Ion Channels and the Electrical Properties of Membranes

Unlike carrier proteins, channel proteins form hydrophilic pores across membranes. One class of channel proteins found in virtually all animals forms gap junctions between two adjacent cells; each plasma membrane contributes equally to the formation of the channel, which connects the cytoplasm of the two cells. These channels are discussed in Chapter 19 and will not be considered further here. Both gap junctions and porins, the channel-forming proteins of the outer membranes of bacteria, mitochondria, and chloroplasts (discussed in Chapter 10) have relatively large and permissive pores, which would be disastrous if they directly connected the inside of a cell to an extracellular space. Indeed, many bacterial toxins do exactly that to kill other cells (discussed in Chapter 25).

In contrast, most channel proteins in the plasma membrane of animal and plant cells that connect the cytosol to the cell exterior necessarily have narrow, highly selective pores that can open and close. Because these proteins are concerned specifically with inorganic ion transport, they are referred to as ion channels. For transport efficiency, channels have an advantage over carriers in that up to 100 million ions can pass through one open channel each second—a rate 10^5 times greater than the fastest rate of transport mediated by any known carrier protein. However, channels cannot be coupled to an energy source to perform active transport, so the transport that they mediate is always passive (“downhill”). Thus, the function of ion channels is to allow specific inorganic ions—primarily Na^+, K^+, Ca^{2+}, or Cl^−—to diffuse rapidly down their electrochemical gradients across the lipid bilayer. As we shall see, the ability to control ion fluxes through these channels is essential for many cell functions. Nerve cells (neurons), in particular, have made a specialty of using ion channels, and we shall consider how they use a diversity of such channels for receiving, conducting, and transmitting signals.

Ion Channels Are Ion-Selective and Fluctuate Between Open and Closed States

Two important properties distinguish ion channels from simple aqueous pores. First, they show ion selectivity, permitting some inorganic ions to pass, but not others. This suggests that their pores must be narrow enough in places to force permeating ions into intimate contact with the walls of the channel so that only ions of appropriate size and charge can pass. The permeating ions have to shed most or all of their associated water molecules to pass, often in single file, through the narrowest part of the channel, which is called the selectivity filter; this limits their rate of passage. Thus, as ion concentrations are increased, the flux of ions through a channel increases proportionally but then levels off (saturates) at a maximum rate.

The second important distinction between ion channels and simple aqueous pores is that ion channels are not continuously open. Instead, they are gated, which allows them to open briefly and then close again (Figure 11-20). In most cases, the gate opens in response to a specific stimulus. The main types of stimuli that are known to cause ion channels to open are a change in the voltage across the membrane (voltage-gated channels), a mechanical stress (mechanically gated channels), or the binding of a ligand (ligand-gated channels). The ligand can be either an extracellular mediator—specifically, a neurotransmitter (transmitter-gated channels)—or an intracellular mediator, such as an ion (ion-gated channels) or a nucleotide (nucleotide-gated channels) (Figure 11-21). The activity of many ion channels is regulated, in addition, by protein phosphorylation and dephosphorylation; this type of channel regulation is discussed, together with nucleotide-gated ion channels, in Chapter 15. Moreover, with prolonged (chemical or electrical) stimulation, most channels go into a closed “desensitized” or “inactivated” state, in which they are refractory to further opening until the stimulus has been removed, as we discuss later.

**Figure 11-20**

A typical ion channel, which fluctuates between closed and open conformations. The channel protein shown here in cross section forms a hydrophilic pore across the lipid bilayer only in the “open” conformational state. Polar groups are (more...).
The membrane potential. This drawing shows different kinds of stimuli channels. Mechanically gated channels often have cytoplasmic extensor channel to the cytoskeleton (not shown).

More than 100 types of ion channels have been described thus far, and new ones are still being added to the list. They are responsible for the electrical excitation of muscle cells, and they mediate most forms of electrical signaling in the nervous system. A single neuron might typically contain 10 kinds of ion channels or more, located in different domains of its plasma membrane. But ion channels are not restricted to electrically excitable cells. They are present in all animal cells and are found in plant cells and microorganisms: they propagate the leaf-closing response of the mimosa plant, for example, and allow the single-celled *Paramaecium* to reverse direction after a collision.

Perhaps the most common ion channels are those that are permeable mainly to K⁺. These channels are found in the plasma membrane of almost all animal cells. An important subset of K⁺ channels are open even in an unstimulated or “resting” cell and are hence sometimes called K⁺ leak channels. Although this term covers a variety of different K⁺ channels, depending on the cell type, they serve a common purpose. By making the plasma membrane much more permeable to K⁺ than to other ions, they have a crucial role in maintaining the membrane potential across all plasma membranes.

### The Membrane Potential in Animal Cells Depends Mainly on K⁺ Leak Channels and the K⁺ Gradient Across the Plasma Membrane

A membrane potential arises when there is a difference in the electrical charge on the two sides of a membrane, due to a slight excess of positive ions over negative ones on one side and a slight deficit on the other. Such charge differences can result both from active electrogenic pumping (see p. 626) and from passive ion diffusion. As we discuss in Chapter 14, most of the membrane potential of the mitochondrion is generated by electrogenic H⁺ pumps in the mitochondrial inner membrane. Electrogenic pumps also generate most of the electrical potential across the plasma membrane in plants and fungi. In typical animal cells, however, passive ion movements make the largest contribution to the electrical potential across the plasma membrane.

As explained earlier, the Na⁺ -K⁺ pump helps maintain an osmotic balance across the animal cell membrane by keeping the intracellular concentration of Na⁺ low. Because there is little Na⁺ inside the cell, other cations have to be plentiful there to balance the charge carried by the cell's fixed anions—the negatively charged organic molecules that are confined inside the cell. This balancing role is performed largely by K⁺, which is actively pumped into the cell by the Na⁺ -K⁺ pump and can also move freely in or out through the K⁺ leak channels in the plasma membrane. Because of the presence of these channels, K⁺ comes almost to equilibrium, where an electrical force exerted by an excess of negative charges attracting K⁺ into the cell balances the tendency of K⁺ to leak out down its concentration gradient. The membrane potential is the manifestation of this electrical force, and its equilibrium value can be calculated from the steepness of the K⁺ concentration gradient. The following argument may help to make this clear.

Suppose that initially there is no voltage gradient across the plasma membrane (the membrane potential is zero), but the concentration of K⁺ is high inside the cell and low outside. K⁺ will tend to leave the cell through the K⁺ leak channels, driven by its concentration gradient. As K⁺ moves out, it leaves behind an unbalanced negative charge, thereby creating an electrical field, or membrane potential, which will tend to oppose the further efflux of K⁺. The net efflux of K⁺ halts when the membrane potential reaches a value at which this electrical driving force on K⁺ exactly balances the effect of its concentration gradient—that is, when the electrochemical gradient for K⁺ is zero. Although Cl⁻ ions also equilibrate across the membrane, the membrane potential keeps most of these ions out of the cell because their charge is negative.

The equilibrium condition, in which there is no net flow of ions across the plasma membrane, defines the resting membrane potential for this idealized cell. A simple but very important formula, the Nernst equation, expresses the equilibrium condition quantitatively and, as explained in Panel 11-2, makes it possible to calculate the theoretical resting membrane potential if the ratio of internal and external ion concentrations is known. As the plasma membrane of a real cell is not exclusively permeable to K⁺ and Cl⁻, however, the actual resting membrane potential is usually not exactly equal to that predicted by the Nernst equation for K⁺ or Cl⁻.
The puzzle was solved when the structure of a bacterial K$^+$ channel was determined by x-ray crystallography.
The channel is made from four identical transmembrane subunits, which together form a central pore through the membrane (Figure 11-23). Negatively charged amino acids are concentrated at the cytosolic entrance to the pore and are thought to attract cations and repel anions, making the channel cation-selective. Each subunit contributes two transmembrane helices, which are tilted outward in the membrane and together form a cone, with its wide end facing the outside of the cell where K\(^+\) ions exit the channel. The polypeptide chain that connects the two transmembrane helices forms a short \(\alpha\) helix (the pore helix) and a crucial loop that protrudes into the wide section of the cone to form the selectivity filter. The selectivity loops from the four subunits form a short, rigid, narrow pore, which is lined by the carbonyl oxygen atoms of their polypeptide backbones. Because the selectivity loops of all known K\(^+\) channels have similar amino acid sequences, it is likely that they form a closely similar structure. The crystal structure shows two K\(^+\) ions in single file within the selectivity filter, separated by about 8 Å. Mutual repulsion between the two ions is thought to help move them through the pore into the extracellular fluid.

**Figure 11-23**
The structure of a bacterial K\(^+\) channel. (A) Only two of the four identical subunits are shown. From the cytosolic side, the pore opens up into a vestibule in the middle of the membrane. The vestibule facilitates transport by allowing the K\(^+\) ions (more...)

The structure of the selectivity filter explains the exquisite ion selectivity of the channel. For a K\(^+\) ion to enter the filter, it must lose almost all of its bound water molecules and interact instead with the carbonyl oxygens lining the selectivity filter, which are rigidly spaced at the exact distance to accommodate a K\(^+\) ion. A Na\(^+\) ion, in contrast, cannot enter the filter because the carbonyl oxygens are too far away from the smaller Na\(^+\) ion to compensate for the energy expense associated with the loss of water molecules required for entry (Figure 11-24).

**Figure 11-24**
K\(^+\) specificity of the selectivity filter in a K\(^+\) channel. The drawing shows K\(^+\) and Na\(^+\) ions (A) in the vestibule and (B) in the selectivity filter of the pore, viewed in cross section. In the vestibule, the ions are hydrated. In the selectivity filter, (more...)

Structural studies of the bacterial K\(^+\) channel have indicated how these channels may open and close. The loops that form the selectivity filter are rigid and do not change conformation when the channel opens or closes. In contrast, the inner and outer transmembrane helices that line the rest of the pore rearrange when the channel closes, causing the pore to constrict like a diaphragm at its cytosolic end (Figure 11-25). Although the pore does not close completely, the small opening that remains is lined by hydrophobic amino acid side chains, which block the entry of ions.

**Figure 11-25**
A model for the gating of a bacterial K\(^+\) channel. The channel is viewed in cross section. To adopt the closed conformation, the four inner transmembrane helices that line the pore on the cytosolic side of the selectivity filter (see Figure 11-22) rearrange (more...)

The cells that make most use of ion channels are neurons. Before discussing how they do so, we must digress to review briefly how a typical neuron is organized.

**The Function of a Nerve Cell Depends on Its Elongated Structure**
The fundamental task of a neuron, or nerve cell, is to receive, conduct, and transmit signals. To perform these functions, neurons are often extremely elongated. A single nerve cell in a human being, extending, for example, from the spinal cord to a muscle in the foot, may be as long as 1 meter. Every neuron consists of a cell body (containing the nucleus) with a number of thin processes radiating outward from it. Usually one long axon conducts signals away from the cell body toward distant targets, and several shorter branching dendrites extend from the cell body like antennae, providing an enlarged surface area to receive signals from the axons...
of other nerve cells (Figure 11-26). Signals are also received on the cell body itself. The typical axon divides at its far end into many branches, passing on its message to many target cells simultaneously. Likewise, the extent of branching of the dendrites can be very great—in some cases, sufficient to receive as many as 100,000 inputs on a single neuron.

Figure 11-26
A typical vertebrate neuron. The arrows indicate the direction in which signals are conveyed. The single axon conducts signals away from the cell body, while the multiple dendrites receive signals from the axons of other neurons. The nerve terminals end (more...)

Despite the varied significance of the signals carried by different classes of neurons, the form of the signal is always the same, consisting of changes in the electrical potential across the neuron's plasma membrane. Communication occurs because an electrical disturbance produced in one part of the cell spreads to other parts. Such a disturbance becomes weaker with increasing distance from its source, unless energy is expended to amplify it as it travels. Over short distances this attenuation is unimportant; in fact, many small neurons conduct their signals passively, without amplification. For long-distance communication, however, passive spread is inadequate. Thus, larger neurons employ an active signaling mechanism, which is one of their most striking features. An electrical stimulus that exceeds a certain threshold strength triggers an explosion of electrical activity that is propagated rapidly along the neuron's plasma membrane and is sustained by automatic amplification all along the way. This traveling wave of electrical excitation, known as an action potential, or nerve impulse, can carry a message without attenuation from one end of a neuron to the other at speeds as great as 100 meters per second or more. Action potentials are the direct consequence of the properties of voltage-gated cation channels, as we shall now see.

Voltage-gated Cation Channels Generate Action Potentials in Electrically Excitable Cells

The plasma membrane of all electrically excitable cells—not only neurons, but also muscle, endocrine, and egg cells—contains voltage-gated cation channels, which are responsible for generating the action potentials. An action potential is triggered by a depolarization of the plasma membrane—that is, by a shift in the membrane potential to a less negative value. (We shall see later how this can be caused by the action of a neurotransmitter.) In nerve and skeletal muscle cells, a stimulus that causes sufficient depolarization promptly causes voltage-gated Na⁺ channels to open, allowing a small amount of Na⁺ to enter the cell down its electrochemical gradient. The influx of positive charge depolarizes the membrane further, thereby opening more Na⁺ channels, which admit more Na⁺ ions, causing still further depolarization. This process continues in a self-amplifying fashion until, within a fraction of a millisecond, the electrical potential in the local region of membrane has shifted from its resting value of about -70 mV to almost as far as the Na⁺ equilibrium potential of about +50 mV (see Panel 11-2, p. 634). At this point, when the net electrochemical driving force for the flow of Na⁺ is almost zero, the cell would come to a new resting state, with all of its Na⁺ channels permanently open, if the open conformation of the channel were stable. The cell is saved from such a permanent electrical spasm by two mechanisms that act in concert: inactivation of the Na⁺ channels, and opening of voltage-gated K⁺ channels.

The Na⁺ channels have an automatic inactivating mechanism, which causes the channels to reclose rapidly even though the membrane is still depolarized. The Na⁺ channels remain in this inactivated state, unable to reopen, until a few milliseconds after the membrane potential has returned to its initial negative value. The Na⁺ channel can therefore exist in three distinct states—closed, open, and inactivated. How they contribute to the rise and fall of the action potential is shown in Figure 11-27.

Figure 11-27
An action potential. (A) An action potential is triggered by a brief pulse of current, which (B) partially depolarizes the membrane, as shown in the plot of membrane potential versus time. The green curve shows how the membrane potential would have simply (more...)

The description just given of an action potential concerns only a small patch of plasma membrane. The self-amplifying depolarization of the patch, however, is sufficient to depolarize neighboring regions of
membrane, which then go through the same cycle. In this way, the action potential spreads as a traveling wave from the initial site of depolarization to involve the entire plasma membrane, as shown in Figure 11-28.

**Figure 11-28**
The propagation of an action potential along an axon. (A) The voltages that would be recorded from a set of intracellular electrodes placed at intervals along the axon. (B) The changes in the Na\(^+\) channels and the current flows *(orange arrows)* that give (more...)

**Voltage-gated K\(^+\) channels** provide a second mechanism in most nerve cells to help bring the activated plasma membrane more rapidly back toward its original negative potential, ready to transmit a second impulse. These channels open, so that the transient influx of Na\(^+\) is rapidly overwhelmed by an efflux of K\(^+\), which quickly drives the membrane back toward the K\(^+\) equilibrium potential, even before the inactivation of the Na\(^+\) channels is complete. These K\(^+\) channels respond to changes in membrane potential in much the same way as the Na\(^+\) channels do, but with slightly slower kinetics; for this reason; they are sometimes called *delayed K\(^+\) channels.*

Like the Na\(^+\) channel, voltage-gated K\(^+\) channels can inactivate. Studies of mutant voltage-gated K\(^+\) channels show that the N-terminal 20 amino acids of the channel protein are required for rapid inactivation of the channel. If this region is altered, the kinetics of channel inactivation are changed, and if the region is entirely removed, inactivation is abolished. Amazingly, in the latter case, inactivation can be restored by exposing the cytoplasmic face of the plasma membrane to a small synthetic peptide corresponding to the missing amino terminus. These findings suggest that the amino terminus of each K\(^+\) channel subunit acts like a tethered ball that occludes the cytoplasmic end of the pore soon after it opens, thereby inactivating the channel (Figure 11-29). A similar mechanism is thought to operate in the rapid inactivation of voltage-gated Na\(^+\) channels (which we discuss later), although a different segment of the protein seems to be involved.

**Figure 11-29**
The “ball-and-chain” model of rapid inactivation for a voltage-gated K\(^+\) channel. When the membrane potential is depolarized, the channel opens and begins to conduct ions. If the depolarization is maintained, the open channel adopts an (more...)

The electrochemical mechanism of the action potential was first established by a famous series of experiments carried out in the 1940s and 1950s. Because the techniques for studying electrical events in small cells had not yet been developed, the experiments exploited the giant neurons in the squid. Despite the many technical advances made since then, the logic of the original analysis continues to serve as a model for present-day work. Panel 11-3 outlines some of the key original experiments.

**Panel 11-3**
Some Classical Experiments on the Squid Giant Axon.

**Myelination Increases the Speed and Efficiency of Action Potential Propagation in Nerve Cells**

The axons of many vertebrate neurons are insulated by a myelin sheath, which greatly increases the rate at which an axon can conduct an action potential. The importance of myelination is dramatically demonstrated by the demyelinating disease *multiple sclerosis,* in which myelin sheaths in some regions of the central nervous system are destroyed; where this happens, the propagation of nerve impulses is greatly slowed, often with devastating neurological consequences.

Myelin is formed by specialized supporting cells called glial cells. Schwann cells myelinate axons in peripheral nerves and oligodendrocytes do so in the central nervous system. These glial cells wrap layer upon layer of their own plasma membrane in a tight spiral around the axon (Figure 11-30), thereby insulating the axonal
membrane so that little current can leak across it. The myelin sheath is interrupted at regularly spaced nodes of Ranvier, where almost all the Na$^+$ channels in the axon are concentrated. Because the ensheathed portions of the axonal membrane have excellent cable properties (in other words, they behave electrically much like well-designed underwater telegraph cables), a depolarization of the membrane at one node almost immediately spreads passively to the next node. Thus, an action potential propagates along a myelinated axon by jumping from node to node, a process called saltatory conduction. This type of conduction has two main advantages: action potentials travel faster, and metabolic energy is conserved because the active excitation is confined to the small regions of axonal plasma membrane at nodes of Ranvier.

**Figure 11-30**
Myelination. (A) A myelinated axon from a peripheral nerve. Each Schwann cell wraps its plasma membrane concentrically around the axon to form a segment of myelin sheath about 1 mm long. For clarity, the layers of myelin in this drawing are not shown (more...)

**Patch-Clamp Recording Indicates That Individual Gated Channels Open in an All-or-Nothing Fashion**

Neuron and skeletal muscle cell plasma membranes contain many thousands of voltage-gated Na$^+$ channels, and the current crossing the membrane is the sum of the currents flowing through all of these. This aggregate current can be recorded with an intracellular microelectrode, as shown in Figure 11-28. Remarkably, however, it is also possible to record current flowing through individual channels. This is achieved by means of patch-clamp recording, a method that has revolutionized the study of ion channels by allowing researchers to examine transport through a single molecule of channel protein in a small patch of membrane covering the mouth of a micropipette (Figure 11-31). With this simple but powerful technique, the detailed properties of ion channels can be studied in all sorts of cell types. This work has led to the discovery that even cells that are not electrically excitable usually have a variety of gated ion channels in their plasma membrane. Many of these cells, such as yeasts, are too small to be investigated by the traditional electrophysiologist's method of impalement with an intracellular microelectrode.

**Figure 11-31**
The technique of patch-clamp recording. Because of the extremely tight seal between the micropipette and the membrane, current can enter or leave the micropipette only by passing through the channels in the patch of membrane covering its tip. The term (more...)

Patch-clamp recording indicates that individual voltage-gated Na$^+$ channels open in an all-or-nothing fashion. The times of a channel's opening and closing are random, but when open, the channel always has the same large conductance, allowing more than 1000 ions to pass per millisecond. Therefore, the aggregate current crossing the membrane of an entire cell does not indicate the degree to which a typical individual channel is open but rather the total number of channels in its membrane that are open at any one time (Figure 11-32).

**Figure 11-32**
Patch-clamp measurements for a single voltage-gated Na$^+$ channel. A tiny patch of plasma membrane was detached from an embryonic rat muscle cell, as in Figure 11-31. (A) The membrane was depolarized by an abrupt shift of potential. (B) Three current records (more...)

The phenomenon of voltage gating can be understood in terms of simple physical principles. The interior of the resting neuron or muscle cell is at an electrical potential about 50–100 mV more negative than the external medium. Although this potential difference seems small, it exists across a plasma membrane only about 5 nm thick, so that the resulting voltage gradient is about 100,000 V/cm. Proteins in the membrane are thus subjected to a very large electrical field. These proteins, like all others, have a number of charged groups, as well as polarized bonds between their various atoms. The electrical field therefore exerts forces on the molecular structure. For many membrane proteins the effects of changes in the membrane electrical field are probably insignificant, but voltage-gated ion channels can adopt a number of alternative conformations whose
stabilities depend on the strength of the field. Voltage-gated Na\(^+\), K\(^+\), and Ca\(^{2+}\) channels, for example, have characteristic positively charged amino acids in one of their transmembrane segments that respond to depolarization by moving outward, triggering conformational changes that open the channel. Each conformation can “flip” to another conformation if given a sufficient jolt by the random thermal movements of the surroundings, and it is the relative stability of the closed, open, and inactivated conformations against flipping that is altered by changes in the membrane potential (see legend to Figure 11-29).

**Voltage-gated Cation Channels Are Evolutionarily and Structurally Related**

Na\(^+\) channels are not the only kind of voltage-gated cation channel that can generate an action potential. The action potentials in some muscle, egg, and endocrine cells, for example, depend on voltage-gated Ca\(^{2+}\) channels rather than on Na\(^+\) channels. Moreover, voltage-gated Na\(^+\), K\(^+\), or Ca\(^{2+}\) channels of unknown function are found in some cell types that are not normally electrically active.

There is a surprising amount of structural and functional diversity within each of these three classes, generated both by multiple genes and by the alternative splicing of RNA transcripts produced from the same gene. Nonetheless, the amino acid sequences of the known voltage-gated Na\(^+\), K\(^+\), and Ca\(^{2+}\) channels show striking similarities, suggesting that they all belong to a large superfamily of evolutionarily and structurally related proteins and share many of the design principles. Whereas the single-celled yeast *S. cerevisiae* contains a single gene that codes for a voltage-gated K\(^+\) channel, the genome of the worm *C. elegans* contains 68 genes that encode different but related K\(^+\) channels. This complexity indicates that even a simple nervous system made up of only 302 neurons uses a large number of different ion channels to compute its responses.

Humans who inherit mutant genes encoding ion channel proteins can suffer from a variety of nerve, muscle, brain, or heart diseases, depending on where the gene is expressed. Mutations in genes that encode voltage-gated Na\(^+\) channels in skeletal muscle cells, for example, can cause *myotonia*, a condition in which muscle relaxation after voluntary contraction is greatly delayed, causing painful muscle spasms. In some cases this is because the abnormal channels fail to inactivate normally; as a result, Na\(^+\) entry persists after an action potential finishes and repeatedly reinitiates membrane depolarization and muscle contraction. Similarly, mutations that affect Na\(^+\) or K\(^+\) channels in the brain can cause *epilepsy*, where excessive synchronized firing of large groups of nerve cells cause epileptic seizures (convulsions, or fits).

**Transmitter-gated Ion Channels Convert Chemical Signals into Electrical Ones at Chemical Synapses**

Neuronal signals are transmitted from cell to cell at specialized sites of contact known as synapses. The usual mechanism of transmission is indirect. The cells are electrically isolated from one another, the *presynaptic cell* being separated from the *postsynaptic cell* by a narrow synaptic cleft. A change of electrical potential in the presynaptic cell triggers it to release small signal molecules known as neurotransmitters, which are stored in membrane-enclosed synaptic vesicles and released by exocytosis. The neurotransmitter diffuses rapidly across the synaptic cleft and provokes an electrical change in the postsynaptic cell by binding to *transmitter-gated ion channels* (Figure 11-33). After the neurotransmitter has been secreted, it is rapidly removed: it is either destroyed by specific enzymes in the synaptic cleft or taken up by the nerve terminal that released it or by surrounding glial cells. Reuptake is mediated by a variety of Na\(^+\)-dependent neurotransmitter carrier proteins; in this way, neurotransmitters are recycled, allowing cells to keep up with high rates of release. Rapid removal ensures both spatial and temporal precision of signaling at a synapse. It decreases the chances that the neurotransmitter will influence neighboring cells, and it clears the synaptic cleft before the next pulse of neurotransmitter is released, so that the timing of repeated, rapid signaling events can be accurately communicated to the postsynaptic cell. As we shall see, signaling via such *chemical synapses* is far more versatile and adaptable than direct electrical coupling via gap junctions at *electrical synapses* (discussed in Chapter 19), which are also used by neurons but to a much smaller extent.

**Figure 11-33**

A chemical synapse. When an action potential reaches the nerve terminal in a presynaptic cell, it stimulates the terminal to release its neurotransmitter. The neurotransmitter molecules are contained in synaptic vesicles and are released to the cell exterior (more...
Transmitter-gated ion channels are specialized for rapidly converting extracellular chemical signals into electrical signals at chemical synapses. The channels are concentrated in the plasma membrane of the postsynaptic cell in the region of the synapse and open transiently in response to the binding of neurotransmitter molecules, thereby producing a brief permeability change in the membrane (see Figure 11-33). Unlike the voltage-gated channels responsible for action potentials, transmitter-gated channels are relatively insensitive to the membrane potential and therefore cannot by themselves produce a self-amplifying excitation. Instead, they produce local permeability changes, and hence changes of membrane potential, that are graded according to how much neurotransmitter is released at the synapse and how long it persists there. An action potential can be triggered from this site only if the local membrane potential increases enough to open a sufficient number of nearby voltage-gated cation channels that are present in the same target cell membrane.

**Chemical Synapses Can Be Excitatory or Inhibitory**

Transmitter-gated ion channels differ from one another in several important ways. First, as receptors, they have a highly selective binding site for the neurotransmitter that is released from the presynaptic nerve terminal. Second, as channels, they are selective as to the type of ions that they let pass across the plasma membrane; this determines the nature of the postsynaptic response. **Excitatory neurotransmitters** open cation channels, causing an influx of Na\(^+\) that depolarizes the postsynaptic membrane toward the threshold potential for firing an action potential. Inhibitory neurotransmitters, by contrast, open either Cl\(^-\) channels or K\(^+\) channels, and this suppresses firing by making it harder for excitatory influences to depolarize the postsynaptic membrane. Many transmitters can be either excitatory and inhibitory, depending on where they are released, what receptors they bind to, and the ionic conditions that they encounter. **Acetylcholine**, for example, can either excite or inhibit, depending on the type of acetylcholine receptors it binds to. Usually, however, **acetylcholine**, **glutamate**, and **serotonin** are used as excitatory transmitters, and **γ-aminobutyric acid (GABA)** and **glycine** are used as inhibitory transmitters. Glutamate, for instance, mediates most of the excitatory signaling in the vertebrate brain.

We have already discussed how the opening of cation channels depolarizes a membrane. The effect of opening Cl\(^-\) channels can be understood as follows. The concentration of Cl\(^-\) is much higher outside the cell than inside (see Table 11-1, p. 616), but its influx is opposed by the membrane potential. In fact, for many neurons, the equilibrium potential for Cl\(^-\) is close to the resting potential—or even more negative. For this reason, opening Cl\(^-\) channels tend to buffer the membrane potential; as the membrane starts to depolarize, more negatively charged Cl\(^-\) ions enter the cell and counteract the effect. Thus, the opening of Cl\(^-\) channels makes it more difficult to depolarize the membrane and hence to excite the cell. The opening of K\(^+\) channels has a similar effect. The importance of inhibitory neurotransmitters is demonstrated by the effects of toxins that block their action: strychnine, for example, by binding to glycine receptors and blocking the action of glycine, causes muscle spasms, convulsions, and death.

However, not all chemical signaling in the nervous system operates through ligand-gated ion channels. Many of the signaling molecules that are secreted by nerve terminals, including a large variety of neuropeptides, bind to receptors that regulate ion channels only indirectly. These so-called **G-protein-linked receptors** and **enzyme-linked receptors** are discussed in detail in Chapter 15. Whereas signaling mediated by excitatory and inhibitory neurotransmitters binding to transmitter-gated ion channels is generally immediate, simple, and brief, signaling mediated by ligands binding to G-protein-linked receptors and enzyme-linked receptors tends to be far slower and more complex, and longer lasting in its consequences.

**The Acetylcholine Receptors at the Neuromuscular Junction Are Transmitter-gated Cation Channels**

The best-studied example of a transmitter-gated ion channel is the **acetylcholine receptor** of skeletal muscle cells. This channel is opened transiently by acetylcholine released from the nerve terminal at a neuromuscular
junction—the specialized chemical synapse between a motor neuron and a skeletal muscle cell (Figure 11-34). This synapse has been intensively investigated because it is readily accessible to electrophysiological study, unlike most of the synapses in the central nervous system.

The acetylcholine receptor has a special place in the history of ion channels. It was the first ion channel to be purified, the first to have its complete amino acid sequence determined, the first to be functionally reconstituted in synthetic lipid bilayers, and the first for which the electrical signal of a single open channel was recorded. Its gene was also the first ion channel gene to be cloned and sequenced, and it is the only ligand-gated channel whose three-dimensional structure has been determined, albeit at moderate resolution. There were at least two reasons for the rapid progress in purifying and characterizing this receptor. First, an unusually rich source of the acetylcholine receptors exists in the electrical organs of electric fish and rays (these organs are modified muscles designed to deliver a large electrical shock to prey). Second, certain neurotoxins (such as α-bungarotoxin) in the venom of certain snakes bind with high affinity \( (K_d = 10^5 \text{ liters/mole}) \) and specificity to the receptor and can therefore be used to purify it by affinity chromatography. Fluorescent or radiolabeled α-bungarotoxin can also be used to localize and count acetylcholine receptors. In this way, it has been shown that the receptors are densely packed in the muscle cell plasma membrane at a neuromuscular junction (about 20,000 such receptors per \( \mu \text{m}^2 \)), with relatively few receptors elsewhere in the same membrane.

The acetylcholine receptor of skeletal muscle is composed of five transmembrane polypeptides, two of one kind and three others, encoded by four separate genes. The four genes are strikingly similar in sequence, implying that they evolved from a single ancestral gene. The two identical polypeptides in the pentamer each have binding sites for acetylcholine. When two acetylcholine molecules bind to the pentameric complex, they induce a conformational change that opens the channel. With ligand bound, the channel still flickers between open and closed states, but now has a 90% probability of being in the open state. This state continues until the concentration of acetylcholine is lowered sufficiently by hydrolysis by a specific enzyme (acetylcholinesterase) located in the neuromuscular junction. Once freed of its bound neurotransmitter, the acetylcholine receptor reverts to its initial resting state. If the presence of acetylcholine persists for a prolonged time as a result of excessive nerve stimulation, the channel inactivates (Figure 11-35).

The general shape of the acetylcholine receptor and the likely arrangement of its subunits have been determined by electron microscopy (Figure 11-36). The five subunits are arranged in a ring, forming a water-filled transmembrane channel that consists of a narrow pore through the lipid bilayer, which widens into vestibules at both ends. Clusters of negatively charged amino acids at either end of the pore help to exclude negative ions and encourage any positive ion of diameter less than 0.65 nm to pass through. The normal traffic consists chiefly of \( \text{Na}^+ \) and \( \text{K}^+ \), together with some \( \text{Ca}^{2+} \). Thus, unlike voltage-gated cation channels, such as the \( \text{K}^+ \) channel discussed earlier, there is little selectivity among cations, and the relative contributions of the different cations to the current through the channel depend chiefly on their concentrations and on the electrochemical driving forces. When the muscle cell membrane is at its resting potential, the net driving force for \( \text{K}^+ \) is near zero, since the voltage gradient nearly balances the \( \text{K}^+ \) concentration gradient across the membrane (see Panel 11-2, p. 634). For \( \text{Na}^+ \), in contrast, the voltage gradient and the concentration gradient both act in the same direction to drive the ion into the cell. (The same is true for \( \text{Ca}^{2+} \), but the extracellular concentration of \( \text{Ca}^{2+} \) is so much lower than that of \( \text{Na}^+ \) that \( \text{Ca}^{2+} \) makes only a small contribution to the total inward current.) Therefore, the opening of the acetylcholine receptor channels leads to a large net influx of \( \text{Na}^+ \) (a peak rate of about 30,000 ions per channel each millisecond). This influx causes a membrane depolarization that signals the muscle to contract, as discussed below.
Transmitter-gated Ion Channels Are Major Targets for Psychoactive Drugs

The ion channels that open directly in response to the neurotransmitters acetylcholine, serotonin, GABA, and glycine contain subunits that are structurally similar, suggesting that they are evolutionarily related and probably form transmembrane pores in the same way, even though their neurotransmitter-binding specificities and ion selectivities are distinct. These channels seem to have a similar overall structure, in each case formed by homologous polypeptide subunits, which probably assemble as a pentamer resembling the acetylcholine receptor. Glutamate-gated ion channels are constructed from a distinct family of subunits and are thought to form tetramers, like the K\(^+\) channels discussed earlier.

For each class of transmitter-gated ion channels, alternative forms of each type of subunit exist, either encoded by distinct genes or generated by alternative RNA splicing of the same gene product. These combine in different variations to form an extremely diverse set of distinct channel subtypes, with different ligand affinities, different channel conductances, different rates of opening and closing, and different sensitivities to drugs and toxins. Vertebrate neurons, for example, have acetylcholine-gated ion channels that differ from those of muscle cells in that they are usually formed from two subunits of one type and three of another; but there are at least nine genes coding for different versions of the first type of subunit and at least three coding for different versions of the second, with further diversity due to alternative RNA splicing. Subsets of acetylcholine-sensitive neurons performing different functions in the brain are characterized by different combinations of these subunits. This, in principle and already to some extent in practice, makes it possible to design drugs targeted against narrowly defined groups of neurons or synapses, thereby influencing particular brain functions specifically.

Indeed, transmitter-gated ion channels have for a long time been important targets for drugs. A surgeon, for example, can make muscles relax for the duration of an operation by blocking the acetylcholine receptors on skeletal muscle cells with curare, a drug from a plant that was originally used by South American Indians to poison arrows. Most drugs used in the treatment of insomnia, anxiety, depression, and schizophrenia exert their effects at chemical synapses, and many of these act by binding to transmitter-gated channels. Both barbiturates and tranquillizers, such as Valium and Librium, for example, bind to GABA receptors, potentiating the inhibitory action of GABA by allowing lower concentrations of this neurotransmitter to open Cl\(^-\) channels. The new molecular biology of ion channels, by revealing both their diversity and the details of their structure, holds out the hope of designing a new generation of psychoactive drugs that will act still more selectively to alleviate the miseries of mental illness.

In addition to ion channels, many other components of the synaptic signaling machinery are potential targets for psychoactive drugs. As discussed earlier, many neurotransmitters are cleared from the synaptic cleft after release by Na\(^+\)-driven carriers. The inhibition of such a carrier prolongs the effect of the transmitter and thereby strengthens synaptic transmission. Many antidepressant drugs, including Prozac, for example, act by inhibiting the uptake of serotonin; others inhibit the uptake of both serotonin and norepinephrine.

Ion channels are the basic molecular components from which neuronal devices for signaling and computation are built. To provide a glimpse of how sophisticated the functions of these devices can be, we consider several examples that demonstrate how groups of ion channels work together in synaptic communication between electrically excitable cells.

Neuromuscular Transmission Involves the Sequential Activation of Five Different Sets of Ion Channels

The importance of ion channels to electrically excitable cells can be illustrated by following the process whereby a nerve impulse stimulates a muscle cell to contract. This apparently simple response requires the sequential activation of at least five different sets of ion channels, all within a few milliseconds (Figure 11-37).

Figure 11-37

The system of ion channels at a neuromuscular junction. These gated ion channels are essential for the stimulation of muscle contraction by a nerve impulse. The various channels are numbered in the sequence in...
which they are activated, as described in (more...)

1. The process is initiated when the nerve impulse reaches the nerve terminal and depolarizes the plasma membrane of the terminal. The depolarization transiently opens voltage-gated Ca\(^{2+}\) channels in this membrane. As the Ca\(^{2+}\) concentration outside cells is more than 1000 times greater than the free Ca\(^{2+}\) concentration inside, Ca\(^{2+}\) flows into the nerve terminal. The increase in Ca\(^{2+}\) concentration in the cytosol of the nerve terminal triggers the localized release of acetylcholine into the synaptic cleft.

2. The released acetylcholine binds to acetylcholine receptors in the muscle cell plasma membrane, transiently opening the cation channels associated with them. The resulting influx of Na\(^{+}\) causes a localized membrane depolarization.

3. The local depolarization of the muscle cell plasma membrane opens voltage-gated Na\(^{+}\) channels in this membrane, allowing more Na\(^{+}\) to enter, which further depolarizes the membrane. This, in turn, opens neighboring voltage-gated Na\(^{+}\) channels and results in a self-propagating depolarization (an action potential) that spreads to involve the entire plasma membrane (see Figure 11-28).

4. The generalized depolarization of the muscle cell plasma membrane activates voltage-gated Ca\(^{2+}\) channels in specialized regions (the transverse [T] tubules—discussed in Chapter 16) of this membrane.

5. This, in turn, causes Ca\(^{2+}\) release channels in an adjacent region of the sarcoplasmic reticulum membrane to open transiently and release the Ca\(^{2+}\) stored in the sarcoplasmic reticulum into the cytosol. It is the sudden increase in the cytosolic Ca\(^{2+}\) concentration that causes the myofibrils in the muscle cell to contract. It is not certain how the activation of the voltage-gated Ca\(^{2+}\) channels in the T-tubule membrane leads to the opening of the Ca\(^{2+}\) release channels in the sarcoplasmic reticulum membrane. The two membranes are closely apposed, however, with the two types of channels joined together in a specialized structure (see Figure 16-74). It is possible, therefore, that a voltage-induced change in the conformation of the plasma membrane Ca\(^{2+}\) channel directly opens the Ca\(^{2+}\) release channel in the sarcoplasmic reticulum through a mechanical coupling.

Whereas the activation of muscle contraction by a motor neuron is complex, an even more sophisticated interplay of ion channels is required for a neuron to integrate a large number of input signals at synapses and compute an appropriate output, as we now discuss.

**Single Neurons Are Complex Computation Devices**

In the central nervous system, a single neuron can receive inputs from thousands of other neurons, and can in turn synapse on many thousands of other cells. Several thousand nerve terminals, for example, make synapses on an average motor neuron in the spinal cord; its cell body and dendrites are almost completely covered with them (Figure 11-38). Some of these synapses transmit signals from the brain or spinal cord; others bring sensory information from muscles or from the skin. The motor neuron must combine the information received from all these sources and react either by firing action potentials along its axon or by remaining quiet.

![Figure 11-38](image)

A motor neuron cell body in the spinal cord. (A) Many thousands of nerve terminals synapse on the cell body and dendrites. These deliver signals from other parts of the organism to control the firing of action potentials along the single axon of this (more...)

Of the many synapses on a neuron, some tend to excite it, others to inhibit it. Neurotransmitter released at an excitatory synapse causes a small depolarization in the postsynaptic membrane called an *excitatory postsynaptic potential (excitatory PSP)*, while neurotransmitter released at an inhibitory synapse generally causes a small hyperpolarization called an *inhibitory PSP*. The membrane of the dendrites and cell body of most neurons contains a relatively low density of voltage-gated Na\(^{+}\) channels, and an individual excitatory PSP is generally too small to trigger an action potential. Instead, each incoming signal is reflected in a local PSP of graded magnitude, which decreases with distance from the site of the synapse. If signals arrive simultaneously at several synapses in the same region of the dendritic tree, the total PSP in that neighborhood will be roughly the sum of the individual PSPs, with inhibitory PSPs making a negative contribution to the total. The PSPs from
Neuronal Computation Requires a Combination of at Least Three Kinds of \( K^+ \) Channels

We have seen that the intensity of stimulation received by a neuron is determined for long-distance transmission by the frequency of action potentials that the neuron fires: the stronger the stimulation, the higher the frequency of action potentials. Action potentials are initiated at the axon hillock, a unique region of each neuron where voltage-gated \( Na^+ \) channels are plentiful. But to perform its special function of encoding, the membrane of the axon hillock also contains at least four other classes of ion channels—three selective for \( K^+ \) and one selective for \( Ca^{2+} \). The three varieties of \( K^+ \) channels have different properties; we shall refer to them as the delayed, the early, and the \( Ca^{2+} \)-activated \( K^+ \) channels.

To understand the need for multiple types of channels, consider first what would happen if the only voltage-gated ion channels present in the nerve cell were the \( Na^+ \) channels. Below a certain threshold level of synaptic stimulation, the depolarization of the axon hillock membrane would be insufficient to trigger an action potential. With gradually increasing stimulation, the threshold would be crossed, the \( Na^+ \) channels would open, and an action potential would fire. The action potential would be terminated in the usual way by inactivation of the \( Na^+ \) channels. Before another action potential could fire, these channels would have to recover from their inactivation. But that would require a return of the membrane voltage to a very negative value, which would not...
occur as long as the strong depolarizing stimulus (from PSPs) was maintained. An additional channel type is needed, therefore, to repolarize the membrane after each action potential to prepare the cell to fire again.

This task is performed by the delayed \( K^+ \) channels discussed previously in relation to the propagation of the action potential (see p. 639). They are voltage-gated, but because of their slower kinetics they open only during the falling phase of the action potential, when the \( Na^+ \) channels are inactive. Their opening permits an efflux of \( K^+ \) that drives the membrane back toward the \( K^+ \) equilibrium potential, which is so negative that the \( Na^+ \) channels rapidly recover from their inactivated state. Repolarization of the membrane also causes the delayed \( K^+ \) channels to close. The axon hillock is now reset so that the depolarizing stimulus from synaptic inputs can fire another action potential. In this way, sustained stimulation of the dendrites and cell body leads to repetitive firing of the axon.

Repetitive firing in itself, however, is not enough. The frequency of the firing has to reflect the intensity of the stimulation, and a simple system of \( Na^+ \) channels and delayed \( K^+ \) channels is inadequate for this purpose. Below a certain threshold level of steady stimulation, the cell will not fire at all; above that threshold level, it will abruptly begin to fire at a relatively rapid rate. The early \( K^+ \) channels solve the problem. These, too, are voltage-gated and open when the membrane is depolarized, but their specific voltage sensitivity and kinetics of inactivation are such that they act to reduce the rate of firing at levels of stimulation that are only just above the threshold required for firing. Thus, they remove the discontinuity in the relationship between the firing rate and the intensity of stimulation. The result is a firing rate that is proportional to the strength of the depolarizing stimulus over a very broad range (see Figure 11-40).

The process of encoding is usually further modulated by the two other types of ion channels in the axon hillock that were mentioned at the outset, voltage-gated \( Ca^{2+} \) channels and \( Ca^{2+} \)-activated \( K^+ \) channels. They act together to decrease the response of the cell to an unchanging, prolonged stimulation—a process called adaptation. These \( Ca^{2+} \) channels are similar to the \( Ca^{2+} \) channels that mediate the release of neurotransmitter from presynaptic axon terminals; they open when an action potential fires, transiently allowing \( Ca^{2+} \) into the axon hillock.

The \( Ca^{2+} \)-activated \( K^+ \) channel is both structurally and functionally different from any of the channel types described earlier. It opens in response to a raised concentration of \( Ca^{2+} \) at the cytoplasmic face of the nerve cell membrane. Suppose that a strong depolarizing stimulus is applied for a long time, triggering a long train of action potentials. Each action potential permits a brief influx of \( Ca^{2+} \) through the voltage-gated \( Ca^{2+} \) channels, so that the intracellular \( Ca^{2+} \) concentration gradually builds up to a level high enough to open the \( Ca^{2+} \) -activated \( K^+ \) channels. Because the resulting increased permeability of the membrane to \( K^+ \) makes the membrane harder to depolarize, it increases the delay between one action potential and the next. In this way, a neuron that is stimulated continuously for a prolonged period becomes gradually less responsive to the constant stimulus.

Such adaptation, which can also occur by other mechanisms, allows a neuron—indeed, the nervous system generally—to react sensitively to change, even against a high background level of steady stimulation. It is one of the strategies that help us, for example, to feel a light touch on the shoulder and yet ignore the constant pressure of our clothing. We discuss adaptation as a general feature in cell signaling processes in more detail in Chapter 15.

Other neurons do different computations, reacting to their synaptic inputs in myriad ways, reflecting the different assortments of members of the various ion channel families that reside in their membranes. There are, for example, at least five known types of voltage-gated \( Ca^{2+} \) channels in the vertebrate nervous system and at least four known types of voltage-gated \( K^+ \) channels. The multiplicity of genes evidently allows for a host of different types of neurons, whose electrical behavior is specifically tuned to the particular tasks that they must perform.

One of the crucial properties of the nervous system is its ability to learn and remember, which seems to depend largely on long-term changes in specific synapses. We end this chapter by considering a remarkable type of ion channel that is thought to have a special role in some forms of learning and memory. It is located at many synapses in the central nervous system, where it is gated by both voltage and the excitatory neurotransmitter glutamate. It is also the site of action of the psychoactive drug phencyclidine, or angel dust.

**Long-term Potentiation (LTP) in the Mammalian Hippocampus Depends on \( Ca^{2+} \)**
Entry Through NMDA-Receptor Channels

Practically all animals can learn, but mammals seem to learn exceptionally well (or so we like to think). In a mammal’s brain, the region called the hippocampus has a special role in learning. When it is destroyed on both sides of the brain, the ability to form new memories is largely lost, although previous long-established memories remain. Correspondingly, some synapses in the hippocampus show marked functional alterations with repeated use: whereas occasional single action potentials in the presynaptic cells leave no lasting trace, a short burst of repetitive firing causes long-term potentiation (LTP), such that subsequent single action potentials in the presynaptic cells evoke a greatly enhanced response in the postsynaptic cells. The effect lasts hours, days, or weeks, according to the number and intensity of the bursts of repetitive firing. Only the synapses that were activated exhibit LTP; synapses that have remained quiet on the same postsynaptic cell are not affected. However, while the cell is receiving a burst of repetitive stimulation via one set of synapses, if a single action potential is delivered at another synapse on its surface, that latter synapse also will undergo LTP, even though a single action potential delivered there at another time would leave no such lasting trace.

The underlying rule in such synapses seems to be that LTP occurs on any occasion when a presynaptic cell fires (once or more) at a time when the postsynaptic membrane is strongly depolarized (either through recent repetitive firing of the same presynaptic cell or by other means). This rule reflects the behavior of a particular class of ion channels in the postsynaptic membrane. Glutamate is the main excitatory neurotransmitter in the mammalian central nervous system, and glutamate-gated ion channels are the most common of all transmitter-gated channels in the brain. In the hippocampus, as elsewhere, most of the depolarizing current responsible for excitatory PSPs is carried by glutamate-gated ion channels that operate in the standard way. But the current has, in addition, a second and more intriguing component, which is mediated by a separate subclass of glutamate-gated ion channels known as NMDA receptors, so named because they are selectively activated by the artificial glutamate analog N-methyl-D-aspartate. The NMDA-receptor channels are doubly gated, opening only when two conditions are satisfied simultaneously: glutamate must be bound to the receptor, and the membrane must be strongly depolarized. The second condition is required for releasing the Mg$^{2+}$ that normally blocks the resting channel. This means that NMDA receptors are normally only activated when conventional glutamate-gated ion channels are activated as well and depolarize the membrane. The NMDA receptors are critical for LTP. When they are selectively blocked with a specific inhibitor, LTP does not occur, even though ordinary synaptic transmission continues. An animal treated with this inhibitor exhibits specific deficits in its learning abilities but behaves almost normally otherwise.

How do NMDA receptors mediate such a remarkable effect? The answer is that these channels, when open, are highly permeable to Ca$^{2+}$, which acts as an intracellular mediator in the postsynaptic cell, triggering a cascade of changes that are responsible for LTP. Thus, LTP is prevented when Ca$^{2+}$ levels are held artificially low in the postsynaptic cell by injecting the Ca$^{2+}$ chelator EGTA into it and can be induced by artificially raising intracellular Ca$^{2+}$ levels. Among the long-term changes that increase the sensitivity of the postsynaptic cell to glutamate is the insertion of new conventional glutamate receptors into the plasma membrane (Figure 11-41). Evidence also indicates that changes can occur in the presynaptic cell as well, so that it releases more glutamate than normal when it is activated subsequently.

![Figure 11-41](image)

The signaling events in long-term potentiation. Although not shown, evidence suggests that changes can also occur in the presynaptic nerve terminals in LTP, which may be stimulated by retrograde signals from the postsynaptic cell.

There is evidence that NMDA receptors have an important role in learning and related phenomena in other parts of the brain, as well as in the hippocampus. In Chapter 21 we see, moreover, that NMDA receptors have a crucial role in adjusting the anatomical pattern of synaptic connections in the light of experience during the development of the nervous system.

Thus, neurotransmitters released at synapses, besides relaying transient electrical signals, can also alter concentrations of intracellular mediators that bring about lasting changes in the efficacy of synaptic transmission. However, it is still uncertain how these changes endure for weeks, months, or a lifetime in the face of the normal turnover of cell constituents.

Some of the ion channel families that we have discussed are summarized in Table 11-2.
Table 11-2

Some Ion Channel Families.

Summary

Ion channels form aqueous pores across the lipid bilayer and allow inorganic ions of appropriate size and charge to cross the membrane down their electrochemical gradients at rates about 1000 times greater than those achieved by any known carrier. The channels are “gated” and usually open transiently in response to a specific perturbation in the membrane, such as a change in membrane potential (voltage-gated channels) or the binding of a neurotransmitter (transmitter-gated channels).

K⁺-selective leak channels have an important role in determining the resting membrane potential across the plasma membrane in most animal cells. Voltage-gated cation channels are responsible for the generation of self-amplifying action potentials in electrically excitable cells, such as neurons and skeletal muscle cells. Transmitter-gated ion channels convert chemical signals to electrical signals at chemical synapses. Excitatory neurotransmitters, such as acetylcholine and glutamate, open transmitter-gated cation channels and thereby depolarize the postsynaptic membrane toward the threshold level for firing an action potential. Inhibitory neurotransmitters, such as GABA and glycine, open transmitter-gated Cl⁻ or K⁺ channels and thereby suppress firing by keeping the postsynaptic membrane polarized. A subclass of glutamate-gated ion channels, called NMDA-receptor channels, are highly permeable to Ca²⁺, which can trigger the long-term changes in synapses that are thought to be involved in some forms of learning and memory.

Ion channels work together in complex ways to control the behavior of electrically excitable cells. A typical neuron, for example, receives thousands of excitatory and inhibitory inputs, which combine by spatial and temporal summation to produce a postsynaptic potential (PSP) in the cell body. The magnitude of the PSP is translated into the rate of firing of action potentials by a mixture of cation channels in the membrane of the axon hillock.
Figure 11-20

The channel protein shown here in cross section forms a hydrophilic pore across the lipid bilayer only in the “open” conformational state. Polar groups are thought to line the wall of the pore, while hydrophobic amino acid side chains interact with the lipid bilayer (not shown). The pore narrows to atomic dimensions in one region (the selectivity filter), where the ion selectivity of the channel is largely determined.
This drawing shows different kinds of stimuli that open ion channels. Mechanically gated channels often have cytoplasmic extensions that link the channel to the cytoskeleton (not shown).
A small flow of ions carries sufficient charge to cause a large change in the membrane potential. The ions that give rise to the membrane potential lie in a thin (< 1 nm) surface layer close to the membrane, held there by their electrical attraction to their oppositely charged counterparts (counterions) on the other side of the membrane. For a typical cell, 1 microcoulomb of charge (6 × 10^{12} monovalent ions) per square centimeter of membrane, transferred from one side of the membrane to the other, changes the membrane potential by roughly 1 V. This means, for example, that in a spherical cell of diameter 10 µm, the number of K⁺ ions that have to flow out to alter the membrane potential by 100 mV is only about 1/100,000 of the total number of K⁺ ions in the cytosol.
Figure 11-23

(A) Only two of the four identical subunits are shown. From the cytosolic side, the pore opens up into a vestibule in the middle of the membrane. The vestibule facilitates transport by allowing the K\(^+\) ions to remain hydrated even though they are halfway across the membrane. The narrow selectivity filter links the vestibule to the outside of the cell. Carbonyl oxygens line the walls of the selectivity filter and form transient binding sites for dehydrated K\(^+\) ions. The positions of the K\(^+\) ions in the pore were determined by soaking crystals of the channel protein in a solution containing rubidium ions, which are more electron-dense but only slightly larger than K\(^+\) ions; from the differences in the diffraction patterns with K\(^+\) ions and with rubidium ions in the channel, the positions of the ions could be calculated. Two K\(^+\) ions occupy sites in the selectivity filter, while a third K\(^+\) ion is located in the center of the vestibule, where it is stabilized by electrical interactions with the more negatively charged ends of the pore helices. The ends of the four pore helices point precisely toward the center of the vestibule, thereby guiding K\(^+\) ions into the selectivity filter. (B) Because of the polarity of the hydrogen bonds (in red) that link adjacent turns of an \(\alpha\) helix, every \(\alpha\) helix has an electric dipole along its axis, with a more negatively charged C-terminal end (\(\delta^-\)) and a more positively charged N-terminal end (\(\delta^+\)). (A, Adapted from D.A. Doyle et al., *Science* 280:69–77, 1998.)
Figure 11-24

The drawing shows K\(^+\) and Na\(^+\) ions (A) in the vestibule and (B) in the selectivity filter of the pore, viewed in cross section. In the vestibule, the ions are hydrated. In the selectivity filter, the carbonyl oxygens are placed precisely to accommodate a dehydrated K\(^+\) ion. The dehydration of the K\(^+\) ion requires energy, which is precisely balanced by the energy regained by the interaction of the ion with the carbonyl oxygens that serve as surrogate water molecules. Because the Na\(^+\) ion is too small to interact with the oxygens, it could enter the selectivity filter only at a great energetic expense. The filter therefore selects K\(^+\) ions with high specificity.

(Adapted from D.A. Doyle et al., Science 280:69–77, 1998.)
Figure 11-25
The channel is viewed in cross section. To adopt the closed conformation, the four inner transmembrane helices that line the pore on the cytosolic side of the selectivity filter (see Figure 11-22) rearrange to close the cytosolic entrance to the channel. (Adapted from E. Perozo et al., *Science* 285:73–78, 1999.)
The arrows indicate the direction in which signals are conveyed. The single axon conducts signals away from the cell body, while the multiple dendrites receive signals from the axons of other neurons. The nerve terminals end on the dendrites or cell body of other neurons or on other cell types, such as muscle or gland cells.
Figure 11-27

(A) An action potential is triggered by a brief pulse of current, which (B) partially depolarizes the membrane, as shown in the plot of membrane potential versus time. The green curve shows how the membrane potential would have simply relaxed back to the resting value after the initial depolarizing stimulus if there had been no voltage-gated ion channels in the membrane; this relatively slow return of the membrane potential to its initial value of -70 mV in the absence of open Na⁺ channels occurs because of the efflux of K⁺ through K⁺ channels, which open in response to membrane depolarization and drive the membrane back toward the K⁺ equilibrium potential. The red curve shows the course of the action potential that is caused by the opening and subsequent inactivation of voltage-gated Na⁺ channels, whose state is shown in (C). The membrane cannot fire a second action potential until the Na⁺ channels have returned to the closed conformation; until then, the membrane is refractory to stimulation.
Figure 11-28

(A) The voltages that would be recorded from a set of intracellular electrodes placed at intervals along the axon.

(B) The changes in the Na⁺ channels and the current flows (orange arrows) that give rise to the traveling disturbance of the membrane potential. The region of the axon with a depolarized membrane is shaded in blue. Note that an action potential can only travel away from the site of depolarization, because Na⁺-channel inactivation prevents the depolarization from spreading backward (see also Figure 11-30). On myelinated axons, clusters of Na⁺ channels can be millimeters apart from each other.
When the membrane potential is depolarized, the channel opens and begins to conduct ions. If the depolarization is maintained, the open channel adopts an inactive conformation, where the pore is occluded by the N-terminal 20 amino acid "ball," which is linked to the channel proper by a segment of unfolded polypeptide chain that serves as the "chain." For simplicity, only two balls are shown; in fact, there are four, one from each subunit. A similar mechanism, using a different segment of the polypeptide chain, is thought to operate in Na\(^+\) channel inactivation. Internal forces stabilize each state against small disturbances, but a sufficiently violent collision with other molecules can cause the channel to flip from one of these states to another. The state of lowest energy depends on the membrane potential because the different conformations have different charge distributions. When the membrane is at rest (highly polarized), the closed conformation has the lowest free energy and is therefore most stable; when the membrane is depolarized, the energy of the open conformation is lower, so the channel has a high probability of opening. But the free energy of the inactivated conformation is lower still; therefore, after a randomly variable period spent in the open state, the channel becomes inactivated. Thus, the open conformation corresponds to a metastable state that can exist only transiently. The red arrows indicate the sequence that follows a sudden depolarization; the black arrow indicates the return to the original conformation as the lowest energy state after the membrane is repolarized.
Figure 11-30

(A) A myelinated axon from a peripheral nerve. Each Schwann cell wraps its plasma membrane concentrically around the axon to form a segment of myelin sheath about 1 mm long. For clarity, the layers of myelin in this drawing are not shown compacted together as tightly as they are in reality (see part B). (B) An electron micrograph of a section from a nerve in the leg of a young rat. Two Schwann cells can be seen: one near the bottom is just beginning to myelinate its axon; the one above it has formed an almost mature myelin sheath. (B, from Cedric S. Raine, in Myelin [P. Morell, ed.]. New York: Plenum, 1976.)
Because of the extremely tight seal between the micropipette and the membrane, current can enter or leave the micropipette only by passing through the channels in the patch of membrane covering its tip. The term clamp is used because an electronic device is employed to maintain, or “clamp,” the membrane potential at a set value while recording the ionic current through individual channels. Recordings of the current through these channels can be made with the patch still attached to the rest of the cell, as in (A), or detached, as in (B). The advantage of the detached patch is that it is easy to alter the composition of the solution on either side of the membrane to test the effect of various solutes on channel behavior. A detached patch can also be produced with the opposite orientation, so that the cytoplasmic surface of the membrane faces the inside of the pipette.
A tiny patch of plasma membrane was detached from an embryonic rat muscle cell, as in Figure 11-31. (A) The membrane was depolarized by an abrupt shift of potential. (B) Three current records from three experiments performed on the same patch of membrane. Each major current step in (B) represents the opening and closing of a single channel. A comparison of the three records shows that, whereas the durations of channel opening and closing vary greatly, the rate at which current flows through an open channel is practically constant. The minor fluctuations in the current records arise largely from electrical noise in the recording apparatus. Current is measured in picoamperes (pA). (C) The sum of the currents measured in 144 repetitions of the same experiment. This aggregate current is equivalent to the usual Na\(^+\) current that would be observed flowing through a relatively large region of membrane containing 144 channels. A comparison of (B) and (C) reveals that the time course of the aggregate current reflects the probability that any individual channel will be in the open state; this probability decreases with time as the channels in the depolarized membrane adopt their inactivated conformation. (Data from J. Patlak and R. Horn, J. Gen. Physiol. 79:333–351, 1982. © The Rockefeller University Press.)
When an action potential reaches the nerve terminal in a presynaptic cell, it stimulates the terminal to release its neurotransmitter. The neurotransmitter molecules are contained in synaptic vesicles and are released to the cell exterior when the vesicles fuse with the plasma membrane of the nerve terminal. The released neurotransmitter binds to and opens the transmitter-gated ion channels concentrated in the plasma membrane of the postsynaptic target cell at the synapse. The resulting ion flows alter the membrane potential of the target cell, thereby transmitting a signal from the excited nerve.
Figure 11-34
Figure 11-35

The binding of two acetylcholine molecules opens this transmitter-gated ion channel. It then maintains a high probability of being open until the acetylcholine has been hydrolyzed. In the persistent presence of acetylcholine, however, the channel inactivates (desensitizes). Normally, the acetylcholine is rapidly hydrolyzed and the channel closes within about 1 millisecond, well before significant desensitization occurs. Desensitization would occur after about 20 milliseconds in the continued presence of acetylcholine.
Five homologous subunits (α, α, β, γ, δ) combine to form a transmembrane aqueous pore. The pore is lined by a ring of five transmembrane α helices, one contributed by each subunit. In its closed conformation, the pore is thought to be occluded by the hydrophobic side chains of five leucines, one from each α helix, which form a gate near the middle of the lipid bilayer. The negatively charged side chains at either end of the pore ensure that only positively charged ions pass through the channel. Both of the α subunits contain an acetylcholine-binding site; when acetylcholine binds to both sites, the channel undergoes a conformational change that opens the gate, possibly by causing the leucines to move outward. (Adapted from N. Unwin, Cell/Neuron 72/10 Suppl.:31-41, 1993.)
These gated ion channels are essential for the stimulation of muscle contraction by a nerve impulse. The various channels are numbered in the sequence in which they are activated, as described in the text.
(A) Many thousands of nerve terminals synapse on the cell body and dendrites. These deliver signals from other parts of the organism to control the firing of action potentials along the single axon of this large cell. (B) Micrograph showing a nerve cell body and its dendrites stained with a fluorescent antibody that recognizes a cytoskeletal protein (green). Thousands of axon terminals (red) from other nerve cells (not visible) make synapses on the cell body and dendrites; they are stained with a fluorescent antibody that recognizes a protein in synaptic vesicles. (B, courtesy of Olaf Mundigl and Pietro de Camilli).
Each presynaptic action potential arriving at a synapse produces a small postsynaptic potential, or PSP (black lines). When successive action potentials arrive at the same synapse, each PSP produced adds to the tail of the preceding one to produce a larger combined PSP (green lines). The greater the frequency of incoming action potentials, the greater the size of the combined PSP.
Figure 11-40

A comparison of (A) and (B) shows how the firing frequency of an axon increases with an increase in the combined PSP, while (C) summarizes the general relationship.
Although not shown, evidence suggests that changes can also occur in the presynaptic nerve terminals in LTP, which may be stimulated by retrograde signals from the postsynaptic cell.