12 Ion Channels in Excitable Membranes

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12.1 Introduction

Excitability. Excitability of cell membranes is crucial for signaling in many types of cell. Excitation in the physiological sense means that the cell membrane potential undergoes characteristic changes which, in most cases, go in the depolarizing direction. Single depolarization from the resting potential to potentials near 0 mV has generally been called an action potential. A schematic representation of a neuronal action potential is given in Fig. 12.1A. The action potential is triggered when the membrane potential, which was at the resting level, depolarizes and reaches the threshold of excitation. This depolarization, which triggers the action potential, is generated by depolarizing synaptic currents, or depolarizing current coming from a membrane region that is already excited (propagation of an action potential), or by pacemaker currents mediated by pacemaker channels, or by current injected externally by an electrode.

The duration of different types of action potential varies from seconds to less than 1 ms. The shortest duration of action potentials has been observed in nerve and skeletal muscle fibers, whereas heart muscle and smooth muscle cells as well as endocrine cells such as pancreatic β-cells exhibit slower action potentials (Fig. 12.1B–E).

Ion Channels. As also described in Chap. 11, fundamental processes underlying most types of plasma membrane excitability could be attributed to a certain class of membrane proteins, designated as ion channels. Ion channels mediate ionic currents across the cell membrane. By mediating currents carried by certain ion species (Na⁺, K⁺, Ca²⁺, Cl⁻), they determine the form of an action potential. Depolarizing currents initiate and maintain the action potential, whereas hyperpolarizing currents terminate, modulate or even prevent action potentials. All ion channels can be in the open or closed state. Most channels flicker between these two states in a time range of milliseconds. The ratio of mean open and closed times can be defined as activity of a particular channel type under certain conditions. Changes in the activity of ion channels therefore underlie changes in ionic currents through cell membranes. These changes can be elicited by changes in membrane potential, concentration of extracellular chemical transmitters or intracellular second messengers, by GTP-binding proteins (G-proteins) or even by mechanical stimuli.

The concept of ion channels was first propounded by B. Katz [54], who was the first to propose the existence of elementary events in currents evoked by acetylcholine (ACh) in the motor endplate. Four years later E. Neher and B. Sakmann [80] succeeded in the first direct observation of elementary current events mediated by ACh-activated ion channels from skeletal muscle. In their paper the term "ion channel" was used for the first time, although it was still unclear whether or not elementary currents were really mediated by any membrane protein. Direct evidence for the protein nature of ion channels came from functional expression studies of cloned ion channel proteins. Cloned
subunits of ACh receptor channels characterized by recombinant DNA techniques were functionally expressed in *Xenopus laevis* oocytes and measured in patch-clamp experiments [72]. Following the first functional expression of protein subunits forming ACh receptor channels, more and more types of ion channel were cloned. This substantially improved our knowledge about molecular mechanisms underlying the phenomenon of ion channels in cell membranes.

On the basis of these results, ion channel proteins as far as known to date fall into structural classes that also correlate with the general properties of a particular channel.

- ACh receptor channels belong to the superfamily of ligand-gated channels. Ligand-gated channels are probably all composed of five subunits having a characteristic secondary structure. With other channel protein families of the same superfamily (glutamate, glycine and GABA<sub>A</sub> receptor channel subunits), ACh receptor channels share some further common properties. That is, they are able to discriminate between cations and anions but not between different ion species of identical charge.

- Voltage-gated cation channels (Na<sup>+</sup> channels, K<sup>+</sup> channels, and Ca<sup>2+</sup> channels) form another superfamily. Each member shows four-fold symmetry in tertiary structure and can be fairly selective in distinguishing between different cations. Not all voltage-gated channels known, however, belong to this superfamily. For example, the voltage-gated K<sup>+</sup> channels, which activate rather slowly, have a completely different structure.

- The anion channels, which are either voltage-gated or regulated by intracellular second messengers, form three further families of ion channels with as yet unknown quaternary structure.

- The cation channels, which are gated by intracellular cyclic nucleotides such as cGMP, form another ion channel family. These nonselective cation channels most likely consist of five subunits. Their physiological role is signal transduction in various receptor cells such as rods and cones in the retina.

- Finally, a number of channels in excitable membranes have up to very recently only been defined by their single-channel currents. This group comprises predominantly K<sup>+</sup> channels that are not opened by depolarization. Examples are ATP-dependent K<sup>+</sup> channels and K<sup>+</sup> channels that are regulated by GTP-binding proteins (G-proteins) such as the M-channel which is linked via a G-protein to the muscarinic ACh receptor. The ion channels addressed in this chapter are summarized in Table 12.1.

### 12.2 Ion Channels Underlying Excitability

**Voltage-Dependent Ion Channels**

Voltage-dependent ion channels mediate characteristic changes in membrane potential called action potentials (Fig. 12.1). Action potentials go from resting potential in the depolarized direction. Their frequency defines the state of activity in many types of cell. Different shapes of action potentials observed in different types of neuron, skeletal muscle, smooth muscle, endocrine gland and heart muscle cells.