Principles of Neuroscience, Chapter 6, Ion Channels

Notes based on Principles of Neuroscience
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1. Ion Channels

Ion channels in our body are not native to just neurons. They are found all over, and regardless of their specificities, they perform three functions in general:

- facilitate passage of ions
- recognize specific ions
- respond to electrical, chemical and mechanical signals

How are ion chaneels that are involved in neuronal signalling different?
They help in conducting signals rapidly, by allowing ions to pass through more easily. Also, neuronal ion channels are surprisingly more selective to K^+ ions in normal conditions and more selective for Na^+ ions during action potentials; which leads to effective transmission of signals.

What makes an ion channel selective for a specific kind of ion?
Ion channels act like molecular sieves; they differentiate between ions on the basics of pore diameter- the ion is stripped of its water of hydration and forms weak chemical bonds with polar amino acid residues inside the ion channel like glutamate and aspartate. Currently it is thought that uch chemical recognition is the basis of the seletivity of different ion channels.

1.1. Investigating ion channels

X-ray crystallographic methods are difficult to apply to ion channel studies because their transmembrane hydrophobic regions make them difficult to crystallize.

The patch clamp technique
The patch clamp technique was especially useful in studying single ion channels. A micropipette of Ach was held against a frog muscle membrane, and small unitary current pulses, signalling the opening and closing of the membrane channels were recorded from the area under the pipette tip. Conductance was found to pe around 25ps (*picosiemens*)

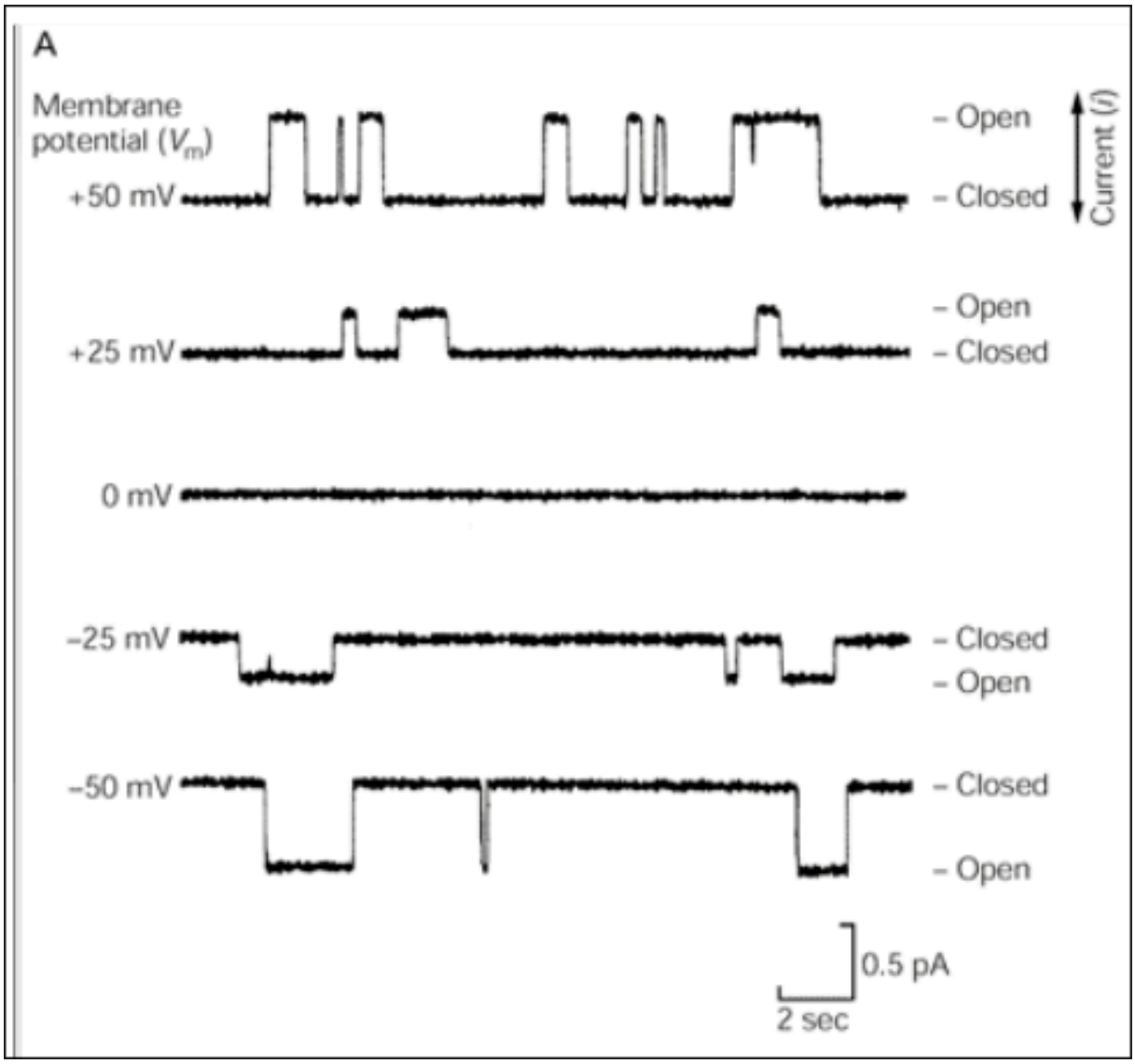

Figure 1: All or none.

A small fire-polished glass micropipette with a tip diameter of around 1 μm is pressed against the membrane of a skeletal muscle fiber that has been treated with proteolytic enzymes to remove connective tissue from the muscle surface. The pipette is filled with a salt solution resembling that normally found in the extracellular fluid. A metal electrode in contact with the electrolyte in the micropipette connects the pipette to a special electrical circuit that measures the current flowing through channels in the membrane under the pipette tip.

1.2. Factors determining the net electrochemical driving force across ion channels

There are two determining factors - the electrical potential difference across the membrane and the concentration gradient of the permeant ions across the membrane.

n some channels the current flow varies linearly with driving force—that is, the channels behave as simple resistors. In others the current flow is a nonlinear function of driving force. This type of channel behaves as a rectifier—it conducts ions more readily in one direction than in the other. Whereas the conductance ($\delta i/\delta V$) of a resistor-like channel is constant—it is the same at all voltages—the conductance of a rectifying channel is variable and must be determined by plotting current versus voltage over the entire physiological range of membrane potential.

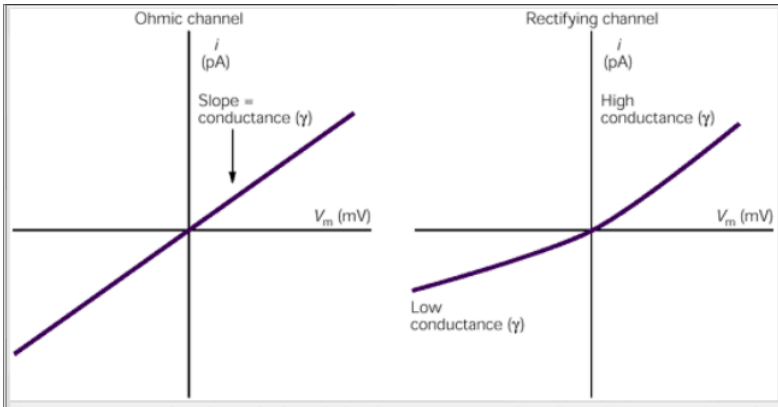

Figure 6-4 In many ion channels the relation between current flow through the open channel and membrane voltage is linear. Such channels are said to be "ohmic," because they follow Ohm's law, $i = V_m/R$ or $V_m \times \gamma$, where γ is conductance **(left plot).** In other channels the relation between current and membrane potential is nonlinear **(right plot).** This kind of channel is said to "rectify," in the sense that it tends to conduct ions more readily in one direction (here positive current) than in the other.

Figure 2: Different types of ion channels

1.3. Gating of ion channels

The channel protein has two or more conformational states that are relatively stable. Each of these stable conformations represents a different functional state. For example, each ion channel has at least one open state and one or two closed states. The transition of a channel between these different states is called gating.

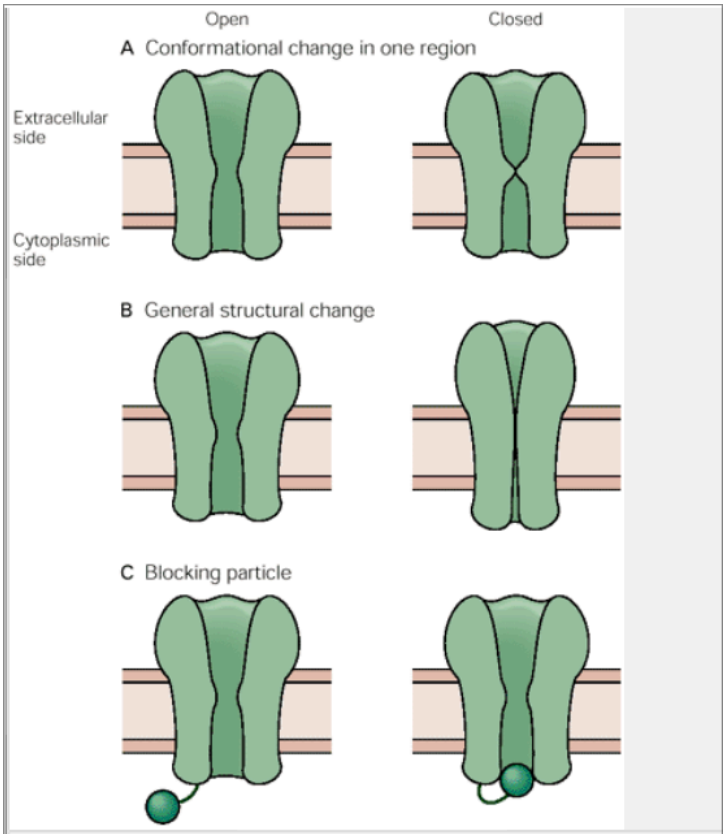

Figure 6-5 Three physical models for the opening and closing of ion channels.

A. A localized conformational change occurs in one region of the channel.

B. A generalized structural change occurs along the length of the channel.

Figure 3: Different physical models of gating

1.4. Controlling the duration of time channels remain active

The amount of time an ion channel remains active is controlled by either:

1. a chemical ligand
2. changes in membrane potential
3. mechanical stretch of the membrane

Desensitization and *inactivation* are some of the effects that control voltage gating.
Som ligand gated channels enter a refractory period on long exposure to the ligand, termed as desensitization. On the other hand, some channels are controlled by intrinsic or extrinsic factors that alter the amount of time the channel remains open or closed. The effect of the binding of curare to nicotinic Ach-gated ion channels, which is weak and reversible, and leads to blockade, is once such example.

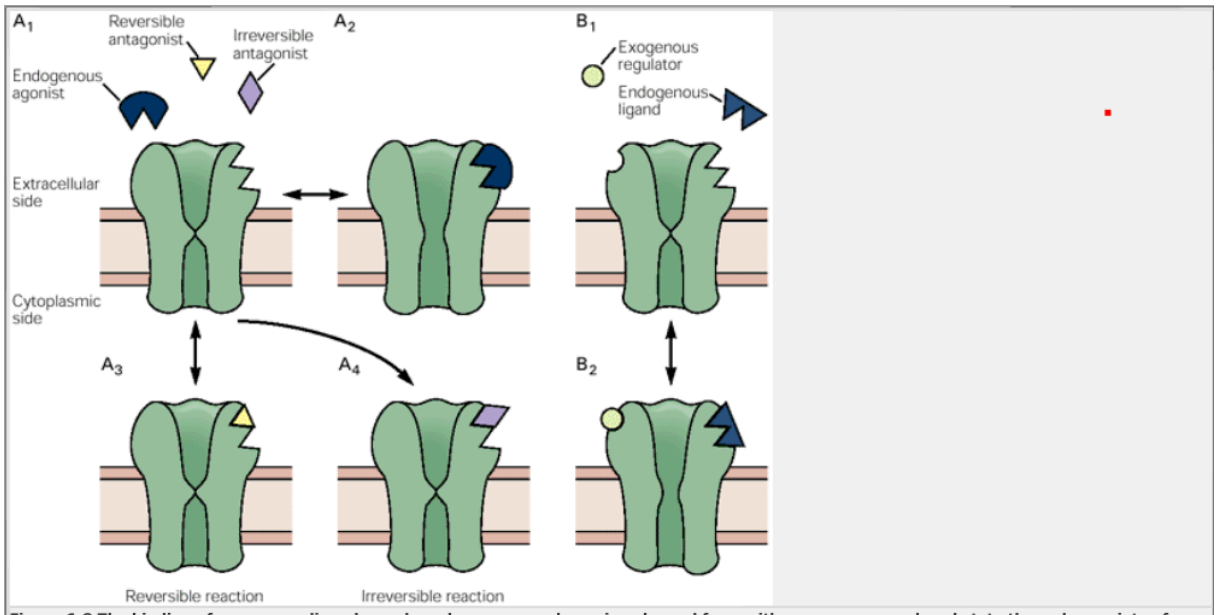

Figure 6-8 The binding of exogenous ligands, such as drugs, can make an ion channel favor either an open or a closed state through a variety of mechanisms.

A. In channels that are normally opened by the binding of an endogenous ligand ($\mathbf{A}_1$, $\mathbf{A}_2$), a drug or toxin may block the binding of the activator by means of either a reversible ($\mathbf{A}_3$) or an irreversible ($\mathbf{A}_4$) reaction.

B. Some exogenous regulators can make a channel favor the open state by binding to a regulatory site, distinct from the endogenous site that normally opens the channel.

Figure 4: Gating

1.5. Structure of ion channels

All ion channels have a basic glycoprotein component consisting of a large integral-membrane protein with carbohydrate groups attached to its surface. A central aqueous pore through the middle of the protein spans the entire width of the membrane. The pore-forming region of many channels is made up of two or more subunits, which may be identical or different. In addition, some channels have auxiliary subunits that modify their functional properties. These subunits may be cytoplasmic or membrane-embedded.

Additional insights into channel structure and function have been obtained by comparing the primary amino acid sequences of the same type of channel from different species. Regions that show a high degree of similarity (ie, have been highly conserved through evolution) are likely to be important in maintaining the effective structure and function of the channel. Likewise, conserved regions in different, but related, channels are likely to serve a common biophysical function in different channels. For example, all voltage-gated channels have a specific membrane-spanning domain that contains positively charged amino acids (lysine or arginine) spaced at every third position along an α-helix. This motif is observed in all voltage-gated channels, but not in transmitter-gated channels, suggesting that this charged region is important for voltage gating.

The functional consequences of changes in a channel's primary amino acid sequence can be explored through a variety of techniques. One particularly versatile approach is to use genetic engineering to construct channels in which various parts are derived from the genes of different species—so-called chimeric channels. This technique

takes advantage of the fact that channels in different species have somewhat different properties. For example, the bovine ACh-gated receptor-channel has a slightly greater single-channel conductance than the same channel in electric fish. By comparing the properties of a chimeric channel to those of the two original channels, we can assess which regions of the channel are involved in which functions. This technique has been used to identify a specific membrane-spanning segment of the ACh-gated channel as the region that forms the lining of the pore.