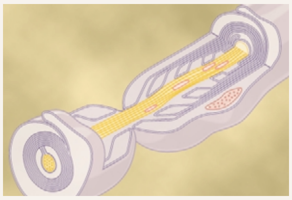
Membrane Potentials and Action Potentials



Electrical potentials exist across the membranes of virtually all cells of the body. In addition, some cells, such as nerve and muscle cells, are capable of generating rapidly changing electrochemical impulses at their membranes, and these impulses are used to transmit signals along the nerve or muscle membranes. In still other types of cells, such as glandular cells, macrophages, and ciliated cells, local changes in membrane potentials also activate many of the cells' functions. The present discussion is concerned with membrane potentials generated both at rest and during action by nerve and muscle cells.

Basic Physics of Membrane Potentials

Membrane Potentials Caused by Diffusion

"Diffusion Potential" Caused by an Ion Concentration Difference on the Two Sides of the Membrane. In Figure 5–1*A,* the potassium concentration is great *inside* a nerve fiber membrane but very low *outside* the membrane. Let us assume that the membrane in this instance is permeable to the potassium ions but not to any other ions. Because of the large potassium concentration gradient from inside toward outside, there is a strong tendency for extra numbers of potassium ions to diffuse outward through the membrane. As they do so, they carry positive electrical charges to the outside, thus creating electropositivity outside the membrane and electronegativity inside because of negative anions that remain behind and do not diffuse outward with the potassium. Within a millisecond or so, the potential difference between the inside and outside, called the *diffusion potential,* becomes great enough to block further net potassium diffusion to the exterior, despite the high potassium ion concentration gradient. In the normal mammalian nerve fiber, *the potential difference required is about 94 millivolts, with negativity inside the fiber membrane.*

Figure 5–1*B* shows the same phenomenon as in Figure 5–1*A,* but this time with high concentration of sodium ions *outside* the membrane and low sodium *inside*. These ions are also positively charged. This time, the membrane is highly permeable to the sodium ions but impermeable to all other ions. Diffusion of the positively charged sodium ions to the inside creates a membrane potential of opposite polarity to that in Figure 5–1*A*, with negativity outside and positivity inside. Again, the membrane potential rises high enough within milliseconds to block further net diffusion of sodium ions to the inside; however, this time, in the mammalian nerve fiber, *the potential is about 61 millivolts positive inside the fiber.*

Thus, in both parts of Figure 5–1, we see that a concentration difference of ions across a selectively permeable membrane can, under appropriate conditions, create a membrane potential. In later sections of this chapter, we show that many of the rapid changes in membrane potentials observed during nerve and muscle impulse transmission result from the occurrence of such rapidly changing diffusion potentials.

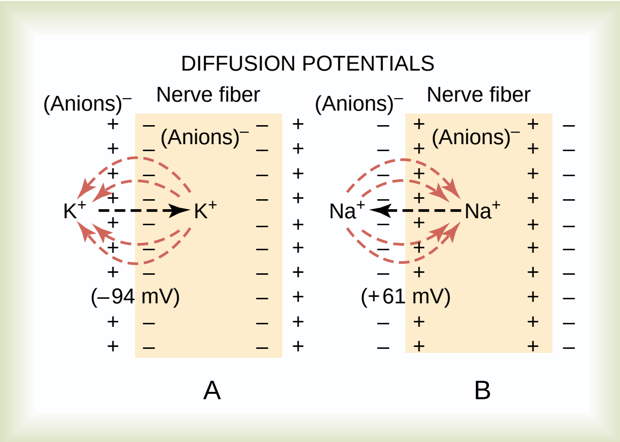


Figure 5–1

A, Establishment of a "diffusion" potential across a nerve fiber membrane, caused by diffusion of potassium ions from inside the cell to outside through a membrane that is selectively permeable only to potassium. *B,* Establishment of a "diffusion potential" when the nerve fiber membrane is permeable only to sodium ions. Note that the internal membrane potential is negative when potassium ions diffuse and positive when sodium ions diffuse because of opposite concentration gradients of these two ions.

Relation of the Diffusion Potential to the Concentration Difference—The Nernst Potential. The diffusion potential level across a membrane that exactly opposes the net diffusion of a particular ion through the membrane is called the *Nernst potential* for that ion, a term that was introduced in Chapter 4. The magnitude of this Nernst potential is determined by the *ratio* of the concentrations of that specific ion on the two sides of the membrane. The greater this ratio, the greater the tendency for the ion to diffuse in one direction, and therefore the greater the Nernst potential required to prevent additional net diffusion. The following equation, called the *Nernst equation,* can be used to calculate the Nernst potential for any univalent ion at normal body temperature of 98.6°F (37°C):

$$\text{EMF (millivolts)} = \pm 61 \log \frac{\text{Concentration inside}}{\text{Concentration outside}}$$

where EMF is electromotive force.

When using this formula, it is usually assumed that the potential in the extracellular fluid outside the membrane remains at zero potential, and the Nernst potential is the potential inside the membrane. Also, the sign of the potential is positive (+) if the ion diffusing from inside to outside is a negative ion, and it is negative (–) if the ion is positive. Thus, when the concentration of positive potassium ions on the inside is 10 times that on the outside, the log of 10 is 1, so that the Nernst potential calculates to be –61 millivolts inside the membrane.

Calculation of the Diffusion Potential When the Membrane Is Permeable to Several Different Ions

When a membrane is permeable to several different ions, the diffusion potential that develops depends on three factors: (1) the polarity of the electrical charge of each ion, (2) the permeability of the membrane (P) to each ion, and (3) the concentrations (C) of the respective ions on the inside (i) and outside (o) of the membrane. Thus, the following formula, called the *Goldman equation,* or the *Goldman-Hodgkin-Katz equation,* gives the calculated membrane potential on the *inside* of the membrane when two univalent positive ions, sodium (Na^+) and potassium (K^+), and one univalent negative ion, chloride (Cl^-), are involved.

$$\text{EMF (millivolts)} = -61 \cdot \log \frac{C_{Na^+_i} P_{Na^+} + C_{K^+_i} P_{K^+} + C_{Cl^-_o} P_{Cl^-}}{C_{Na^+_o} P_{Na^+} + C_{K^-_o} P_{K^+} + C_{Cl^-_i} P_{Cl^-}}$$

Let us study the importance and the meaning of this equation. First, sodium, potassium, and chloride ions are the most important ions involved in the development of membrane potentials in nerve and muscle fibers, as well as in the neuronal cells in the nervous system. The concentration gradient of each of these ions across the membrane helps determine the voltage of the membrane potential.

Second, the degree of importance of each of the ions in determining the voltage is proportional to the membrane permeability for that particular ion. That is, if the membrane has zero permeability to both potassium and chloride ions, the membrane potential becomes entirely dominated by the concentration gradient of sodium ions alone, and the resulting potential will be equal to the Nernst potential for sodium. The same holds for each of the other two ions if the membrane should become selectively permeable for either one of them alone.

Third, a positive ion concentration gradient from *inside* the membrane to the *outside* causes electronegativity inside the membrane. The reason for this is that excess positive ions diffuse to the outside when their concentration is higher inside than outside. This carries positive charges to the outside but leaves the nondiffusible negative anions on the inside, thus creating electronegativity on the inside. The opposite effect occurs when there is a gradient for a negative ion. That is, a chloride ion gradient from the *outside to the inside* causes negativity inside the cell because excess negatively charged chloride ions diffuse to the inside, while leaving the nondiffusible positive ions on the outside.

Fourth, as explained later, the permeability of the sodium and potassium channels undergoes rapid changes during transmission of a nerve impulse, whereas the permeability of the chloride channels does not change greatly during this process. Therefore, rapid changes in sodium and potassium permeability are primarily responsible for signal transmission in nerves, which is the subject of most of the remainder of this chapter.

Measuring the Membrane Potential

The method for measuring the membrane potential is simple in theory but often difficult in practice because

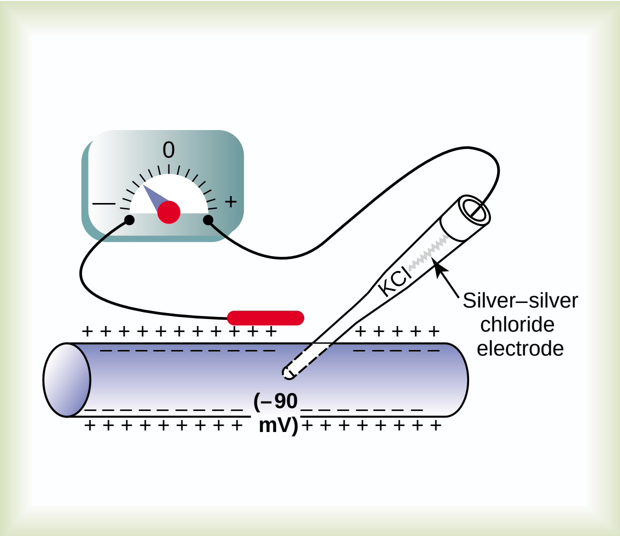


Figure 5–2

Measurement of the membrane potential of the nerve fiber using a microelectrode.

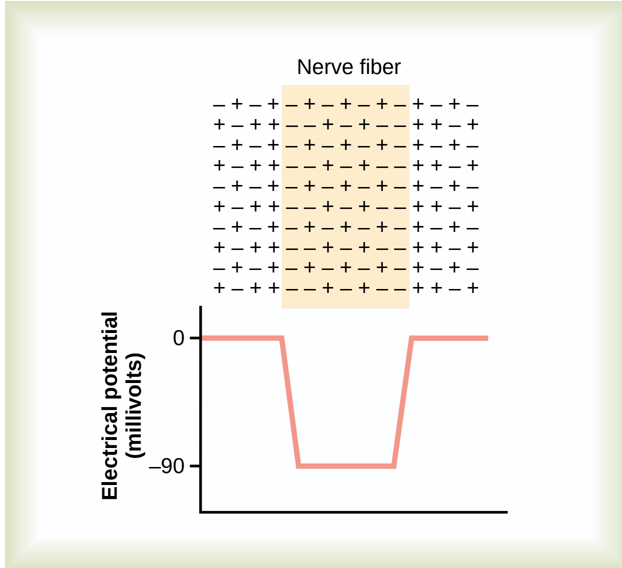


Figure 5–3

Distribution of positively and negatively charged ions in the extracellular fluid surrounding a nerve fiber and in the fluid inside the fiber; note the alignment of negative charges along the inside surface of the membrane and positive charges along the outside surface. The lower panel displays the abrupt changes in membrane potential that occur at the membranes on the two sides of the fiber.

of the small size of most of the fibers. Figure 5–2 shows a small pipette filled with an electrolyte solution. The pipette is impaled through the cell membrane to the interior of the fiber. Then another electrode, called the "indifferent electrode," is placed in the extracellular fluid, and the potential difference between the inside and outside of the fiber is measured using an appropriate voltmeter. This voltmeter is a highly sophisticated electronic apparatus that is capable of measuring very small voltages despite extremely high resistance to electrical flow through the tip of the micropipette, which has a lumen diameter usually less than 1 micrometer and a resistance more than a million ohms. For recording rapid *changes* in the membrane potential during transmission of nerve impulses, the microelectrode is connected to an oscilloscope, as explained later in the chapter.

The lower part of Figure 5–3 shows the electrical potential that is measured at each point in or near the nerve fiber membrane, beginning at the left side of the figure and passing to the right. As long as the electrode is outside the nerve membrane, the recorded potential is zero, which is the potential of the extracellular fluid. Then, as the recording electrode passes through the voltage change area at the cell membrane (called the *electrical dipole layer*), the potential decreases abruptly to –90 millivolts. Moving across the center of the fiber, the potential remains at a steady –90-millivolt level but reverses back to zero the instant it passes through the membrane on the opposite side of the fiber.

To create a negative potential inside the membrane, only enough positive ions to develop the electrical dipole layer at the membrane itself must be transported outward. All the remaining ions inside the nerve fiber can be both positive and negative, as shown in the upper panel of Figure 5–3. Therefore, an incredibly small number of ions needs to be transferred through the membrane to establish the normal "resting potential" of –90 millivolts inside the nerve fiber; this means that only about 1/3,000,000 to 1/100,000,000 of the total positive charges inside the fiber needs to be transferred. Also, an equally small number of positive ions moving from outside to inside the fiber can reverse the potential from –90 millivolts to as much as +35 millivolts within as little as 1/10,000 of a second. Rapid shifting of ions in this manner causes the nerve signals discussed in subsequent sections of this chapter.

Resting Membrane Potential of Nerves

The resting membrane potential of large nerve fibers when not transmitting nerve signals is about –90 millivolts. That is, the potential *inside the fiber* is 90 millivolts more negative than the potential in the extracellular fluid on the outside of the fiber. In the next few paragraphs, we explain all the factors that determine the level of this resting potential, but before doing so, we must describe the transport properties of the resting nerve membrane for sodium and potassium.

Active Transport of Sodium and Potassium Ions Through the Membrane—The Sodium-Potassium (Na^+-K^+) Pump. First, let us recall from Chapter 4 that all cell membranes of the body have a powerful Na^+-K^+ that continually pumps sodium ions to the outside of the cell and potassium ions to the inside, as illustrated on the left-hand side in Figure 5–4. Further, note that this is an *electrogenic pump* because more positive charges are pumped to the outside than to the inside (three Na^+ ions to the outside for each two K^+ ions to the inside), leaving a net deficit of positive ions on the inside; this causes a negative potential inside the cell membrane.

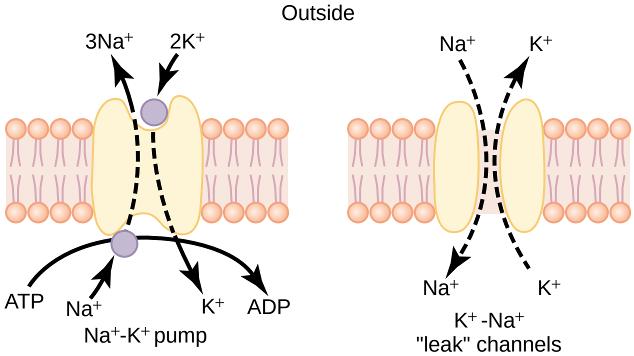


Figure 5–4

Functional characteristics of the Na^+-K^+ pump and of the K^+-Na^+ "leak" channels. ADP, adenosine diphosphate; ATP, adenosine triphosphate.

The Na^+-K^+ also causes large concentration gradients for sodium and potassium across the resting nerve membrane. These gradients are the following:

Na^+ (outside): 142 mEq/L
Na^+ (inside): 14 mEq/L
K^+ (outside): 4 mEq/L
K^+ (inside): 140 mEq/L

The ratios of these two respective ions from the inside to the outside are

$$Na^+_{inside}/Na^+_{outside} = 0.1$$
$$K^+_{inside}/K^+_{outside} = 35.0$$

Leakage of Potassium and Sodium Through the Nerve Membrane. The right side of Figure 5–4 shows a channel protein in the nerve membrane through which potassium and sodium ions can leak, called a *potassium-sodium* (K^+-Na^+) *"leak" channel.* The emphasis is on potassium leakage because, on average, the channels are far more permeable to potassium than to sodium, normally about 100 times as permeable. As discussed later, this differential in permeability is exceedingly important in determining the level of the normal resting membrane potential.

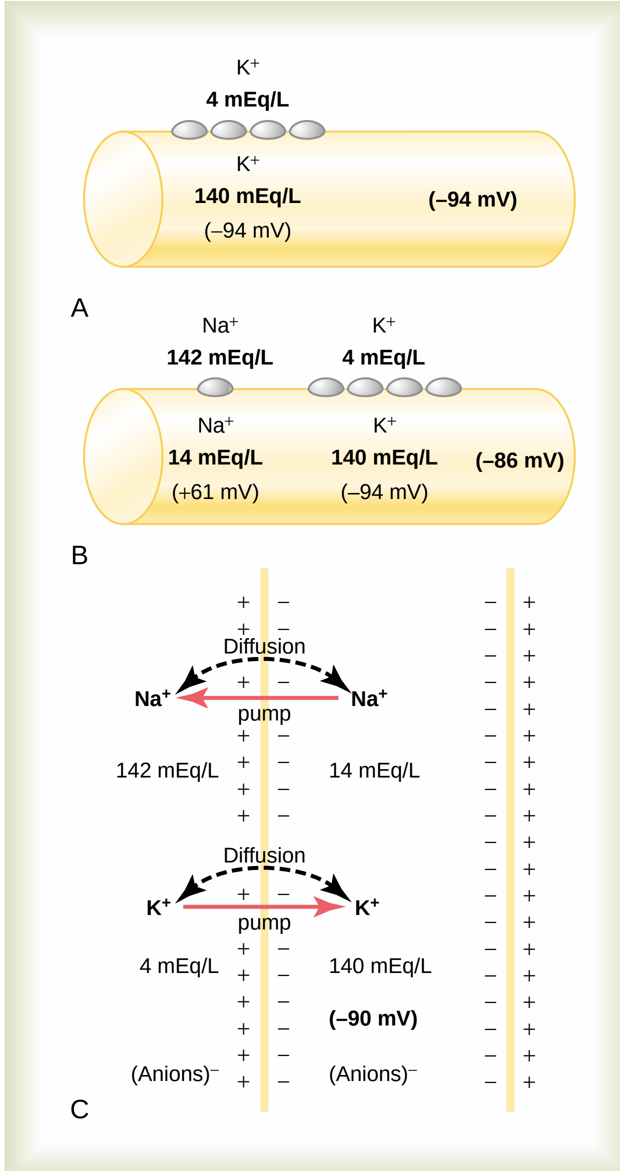


Figure 5–5

Establishment of resting membrane potentials in nerve fibers under three conditions: *A,* when the membrane potential is caused entirely by potassium diffusion alone; *B,* when the membrane potential is caused by diffusion of both sodium and potassium ions; and *C,* when the membrane potential is caused by diffusion of both sodium and potassium ions plus pumping of both these ions by the Na^+-K^+ pump.

Origin of the Normal Resting Membrane Potential

Figure 5–5 shows the important factors in the establishment of the normal resting membrane potential of –90 millivolts. They are as follows.

Contribution of the Potassium Diffusion Potential. In Figure 5–5*A,* we make the assumption that the only movement of ions through the membrane is diffusion of potassium ions, as demonstrated by the open channels between the potassium symbols (K^+) inside and outside the membrane. Because of the high ratio of potassium ions inside to outside, 35:1, the Nernst potential corresponding to this ratio is –94 millivolts because the logarithm of 35 is 1.54, and this times –61 millivolts is –94 millivolts. Therefore, if potassium ions were the only factor causing the resting potential, the resting potential *inside the fiber* would be equal to –94 millivolts, as shown in the figure.

Contribution of Sodium Diffusion Through the Nerve Membrane. Figure 5–5*B* shows the addition of slight permeability of the nerve membrane to sodium ions, caused by the minute diffusion of sodium ions through the K^+-Na^+

leak channels. The ratio of sodium ions from inside to outside the membrane is 0.1, and this gives a calculated Nernst potential for the inside of the membrane of +61 millivolts. But also shown in Figure 5–5*B* is the Nernst potential for potassium diffusion of –94 millivolts. How do these interact with each other, and what will be the summated potential? This can be answered by using the Goldman equation described previously. Intuitively, one can see that if the membrane is highly permeable to potassium but only slightly permeable to sodium, it is logical that the diffusion of potassium contributes far more to the membrane potential than does the diffusion of sodium. In the normal nerve fiber, the permeability of the membrane to potassium is about 100 times as great as its permeability to sodium. Using this value in the Goldman equation gives a potential inside the membrane of –86 millivolts, which is near the potassium potential shown in the figure.

Contribution of the Na^+-K^+ Pump. In Figure 5–5*C*, the Na^+-K^+ pump is shown to provide an additional contribution to the resting potential. In this figure, there is continuous pumping of three sodium ions to the outside for each two potassium ions pumped to the inside of the membrane. The fact that more sodium ions are being pumped to the outside than potassium to the inside causes continual loss of positive charges from inside the membrane; this creates an additional degree of negativity (about –4 millivolts additional) on the inside beyond that which can be accounted for by diffusion alone. Therefore, as shown in Figure 5–5*C*, the net membrane potential with all these factors operative at the same time is about –90 millivolts.

In summary, the diffusion potentials alone caused by potassium and sodium diffusion would give a membrane potential of about –86 millivolts, almost all of this being determined by potassium diffusion. Then, an additional –4 millivolts is contributed to the membrane potential by the continuously acting electrogenic Na^+-K^+ pump, giving a net membrane potential of –90 millivolts.

Nerve Action Potential

Nerve signals are transmitted by *action potentials,* which are rapid changes in the membrane potential that spread rapidly along the nerve fiber membrane. Each action potential begins with a sudden change from the normal resting negative membrane potential to a positive potential and then ends with an almost equally rapid change back to the negative potential. To conduct a nerve signal, the action potential moves along the nerve fiber until it comes to the fiber's end.

The upper panel of Figure 5–6 shows the changes that occur at the membrane during the action potential, with transfer of positive charges to the interior of the fiber at its onset and return of positive charges to the exterior at its end. The lower panel shows graphically the successive changes in membrane potential over a few 10,000ths of a second, illustrating the explosive onset of the action potential and the almost equally rapid recovery.

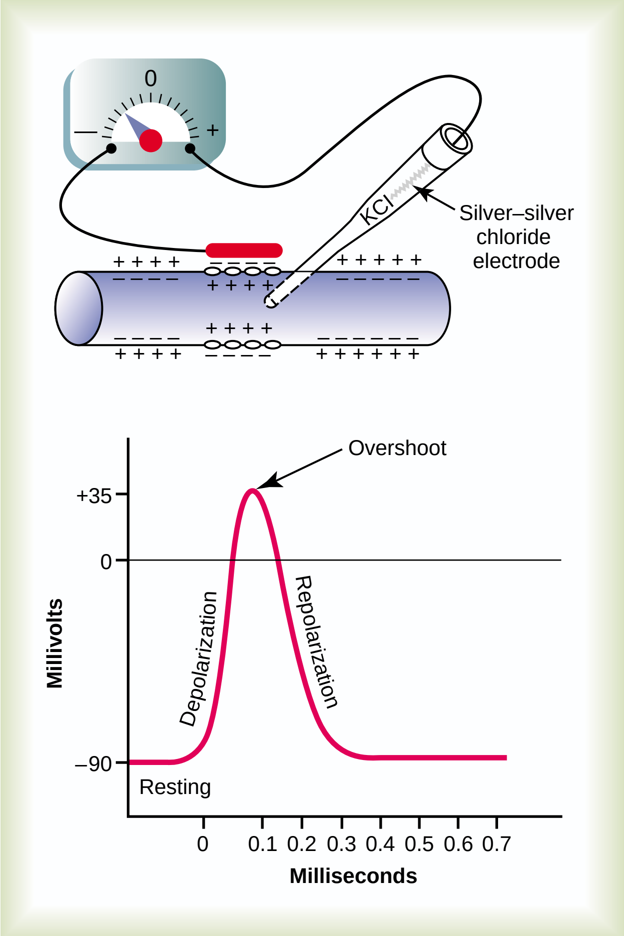


Figure 5–6

Typical action potential recorded by the method shown in the upper panel of the figure.

The successive stages of the action potential are as follows.

Resting Stage. This is the resting membrane potential before the action potential begins. The membrane is said to be "polarized" during this stage because of the –90 millivolts negative membrane potential that is present.

Depolarization Stage. At this time, the membrane suddenly becomes very permeable to sodium ions, allowing tremendous numbers of positively charged sodium ions to diffuse to the interior of the axon. The normal "polarized" state of –90 millivolts is immediately neutralized by the inflowing positively charged sodium ions, with the potential rising rapidly in the positive direction. This is called *depolarization.* In large nerve fibers, the great excess of positive sodium ions moving to the inside causes the membrane potential to actually "overshoot" beyond the zero level and to become somewhat positive. In some smaller fibers, as well as in