descriptions of their relevant functional properties.

<u>Voltage-gated sodium channels</u>

Neurons express several types of sodium channels. For our purposes, we will lump all of them together in a single category because of their common functional similarities. The defining features of sodium channels are that the resulting sodium currents (INa) activate rapidly and inactivate rapidly, with recovery from inactivation requiring delays of a few milliseconds to tens of milliseconds.

<u>Voltage-gated potassium channels</u>

In contrast to sodium and calcium channels, potassium channels are an extremely diverse group, with pronounced differences in their functional characteristics. Dozens of different potassium channels are expressed in the nervous system. At this stage, we will consider only what is known as the “Classical Delayed Rectifier” potassium channel. This is a channel that opens after membrane depolarization, and does not inactivate. That is, this channel remains in its conductive state as long as the membrane is sufficiently depolarized. This channel deactivates when the membrane returns to resting potential.