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8

Ion Channels

Signaling in the brain depends on the ability of nerve cells to respond to very small stimuli with rapid and large changes in the electrical potential difference across the cell membrane. In sensory cells, the membrane potential changes in response to minute physical stimuli: Receptors in the eye respond to a single photon of light; olfactory neurons detect a single molecule of odorant; and hair cells in the inner ear respond to tiny movements of atomic dimensions. These sensory responses ultimately lead to the firing of an action potential during which the membrane potential changes at up to 500 volts per second.

The rapid changes in membrane potential that underlie signaling throughout the nervous system are mediated by specialized pores or openings in the membrane called ion channels, a class of integral membrane proteins found in all cells of the body. The ion channels of nerve cells are optimally tuned to respond to specific physical and chemical signals. They are also heterogeneous—in different parts of the nervous system different types of channels carry out specific signaling tasks.

Because of their key roles in electrical signaling, malfunctioning of ion channels can cause a wide variety of neurological diseases (Chapters 57 and 58). Diseases caused by ion channel malfunction are not limited to the brain; for example, cystic fibrosis, skeletal muscle disease, and certain types of cardiac arrhythmia are also caused by ion channel malfunction. Moreover, ion channels are often the site of action of drugs, poisons, or toxins. Thus, ion channels have crucial roles in both the normal physiology and pathophysiology of the nervous system.

In addition to ion channels, nerve cells contain a second important class of proteins specialized for moving ions across cell membranes, the ion transporters and pumps. These proteins do not participate in rapid neuronal signaling but rather are important for establishing and maintaining the concentration gradients of physiologically important ions between the inside and outside of the cell. As we will see in this and

the next chapters, ion transporters and pumps differ in important aspects from ion channels, but also share certain common features.

Ion channels have three important properties: (1) They recognize and select specific ions; (2) they open and close in response to specific electrical, chemical, or mechanical, signals; and (3) they conduct ions across the membrane. The channels in nerve and muscle conduct ions across the cell membrane at extremely rapid rates, thereby providing a large flow of electric charge. Up to 100 million ions can pass through a single channel each second. This current causes the rapid changes in membrane potential required for signaling (Chapter 10). The fast flow of ions through channels is comparable to the turnover rate of the fastest enzymes, catalase and carbonic anhydrase, which are limited by diffusion of substrate. (The turnover rates of most other enzymes are considerably slower, ranging from 10 to 1,000 per second.)

Despite such an extraordinary rate of ion flow, channels are surprisingly selective for the ions they allow to permeate. Each type of channel allows only one or a few types of ions to pass. For example, the negative resting potential of nerve cells is largely determined by a class of K^+ channels that are 100-fold more permeable to K^+ than to Na^+. In contrast, generation of the action potential involves a class of Na^+ channels that are 10- to 20-fold more permeable to Na^+ than to K^+. Thus, a key to the great versatility of neuronal signaling is the regulated activation of different classes of ion channels, each of which is selective for specific ions.

Many channels open and close in response to a specific event: Voltage-gated channels are regulated by changes in membrane potential, ligand-gated channels by binding of chemical transmitters, and mechanically gated channels by membrane stretch. Other channels are normally open when the cell is at rest. The ion flux through these "resting" channels largely determines the resting potential.

The flux of ions through ion channels is passive, requiring no expenditure of metabolic energy by the channels. Ion channels are limited to catalyzing the passive movement of ions down their thermodynamic concentration and electrical gradients. The direction of this flux is determined not by the channel itself, but rather by the electrostatic and diffusional driving forces across the membrane. For example, Na^+ ions flow into a cell through voltage-gated Na^+ channels during an action potential because the external Na^+ concentration is much greater than the internal concentration; the open channels allow Na^+ to diffuse into the cell down its concentration gradient. With such passive ion movement, the Na^+ concentration gradient would eventually dissipate were it not for ion pumps. Different types of ion pumps maintain the concentration gradients for Na^+, K^+, $Ca^{2+}$and other ions.

These pumps differ from ion channels in two important details. First, whereas open ion channels have a continuous water-filled pathway through which ions flow unimpeded from one side of the membrane to the other, each time a pump moves an ion or group of ions across the membrane, it must undergo a series of conformational changes. As a result, the rate of ion flow through pumps is 100 to 100,000 times slower than through channels. Second, pumps that maintain ion gradients use chemical energy, often in the form of adenosine triphosphate (ATP), to transport ions against their electrical and chemical gradients. Such ion movements are termed *active transport*. The function and structure of ion pumps and transporters are considered in detail at the end of this chapter and in Chapter 9.

In this chapter, we examine six questions: Why do nerve cells have channels? How can channels conduct ions at such high rates and still be selective? How are channels gated? How are the properties of these channels modified by various intrinsic and extrinsic conditions? How does channel structure explain function? Finally, how do ion movements through channels differ from ion movements through transporters? In succeeding chapters, we consider how resting channels and pumps generate the resting potential (Chapter 9), how voltage-gated channels generate the action potential (Chapter 10), and how ligand-gated channels produce synaptic potentials (Chapters 11, 12, and 13).

Ion Channels Are Proteins That Span the Cell Membrane

To appreciate why nerve cells use channels, we need to understand the nature of the plasma membrane and the physical chemistry of ions in solution. The plasma membrane of all cells, including nerve cells, is approximately 6 to 8 nm thick and consists of a mosaic of lipids and proteins. The core of the membrane is formed by a double layer of phospholipids approximately 3 to 4 nm thick. Embedded within this continuous lipid sheet are integral membrane proteins, including ion channels.

The lipids of the membrane do not mix with water—they are hydrophobic. In contrast, the ions within the cell and those outside strongly attract water

molecules—they are hydrophilic (Figure 8–1). Ions attract water because water molecules are dipolar: Although the net charge on a water molecule is zero, charge is separated within the molecule. The oxygen atom in a water molecule tends to attract electrons and so bears a small net negative charge, whereas the hydrogen atoms tend to lose electrons and therefore carry a small net positive charge. As a result of this unequal distribution of charge, positively charged ions (cations) are strongly attracted electrostatically to the oxygen atoms of water, and negatively charged ions (anions) are attracted to the hydrogen atoms. Similarly, ions attract water; they become surrounded by electrostatically bound *waters of hydration* (Figure 8–1).

An ion cannot move from water into the uncharged hydrocarbon tails of the lipid bilayer in the membrane unless a large amount of energy is expended to overcome the attraction between the ion and the surrounding water molecules. For this reason, it is extremely unlikely that an ion will move from solution into the lipid bilayer, and therefore, the bilayer itself is almost completely impermeable to ions. Rather, ions cross the membrane through ion channels, where the energetics favor ion movement.

Although their molecular nature has been known with certainty for only approximately 35 years, the idea of ion channels dates to the work of Ernst Brücke at the end of the 19th century. Physiologists had long known that, despite the fact that the cell membrane acts as a barrier, cell membranes are nevertheless permeable to water and many small solutes, including some ions. To explain osmosis, the flow of water across biological membranes, Brücke proposed that membranes contain channels or pores that allow water but not larger solutes to flow. Over 100 years later, Peter Agre found that a family of proteins termed *aquaporins* form channels with a highly selective permeability to water. At the beginning of the 20th century, William Bayliss suggested that water-filled channels would permit ions to cross the cell membrane easily, as the ions would not need to be stripped of their waters of hydration.

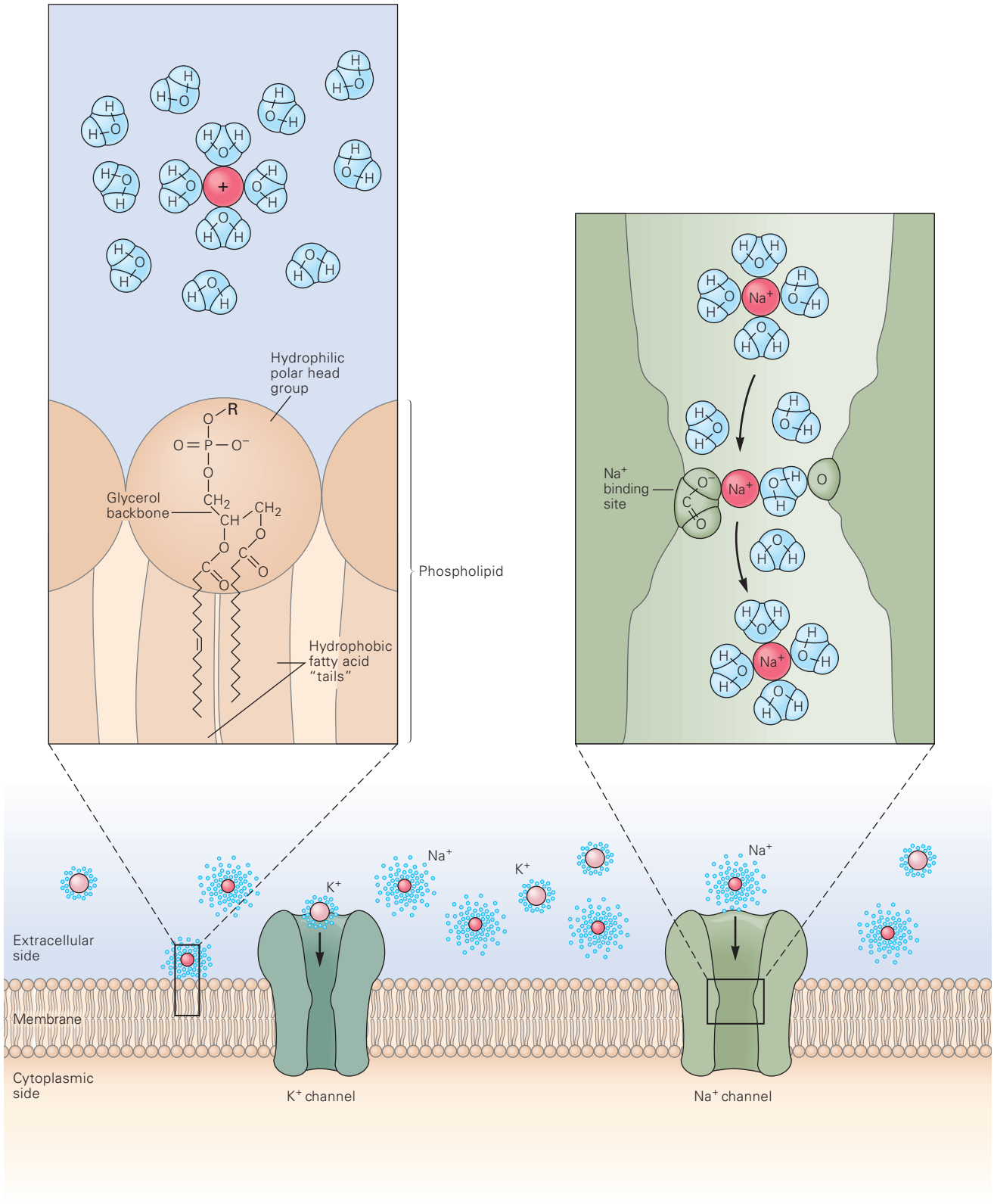
The idea that ions move through channels leads to a question: How can a water-filled channel conduct ions at high rates and yet be selective? How, for instance, does a channel allow K^+ ions to pass while excluding Na^+ ions? Selectivity cannot be based solely on the diameter of the ion because K^+, with a crystal radius of 0.133 nm, is larger than Na^+ (crystal radius of 0.095 nm). One important factor that determines ion selectivity is the size of an ion's shell of waters of hydration, because the ease with which an ion moves in solution (its mobility) depends on the size of the ion together with the shell of water surrounding it. The smaller an ion, the more highly localized is its charge and the stronger its electric field. As a result, smaller ions attract water more strongly. Thus, as Na^+ moves through solution, its stronger electrostatic attraction for water causes it to have a larger water shell, which tends to slow it down relative to K^+. Because of its larger water shell, Na^+ behaves as if it is larger than K^+. The smaller an ion, the lower its mobility in solution. Therefore, we can construct a model of a channel that selects K^+ rather than Na^+ simply on the basis of the interaction of the two ions with water in a water-filled channel (Figure 8–1).

Although this model explains how a channel can select K^+ and exclude Na^+, it does not explain how a channel could select Na^+ and exclude K^+. This problem led many physiologists in the 1930s and 1940s to abandon the channel theory in favor of the idea that ions cross cell membranes by first binding to a specific carrier protein, which then shuttles the ion through the membrane. In this carrier model, selectivity is based on the chemical binding between the ion and the carrier protein, not on the mobility of the ion in solution.

Even though we now know that ions can cross membranes by means of a variety of transport macromolecules, the Na^+-K^+ pump being a well-characterized example (Chapter 9), many properties of membrane ion permeability do not fit the carrier model. Most important is the rapid rate of ion transfer across membranes. An example is provided by the transmembrane current that is initiated when the neurotransmitter acetylcholine (ACh) binds its receptor in the postsynaptic membrane of the nerve–muscle synapse. As described later, the current conducted by a single ACh receptor is 12.5 million ions per second. In contrast, the Na^+-K^+ pump transports at most 100 ions per second.

If the ACh receptor acted as a carrier, it would have to shuttle an ion across the membrane in 0.1 µs (one ten-millionth of a second), an implausibly fast rate. The 100,000-fold difference in rates between the Na^+-K^+ pump and ACh receptor strongly suggests that the ACh receptor (and other ligand-gated receptors) must conduct ions through a channel. Later measurements in many voltage-gated pathways selective for K^+, Na^+, and Ca^{2+} also demonstrated large currents carried by single macromolecules, indicating that they too are channels.

But we are still left with the problem of what makes a channel selective. To explain selectivity, Bertil Hille extended the pore theory by proposing that channels have narrow regions that act as molecular sieves. At this *selectivity filter*, an ion must shed most of its waters of hydration to traverse the channel; in their place, weak chemical bonds (electrostatic interactions) form


Hydrophilic polar head group
Glycerol backbone
Hydrophobic fatty acid "tails"
Phospholipid
Na+ binding site
Extracellular side
Membrane
Cytoplasmic side
K+ channel
Na+ channel
Na+
K+

with polar (charged) amino acid residues that line the walls of the channel (Figure 8–1). Because shedding its waters of hydration is energetically unfavorable, the ion will traverse a channel only if its energy of interaction with the selectivity filter compensates for the loss of the energy of interaction with its waters of hydration. Ions traversing the channel are normally bound to the selectivity filter for only a short time (less than 1 μs), after which electrostatic and diffusional forces propel the ion through the channel. In channels where the pore diameter is large enough to accommodate several water molecules, an ion need not be stripped completely of its water shell.

How is this chemical recognition and specificity established? One theory was developed in the early 1960s by George Eisenman to explain the properties of ion-selective glass electrodes. According to this theory, a binding site with high negative field strength—for example, one formed by negatively charged carboxylic acid groups of glutamate or aspartate—will bind Na^+ more tightly than K^+. This selectivity results because the electrostatic interaction between two charged groups, as governed by Coulomb's law, depends inversely on the distance between the two groups.

Because it has a smaller crystal radius than K^+, Na^+ can approach a binding site with a high negative field strength more closely than K^+ can and thus will derive a more favorable free-energy change on binding. This compensates for the requirement that Na^+ lose some of its waters of hydration in order to traverse the narrow selectivity filter. In contrast, a binding site with a low negative field strength—one that is composed, for example, of polar carbonyl or hydroxyl oxygen atoms—would select K^+ over Na^+. At such a site, the binding of Na^+ would not provide a sufficient free-energy change to compensate for the loss of the ion's waters of hydration, which Na^+ holds strongly. However, such a site would be able to compensate for the loss of a K^+ ion's waters of hydration since the larger K^+ ions interact more weakly with water. It is currently thought that ion channels are selective both because of such specific chemical interactions and because of molecular sieving based on pore diameter.

Ion Channels in All Cells Share Several Functional Characteristics

Most cells are capable of local signaling, but only nerve and muscle cells are specialized for rapid signaling over long distances. Although nerve and muscle cells have a particularly rich variety and high density of membrane ion channels, their channels do not differ fundamentally from those of other cells in the body. Here we describe the general properties of ion channels in a wide variety of cells determined by recording current flow through channels under various experimental conditions.

Currents Through Single Ion Channels Can Be Recorded

Studies of ion channels were originally limited to recording the total current through the entire population of a class of ion channels, an approach that obscures some details of channel function. Later developments

Figure 8–1 (Opposite) **The permeability of the cell membrane to ions is determined by the interaction of ions with water, the membrane lipid bilayer, and ion channels.** Ions in solution are surrounded by a cloud of water molecules (waters of hydration) that are attracted by the net charge of the ion. This cloud is carried along by the ion as it diffuses through solution, increasing the effective size of the ion. It is energetically unfavorable, and therefore improbable, for the ion to leave this polar environment to enter the nonpolar environment of the lipid bilayer formed from phospholipids.

Phospholipids have a hydrophilic head and a hydrophobic tail. The hydrophobic tails join to exclude water and ions, whereas the polar hydrophilic heads face the aqueous environments of the extracellular fluid and cytoplasm. The phospholipid is composed of a backbone of glycerol in which two –OH groups are linked by ester bonds to fatty acid molecules. The third –OH group of glycerol is linked to phosphoric acid. The phosphate group is further linked to one of a variety of small, polar alcohol head groups (**R**).

Ion channels are integral membrane proteins that span the lipid bilayer, providing a pathway for ions to cross the membrane. The channels are selective for specific ions.

Potassium channels have a narrow pore that excludes Na^+. Although a Na^+ ion is smaller than a K^+ ion, in solution, the effective diameter of Na^+ is larger because its local field strength is more intense, causing it to attract a larger cloud of water molecules. The K^+ channel pore is too narrow for the hydrated Na^+ ion to permeate.

Sodium channels have a selectivity filter that weakly binds Na^+ ions. According to the hypothesis developed by Bertil Hille and colleagues, a Na^+ ion binds transiently at an active site as it moves through the filter. At the binding site, the positive charge of the ion is stabilized by a negatively charged amino acid residue on the channel wall and also by a water molecule that is attracted to a second polar amino acid residue on the other side of the channel wall. It is thought that a K^+ ion, because of its larger diameter, cannot be stabilized as effectively by the negative charge and therefore will be excluded from the filter. (Adapted from Hille 1984.)

Box 8–1 Recording Current in Single Ion Channels: The Patch Clamp

The *patch-clamp* technique was developed in 1976 by Erwin Neher and Bert Sakmann to record current from single ion channels. It is a refinement of the original voltage clamp technique (see Box 10–1).

A small fire-polished glass micropipette with a tip diameter of approximately 1 µm is pressed against the membrane of a skeletal muscle fiber. A metal electrode in contact with the electrolyte in the micropipette connects the pipette to a special electrical circuit that measures the current through channels in the membrane under the pipette tip (Figure 8–2A).

In 1980, Neher discovered that applying a small amount of suction to the patch pipette greatly increased the tightness of the seal between the pipette and the membrane. The result was a seal with extremely high resistance between the inside and the outside of the pipette. The seal lowered the electronic noise and extended the usefulness of the patch-clamp technique to the whole range of ion channels. Since this discovery, the patch-clamp technique has been used to study all the major classes of ion channels in a variety of neurons and other cells (Figure 8–2B).

Christopher Miller independently developed a method for incorporating ion channels from biological membranes into artificial lipid bilayers. He first homogenized the membranes in a blender; using centrifugation of the homogenate, he then separated out a fraction composed only of membrane vesicles. He studied the functional components of these vesicles using a technique developed by Paul Mueller and Donald Rudin in the 1960s. They discovered how to create an artificial lipid bilayer by painting a thin drop of phospholipid over a hole in a nonconducting barrier separating two salt solutions. Miller found that under appropriate ionic conditions his membrane vesicles fused with the planar phospholipid membrane, incorporating any ion channel in the vesicle into the planar membrane.

This technique has two experimental advantages. First, it allows recording from ion channels in regions of cells that are inaccessible to patch clamp; for example, Miller has successfully studied a K^+ channel isolated from the internal membrane of skeletal muscle (the sarcoplasmic reticulum). Second, it allows researchers to study how the composition of the membrane lipids influences channel function.

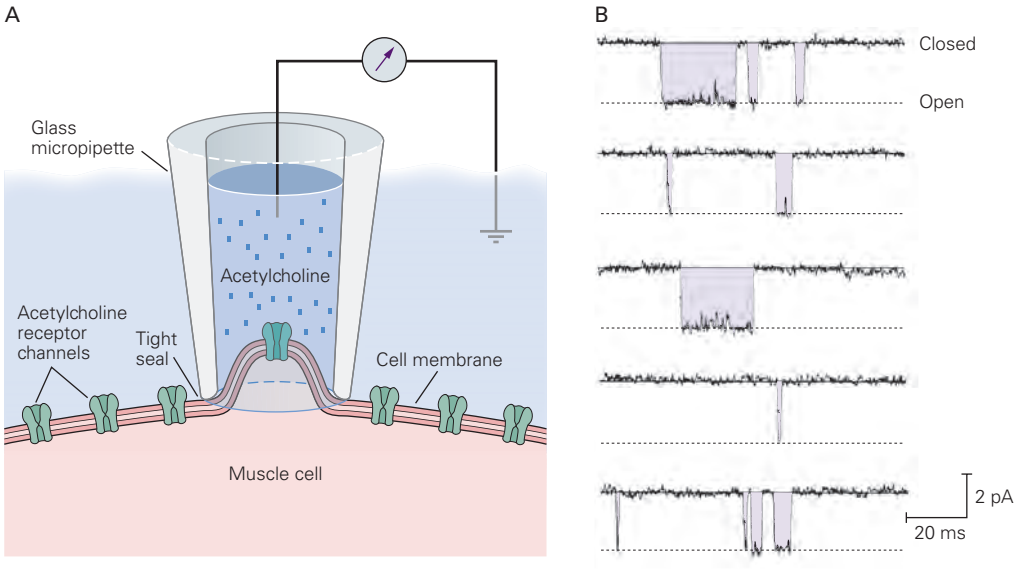


Figure 8–2 Patch-clamp setup and recording.

A. A pipette containing a low concentration of acetylcholine (**ACh**) in saline solution is used to record current through ACh receptor channels in skeletal muscle. (Adapted from Alberts et al. 1994.)

B. Patch-clamp recording of the current through a single ACh receptor channel as the channel switches between closed and open states. (Reproduced, with permission, from B. Sakmann.)

have made it possible to obtain much higher resolution by recording the current through single ion channels. The first direct recordings of individual ion channels in biological membranes were obtained by Erwin Neher and Bert Sakmann in 1976. A glass micropipette containing ACh—the neurotransmitter that activates the ACh receptors in the membrane of skeletal muscle—was pressed tightly against a muscle membrane. Small unitary current pulses representing the opening and closing of a single ACh receptor channel were recorded from the membrane under the pipette tip. The current pulses all had the same amplitude, indicating that the channels open in an all-or-none fashion (Box 8–1).

The pulses measured 2 pA (2×10^{-12} A) at a membrane potential of –80 mV, which according to Ohm's law ($I = V/R$) indicates that the channels had a resistance of 5×10^{11} ohms. In dealing with ion channels, it is more useful to speak of conductance, the reciprocal of resistance ($\gamma = 1/R$), as this provides an electrical measure related to ion permeability. Thus, Ohm's law for a single ion channel can be expressed as $i = \gamma \times V$. The conductance of the ACh receptor channel is approximately 25×10^{-12} siemens (S), or 25 picosiemens (pS), where 1 S equals 1/ohm.

The Flux of Ions Through a Channel Differs From Diffusion in Free Solution

The kinetic properties of ion permeation are best described by the channel's conductance, which is determined by measuring the current (ion flux) through the open channel in response to an electrochemical driving force. The net electrochemical driving force is determined by two factors: the electrical potential difference across the membrane and the concentration gradients of the permeant ions across the membrane. Changing either one can change the net driving force (Chapter 9).

In some open channels, the current varies linearly with driving force—that is, the channels behave as simple resistors. In others, the current 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 because of asymmetry in the channel's structure or ionic environment (Figure 8–3).

The rate of net ion flux (current) through a channel depends on the concentration of the permeant ions in the surrounding solution. At low concentrations, the current increases almost linearly with concentration. At higher concentrations, the current tends to reach a point at which it no longer increases. At this point, the current is said to *saturate*. This saturation effect indicates that ion flux across the cell membrane is not like electrochemical diffusion in free solution but involves the binding of ions to specific polar sites within the pore of the channel. A simple electrodiffusion model would predict that the ionic current should increase in proportion to increases in concentration.

The relation between current and ionic concentration for a wide range of ion channels is well described by a simple chemical binding equation, identical to the Michaelis-Menten equation for enzymes, suggesting that a single ion binds within the channel during permeation. The ionic concentration at which current reaches half its maximum defines the *dissociation constant*, the concentration at which half of the channels will be occupied by a bound ion. The dissociation constant in plots of current versus concentration is typically quite high, approximately 100 mM, indicating weak binding. (In typical interactions between enzymes and substrates, the dissociation constant is below 1 μM.) The rapid rate at which an ion unbinds is necessary for the channel to achieve the very high conduction rates responsible for the rapid changes in membrane potential during signaling.

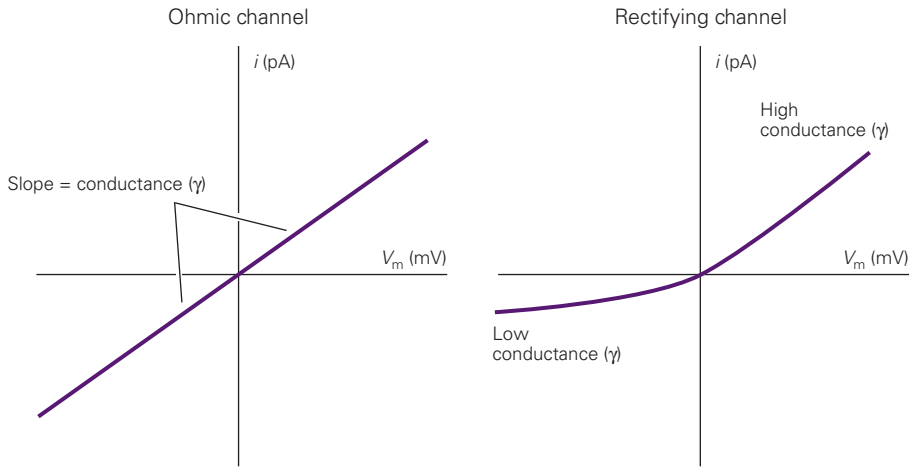


Figure 8–3 Current–voltage relations. In many ion channels, the relation between current (i) through the open channel and membrane voltage (V_m) is linear (left plot). Such channels are said to be "ohmic" because they follow Ohm's law, $i = V_m/R$ or $V_m \times \gamma$, where γ is conductance. In other channels, the relation between current and membrane potential is nonlinear. This kind of channel is said to "rectify," in the sense that it conducts current more readily in one direction than the other. The right plot shows an outwardly rectifying channel for which positive current (right side) is larger than the negative current (left side) for a given absolute value of voltage.

Some ion channels can be blocked by certain free ions or molecules in the cytoplasm or extracellular fluid that bind either to the mouth of the aqueous pore or somewhere within the pore. If the blocker is an ion that binds to a site within the pore, it will be influenced by the membrane electric field as it enters the channel. For example, if a positively charged blocker enters the channel from outside the membrane, then making the cytoplasmic side of the membrane more negative will drive the blocker into the channel by electrostatic attraction, increasing the block. Although some blockers are toxins or drugs that originate outside the body, others are common ions normally present in the cell or its environment. Physiological blockers of certain classes of channels include Mg^{2+}, Ca^{2+}, Na^{+}, and polyamines such as spermine.

The Opening and Closing of a Channel Involve Conformational Changes

In ion channels that mediate electrical signaling, the channel protein has two or more conformational states that are relatively stable. Each conformation 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*.

The molecular mechanisms of gating are only partially understood. In some cases, such as the voltage-gated Cl^{-} channel described later in the chapter, a local conformational change along the channel lumen gates the channel (Figure 8–4A). In most cases, channel gating involves widespread changes in the channel's conformation (Figure 8–4B). For example, concerted movements, such as twisting, bending, or tilting, of the subunits that line the channel pore mediate the opening and closing of some ion channels (see Figure 8–14 and Chapters 11 and 12). The molecular rearrangements that occur during the transition from closed to open states appear to enhance ion conduction through the channel not only by creating a wider lumen, but also by positioning relatively more polar amino acid constituents at the surface that lines the aqueous pore. In other cases (eg, inactivation of K^{+} channels described in Chapter 10), part of the channel protein acts as a particle that can close the channel by blocking the pore (Figure 8–4C).

Three major transduction mechanisms have evolved to control channel opening in neurons. Certain channels are opened by the binding of chemical ligands, known as agonists (Figure 8–5A). Some ligands bind directly to the channel either at an extracellular or intracellular site; transmitters bind at extracellular sites, whereas certain cytoplasmic constituents, such as Ca^{2+}, cyclic nucleotides, and GTP-binding proteins, bind at intracellular sites, as do certain dynamically regulated mobile lipid components of the membrane (Chapter 14). Other ligands activate intracellular second messenger signaling cascades that can covalently modify channel gating through protein phosphorylation (Figure 8–5B). Many ion channels are regulated by changes in membrane potential (Figure 8–5C). Some voltage-gated channels act as temperature sensors; changes in temperature shift their voltage gating to higher or lower membrane potentials, giving rise to heat- or cold-sensitive channels. Finally, some channels are regulated by mechanical force (Figure 8–5D).

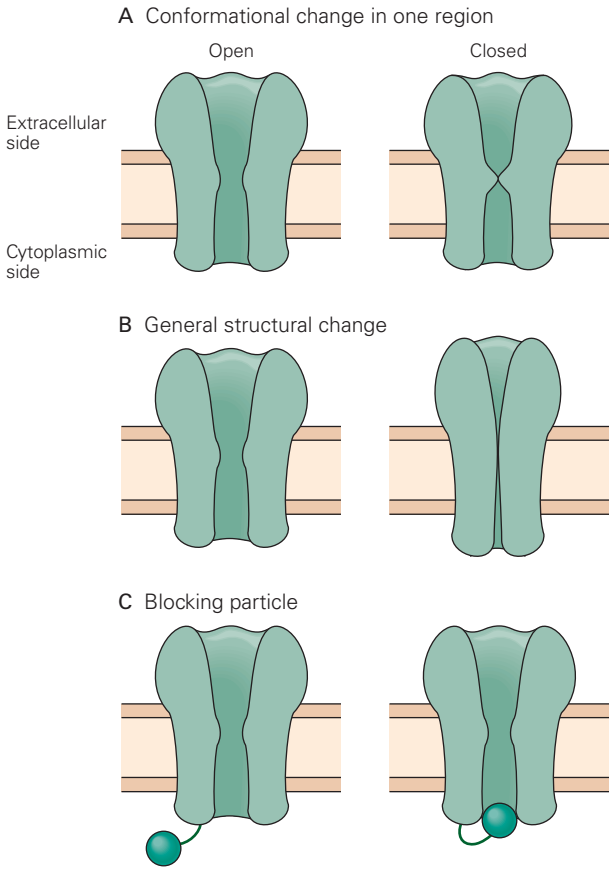


Figure 8–4 Three physical models for the opening and closing of ion channels.

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

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

C. A blocking particle swings into and out of the channel mouth.