SPECIAL ARTICLE

The Electrical Potential Difference Across the Cell Membrane of Heart Muscle

Biophysical Considerations

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THE CELL MEMBRANE of mammalian heart muscle cells may be characterized by three interrelated observations. In the first place, the membrane separates an intracellular solution having a high potassium (K) and a low sodium (Na) concentration from an extracellular solution with a high Na and low K concentration. Secondly, K and Na ions can be shown with radioactive tracer technics to be continuously passing into and out of the cell; to do so, these ions must cross the cell membrane, which is therefore said to be permeable to them. In spite of the apparent permeability of the membrane to both Na and K, the intracellular concentrations of these ions are observed to remain remarkably constant. Finally, an electrical potential difference of 80 to 90 millivolts can be measured across the cell membrane of quiescent (noncontracting) heart muscle cells between an electrode in the intracellular solution and a similar electrode in the solution bathing the exterior of the cell. This electrical potential difference cannot be detected by measurements from the outside of intact cells as in the electrocardiogram. It may, however, be observed either as the "injury potential" of cells with damaged cell membranes or as the somewhat larger "resting potential" in cells whose cell membrane has been pierced with a microelectrode. The sign of the electrical potential difference across the cell membrane undergoes periodic reversals called "action potentials." The time course of the vectorial summation of such action potentials from many cells is reflected in the QRST complexes of the surface electrogram and conventional electrocardiogram.

Theory

The study of the electrical potential difference across ion-permeable membranes separating two salt solutions of different ionic composition is a province of physics and of physical chemistry, which attempt to formulate in mathematical terms an exact and rigorous description of the processes involved. The present article explains the same physical and physicochemical processes in nontechnical language in order to promote a better understanding of cell-membrane phenomena among clinical cardiac physiologists.

Since many aspects of the behavior of cell membranes can be reproduced experimentally with artificial membranes, it is useful to begin by inquiring how electrical potential differences may arise across such artificial membranes. To take an apparently simple model, consider two well-stirred reservoirs of equal and fixed volume separated by a porous partition or membrane (fig. 1a). Let the left reservoir be filled with a solution of potassium chloride (KCl) at a concentration of 200 millimoles per liter and the right reservoir with a KCl solution at a concentration of 5 millimoles per liter. Assume that movements of

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The electrical potential difference produced during diffusion of a KCl solution across a model membrane.

water through the porous partition are prevented. Only KCl can then move through the membrane. When dissolved in water, this salt separates into two particles of equal and opposite charge, the K and Cl ions. Each ion surrounds itself with a number of molecules of the solvent, water (the so-called hydration shell), and henceforth behaves as an independent molecule, an important restriction being that for the solution as a whole or any microscopic portion of it the sum of the K ions be always equal to the sum of the Cl ions.

The unequal partition of dissolved KCl on the two sides of the membrane will give rise to a redistribution of the dissolved salt by a random process called diffusion. Since the concentration of KCl in the left reservoir is initially 40 times as great as that in the right reservoir; there will initially be 40 times as great a tendency for KCl to diffuse from left to right as from right to left. As a consequence, a net movement of KCl from left to right is set up. This net movement will continue until the concentrations in the two reservoirs have become equal, i.e., until the gradient of concentration has been abolished by the transfer of KCl from left to right. If the positively charged K ions and the negatively charged Cl ions move through the membrane with equal ease, the membrane is said to be equally permeable to K and Cl. These positively and negatively charged particles will then pass together through the pores in the membrane, electrically neutralizing each other. The net movement of KCl will occur without a separation of positive from negative charge, and a device for measuring the electrical potential difference across the membrane will accordingly register zero volts while the diffusion is in progress (fig. 1b).

Suppose, now, the membrane is altered so that the passage of the Cl ion across the membrane is made more difficult than that of the K ion. Then, as K and Cl move from left to right under the force set up by the gradient of concentration, a thin cross-section of the membrane will show the advancing front of the net diffusion process to consist of the readily penetrating, positively charged K ions. These K ions will drag behind them by the force of electrostatic attraction the negatively charged Cl ions whose movement is impeded by the membrane (fig. 1c). KCl now diffuses as a dipole, oriented so that the positive pole...
(the K ion) is leading and the negative pole (the Cl ion) is following. A sufficiently sensitive voltmeter across the thin section of the membrane will indicate that the right face of the membrane is electrically positive with respect to the left face. The reading on the voltmeter reflects a separation of positive from negative charges such that the positively charged K ions are at a relatively higher concentration toward the right face of the membrane and the negatively charged Cl ions are more concentrated toward the left face. An electrical potential difference arising in this way is called a diffusion potential. It stems from the difference in the mobility within the membrane pores of the positive and negative ions of a salt diffusing through the membrane. The spatial separation produced by the membrane between the K and Cl ions need be very slight, a separation of a small fraction of an Angstrom unit involving only a small number of KCl molecules sufficing to generate a very appreciable potential difference. [One Angstrom unit (abbreviated Å = 10^{-10} meters = one ten billionth of a meter.)] A diffusion potential exists while an actual net movement of KCl through the membrane is under way. The existence of a diffusion potential and the fact that its magnitude can be shown to depend on the concentration of a given ion are therefore evidence that the membrane is permeable to that particular ion.

In the interaction between membranes and salts like KCl there is a continuous gradation in the degree to which the membrane restricts the movements of either positively charged ions (cations) or negatively charged ions (anions). At the one extreme, the membrane brings about no separation of positive from negative charge and no diffusion potential (fig. 1b); the mobilities of cation and anion in the membrane are equal. At the other extreme, the membrane is permeable only to ions of one charge (e.g., to the cation, K) and totally impermeable to ions of the opposite charge (e.g., to the anion, Cl). The separation of charge and hence the electrical potential difference produced are maximal (fig. 1d). Intermediate between these two extremes is the type of diffusion potential (fig. 1c) that corresponds to the situation at many cell membranes (See Appendix 1).

The three cases are summarized mathematically by the Nernst Equation. For the diffusion of a potassium salt at 37° C this equation takes the form

\[ V_m = \frac{u_+ - u_-}{u_+ + u_-} \times 61.5 \log \left( \frac{[K]_1}{[K]_o} \right) \]

in which \( V_m \) is the electrical potential difference across the membrane, \( u_+ \) and \( u_- \) are the mobilities (velocities per unit force) of K and Cl within the membrane, and \([K]_1\) and \([K]_o\) are the concentrations of K in the solutions on either side of the membrane (the "inside" and "outside" solutions, respectively). When the electrochemical mobilities of cation and anion are equal (\( u_+ = u_- \)), the fraction containing the mobility terms vanishes and \( V_m = 0 \). When the anion mobility in the membrane, \( u_- \), is zero (the membrane is impermeable to Cl), the \( u_+ \)'s cancel and \( V_m \) becomes equal to \(-61.5 \log (\frac{[K]_1}{[K]_o})\). Under these conditions \( V_m \) depends only on the ratio of the K concentrations in the solutions bathing the two sides of the membrane. Finally, if \( u_+ \) and \( u_- \) are unequal and neither is zero, \( V_m \) is the type of diffusion potential believed to exist across heart muscle cell membrane (See Appendix 2).

It is pertinent to consider next by what mechanisms a porous membrane may impede the diffusion of one ion of salt like KCl so as to bring about a separation of positive from negative charges and, hence, to set up a diffusion potential. Diffusion of ions through the membrane probably occurs via the water-filled pores in the membrane. A membrane may therefore be expected to impede the transit of ions of a size large compared to the diameter of its pores, while permitting the movement of ions whose diameter is relatively small. Figure 2 compares the hydrated ion diameters (the diameter of the ion plus the shell of water molecules that moves with it) of K, Na, and Cl with the diameter of the pores in the cell membrane of cat ventricular muscle. These pores have recently been shown to have a diameter not in excess of 8Å. It will be seen from figure 2 that the membrane might be expected on the basis of relative ion size to be more permeable to K and Cl ions.

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than to the larger Na ion. The diameters of the K and Cl ions, however, are sufficiently similar that the pores of the membrane cannot discriminate between them by virtue of their size. Since such discrimination is required in order to generate a diffusion potential, it is necessary to look for an additional mechanism for separating the positively charged K ion from its negatively charged ion partner.

In figure 3 a simplified model of a membrane pore is depicted as lined with fixed negative electrical charges, that is, with negatively charged molecules built into the substance of the walls of the pore. These fixed charges attract, by the force of electrostatic attraction, ions having an electrical charge opposite to their own charge, and repel, by the force of electrostatic repulsion, ions having the same charge as their own. The sites at which the fixed charge groups abut on the water-filled lumen of the pore become coated with oppositely charged ions from the solution, the counter-ions. Unlike the fixed charges themselves, counter-ions are free to exchange with other K ions in the solution. If the pore is wide enough (fig. 3a), the electrostatic effects of the fixed charges do not appreciably influence the diffusion of ions through the membrane. As the pore becomes progressively narrower, however, the fixed charges become increasingly effective in excluding ions of like sign (fig. 3b). At a certain critical pore diameter, only ions of opposite sign, in this case, K ions, can pass (fig. 3c). The existence of fixed charges in cell membranes is strongly suggested by their selective permeability to ions and by the finding that isolated membrane fragments contain lipid-carbohydrate-protein complexes with electrically charged lipid components.*

The nature of a diffusion potential has been discussed with reference to the two-compartment model of figure 1a in which a porous membrane separates a 200 mM KCl solution from a 5 mM KCl solution. It is apparent that with the passage of time the model will tend to run down, i.e., when both K and Cl can permeate, the diffusion will come to an end as the concentrations of KCl on the two sides of the membrane approach equality. What is required for a maintained diffusion and therefore for a maintained diffusion potential is a mechanism that continually replenishes the KCl concentration in the 200 mM reservoir and continually depletes the KCl concentration in the 5 mM reservoir. The rates of depletion and replenishment must be sufficient to keep up with the rate at which KCl diffuses from left to right, down the concentration gradient, through the pores in the membrane. Such a mechanism would set up a steady state in which, by some energy-consuming process, KCl is transported "uphill" against the concentration gradient from the 5 mM compartment into the 200 mM compartment as fast as it is lost from the 200 mM compartment by diffusion "downhill."

The situation is analogous to that of two lakes with different water levels separated by a leaky dam. For the purposes of this analogy, the difference in water levels is maintained by pumping water from the lower lake into the upper at a rate equal to that at which

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*Figure 2
Comparison of size of ions and water with pore size of cat heart muscle cell membrane.7, 34, 46 *Ion diameters include the hydration shell of the ion.
water leaks through the dam from the upper into the lower lake. The same pumping mechanism that maintains the difference of water levels also perpetuates the leak.

The cell membrane of heart muscle, in common with that of virtually all living cells, is the site of energy-consuming mechanisms for moving ions and other molecules against concentration and electrical gradients. These "uphill" processes, often referred to as "active transport," derive their energy supply from cellular metabolic reactions, most probably from the terminal high-energy phosphate bond of adenosine triphosphate. By contrast, the "downhill" diffusion, which the "uphill" processes serve to maintain, occurs spontaneously without the necessity for a special metabolic energy input, and such "downhill" diffusion is consequently termed "passive transport" (See Appendix 3). Unlike "downhill" diffusion, active transport does not occur through water-filled pores in the membrane. Instead, for the purpose of transport against concentration and electrical gradients, K and Na appear to combine at the membrane surface with certain molecules called carriers or, colloquially, "ion pumps," which are part of the substance (matrix) of the membrane itself. In heart muscle this combination, usually referred to as an ion-carrier complex, will have to remain hypothetical until it is chemically identified. In tissues in which such ion-carrier complexes have been more closely studied, they display many of the characteristics of enzymes.

**Experimental Approaches**

The theoretical considerations presented so far suggest that the ion permeability of heart muscle-cell membrane should be accessible to measurement by three experimental approaches. These include the measurement of intracellular ion concentrations and cell volumes, of the electrical potential difference across the cell membrane, and of the rate at which radioactively labeled ions pass through the membrane into and out of the cell.

Figure 4a shows the intracellular K and Na concentrations in papillary muscles from the right ventricles of cat hearts, immersed in a solution having the approximate K and Na concentration of cat plasma. It is apparent from the figure that the cell membrane is the site of a steep concentration gradient of 200 mM to 5.3 mM favoring the diffusion of K out of the cell, and an almost equally steep concentration gradient of 178 mM to 5 mM favoring the diffusion of Na into the cell. Now assume that the anion, Cl, will passively accompany any outward diffusion of K or inward diffusion of Na. Then, in terms of the model previously developed, the concentration gradients for K and Na produce a curious

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**Figure 3**

*Effect of fixed charges on permeability of membrane to ions. The schematically indicated pores are shown as lined with fixed negative electrical charges. KCl is diffusing from the 200 mM solution on the left into the 5 mM solution on the right. Modified after Sollner.*

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situation (fig. 4b), with the possibility of two oppositely directed diffusion processes setting up diffusion potentials of opposite algebraic sign. The electrical potential difference actually measured across the cell membrane will represent a summation of these two opposite diffusion potentials. Since only ions that can diffuse through the membrane can be effective in producing a diffusion potential, the relative contributions of K and Na to the electrical potential difference in heart muscle depend on the relative permeability of the cell membrane to these two cations (See Appendix 4).

Figure 5 illustrates an experimental method for comparing the K and Na permeabilities of the cell membrane of quiescent cat papillary muscle. The experimental procedure was to raise the K concentration of the solution bathing the external surface of the cell membrane approximately 10-fold by a mole-for-mole substitution of K for Na, keeping the total concentration (K + Na) constant. After a period of equilibration sufficiently long for completion of all net movements of ions and water, the cell volumes and intracellular ion concentrations of the muscle were determined. When K was substituted for Na in this way, the cells behaved as if they had been placed in a hypotonic solution, i.e., they took up water and swelled. Chemical analysis of the muscle revealed the intracellular K concentration to be unchanged, while the cellular water and K content had increased. The cellular uptake of K, Cl, and water shows that the cells are permeable to these three molecules. Looked at in another way, the experiment demonstrates that resting heart muscle is normally sufficiently impermeable to the Na ion for the extracellular Na to behave osmotically like an impermeant substance. Thus, when the external Na concentration is lowered to 133 mM, the deficit in tonicity cannot be made up by an equivalent concentration of K, since K, unlike Na, is an ion to which the cell membrane is readily permeable.

As previously stated, those ions to which the cell membrane is most permeable will contribute most significantly to the observed electrical potential difference across the membrane. Figure 6 illustrates the dependence of the electrical potential difference across the cell membrane of quiescent cat papillary muscle on the concentration of external K, shown by the experiments just described to be a relatively permeant cation. In figure 6, the full line is the value the potential difference should have if it depended only on the ratio of the intracellular and extracellular K concentrations according to the relation, $V_m = -59.6 \log([K]_i/[K]_o)$. The broken line connecting the experimental points indicates the electrical potential difference actually measured.

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**Figure 4**

(a) Intracellular and extracellular K and Na concentrations in resting cat papillary muscle. (b) Steady state model corresponding to (a). K and Na diffuse "downhill" through the pores in the membrane in the direction indicated by the solid arrows; they are returned "uphill" by an active transport mechanism located within the substance of the membrane.
Comparison of permeability of cat papillary muscle cell membrane to K and Na. Left: Cell volume and intracellular K concentration in solution with normal external K concentration; right: in solution with 10× normal external K concentration, made by a mole for mole substitution of K for external Na. Increase in cell volume exaggerated for illustrative purposes.

with the intracellular microelectrode technic. In this technic a glass electrode with a tip of less than 0.5 micron is introduced into the cell; the hole so made in the cell membrane is well sealed and small enough so that there is no significant admixture of intracellular and extracellular solutions. The observed potential difference is large at physiological (5.3 mM) and lower external K concentrations; it diminishes progressively as the external K concentration is raised, i.e., as the difference in K concentrations on the two sides of the membrane becomes smaller. At the higher external K concentrations the slope of the broken line approaches that of the theoretical line; at physiological and lower external K concentrations the experimental slope is much less steep than the theoretical, and the observed electrical potential difference is progressively less than that predicted from the ratio of the intracellular and extracellular K concentrations. These phenomena are conveniently interpreted in terms of the two-compartment model of figure 4b, which represents a summation of two oppositely directed diffusion processes setting up a potential difference whose magnitude depends on the relative permeabilities to K and Na. The experimental observation is that at low external K concentrations the electrical potential difference across the membrane does not depend solely on the outward diffusion of K. The membrane permeability to Na in the resting steady state, though small relative to that for K, is sufficiently important that the inward diffusion of NaCl contributes significantly to the potential difference.

A third method for characterizing the cell membrane is the measurement of the rates of movement of ions across the membrane by use of radioactive tracer technics. The rate of movement of an ion across a membrane is referred to as an ion flux; such a flux might be expressed, for example, as picomoles of K crossing unit area of cell membrane per unit time (pmol/cm² min). (One picomole = 10⁻¹² mole = one millionth millionth mole.) A sub-

**Figure 5**

Comparison of permeability of cat papillary muscle cell membrane to K and Na. 

- **Molar Concentrations:**
  - External K concentration: [K]₀ = 5 mM
  - External Na concentration: [Na]₀ = 178 mM
  - Intracellular K concentration: [K]ᵢ = 200 mM
  - Intracellular Na concentration: [Na]ᵢ = 200 mM
  - Specific solution concentration: [K]ᵢ/[Na]₀ = 183 mM

**Figure 6**

Dependence of electrical potential difference across the cell membrane of quiescent cat papillary muscle on external K concentration. The intracellular K concentration is constant at 200 mM. Experimental points connected by broken line are the values of the electrical potential difference obtained with the intracellular microelectrode technic. The solid line is the value the electrical potential difference would have, if it depended exclusively on the ratio of intracellular to extracellular K concentrations according to the relation $V_m = -59.6 \log ([K]_i/[K]_o)$ (temperature 27.5°C).
stance to which the membrane is permeable is continuously passing through it in both directions. Accordingly, the ion movement may be considered as made up of two components, one directed into the cell, called the influx, and one directed outward, called the outflux. The net flux, representing the difference between influx and outflux, determines whether the cell is gaining or losing the substance being traced. The net flux is zero in the steady state, an important special case in which the influx and outflux are equal, i.e., in which the rate of cellular accumulation equals the rate of loss. This condition, which prevails in the quiescent heart muscle cell, is necessary if the intracellular ion concentrations and the related electrical potential difference are to remain constant. In terms of the model of figure 4b, the Na influx occurs “downhill” with respect to electrical and concentration gradients; it must therefore in the steady state be equal to the Na outflux against the electrochemical gradient, and, similarly, the “downhill” K outflux must be balanced by an equal and opposite “uphill” K influx.

As indicated in figure 4b, the “downhill” fluxes of Na and K probably occur through water-filled pores in the membrane. Accordingly, these “downhill” movements may be expected to obey in a general way the physicochemical laws applicable to electrolytes in aqueous solutions. The “uphill” fluxes, on the other hand, appear to involve surface reactions with the substance of the membrane and obey a different set of physicochemical laws applicable to such surfaces. Consequently, the criterion of whether a particular ion flux obeys the physicochemical laws of aqueous solutions or of reactions at surfaces is useful in identifying the flux as passive or active. A detailed consideration of this and other criteria of active and passive transport, as well as of the carrier hypothesis of active transport, is beyond the scope of this article. It is, however, instructive to point out certain other characteristics of the energy-consuming “uphill” fluxes. An inadequate oxygen supply, inhibition of respiration with carbon monoxide or cyanide, failure to supply a substrate to act as a “metabolic fuel,” or the uncoupling of oxidation from phosphorylation with dinitrophenol, all inhibit active transport by depriving it of its energy supply. Similarly, the cardiac glycosides appear to interfere with active transport, possibly by competing with the ion transported for the site of combination with the carrier molecule. Regardless of the mechanism, interference with active transport reduces or abolishes the capacity of the cell to take up K and extrude Na in an “uphill” direction at a rate sufficient to compensate for the “downhill” diffusion of these ions. The consequent net cellular K loss and Na uptake result in a decreased intracellular K concentration and an increased intracellular Na concentration.

The Action Potential

The discussion to this point has dealt with the electrical potential difference during the steady state prevailing in quiescent heart muscle. It is expedient to consider next the disturbances of the steady state called action potentials, the clinical counterparts of which are the QRST complexes of the electrocardiogram. The experimental observations, obtained with the intracellular microelectrode technique, are comparatively simple (fig. 7). The electrical potential difference across the cell membrane of the resting mammalian ventricular muscle cell bathed in solutions having the same K concentration as that of plasma is between 80 and 90 millivolts, the interior of the resting cell being negative with respect to the extracellular solution. The action potential is propagated along the length of the heart muscle-cell membrane. The electrical potential difference across the membrane is observed to reverse its electrical sign, changing from its resting value of \(-80\) to \(-90\) mV to a value of \(+20\) to \(+40\) mV, the cell interior becoming positive with respect to the extracellular solution. After the initial reversal, the potential difference falls to its resting value with a delayed time course that results in the characteristic plateau configuration of the repolarization phase. It is instructive to
correlate these observations with changes in the permeability of the cell membrane to Na and K. The significant experiments on which this interpretation rests are the work of a pioneer Swiss physiologist, Sylvio Weidmann.21-27 Weidmann's contribution consisted of the application of the theory of Hodgkin and Huxley to Purkinje fibers from hearts of large mammals. This theory deals with the generation and conduction of the electrical impulse and was developed by Hodgkin and Huxley on the basis of extensive studies on giant nerve fibers of marine invertebrates.28

For a detailed account of the electrophysiological research on heart muscle growing out of Weidmann's observations, the reader is referred to the appropriate reviews.29, 30

The discussion that follows describes in simplified form the changes in electrical potential difference during the action potential in terms of the associated permeability changes. While changes in membrane permeability to ions can bring about alterations in the electrical potential difference, it is to be emphasized that changes in the electrical potential difference can themselves affect membrane permeability to ions.

In the steady state characteristic of resting heart muscle cells the predominant "downhill" cation flux through the membrane is an outwardly directed K diffusion, since the resting membrane is permeable to K and relatively impermeable to Na. Moreover, in this resting steady state there is no net ion current; the "downhill" outflux of K is returned by an equal and opposite K influx and the "downhill" influx of Na by an equal and opposite Na outflux. By contrast, the course of the action potential is characterized by temporary imbalances between influx and outflux for Na and probably for K. These imbalances are reflected by a transient cellular accumulation of Na early in the action potential and a probable transient cellular loss of K during the repolarization phase.

The beginning of the action potential is accompanied by a rapid increase of the permeability of the cell membrane to Na ions, so that it becomes much more permeable to Na than to K. This permeability change is observed whether the potential difference across the membrane is allowed to fall spontaneously to the threshold for all-or-none depolarization ("autorhythmicity") or is artificially lowered by passing an electric current across the membrane ("excitation") (See Appendix 5). Whatever the mechanism by which the increase in Na permeability is brought about, its result is a greatly augmented NaCl influx as the Na ion moves "downhill" along its electrochemical gradient. The permeability of heart muscle-cell membrane to Cl ions relative to that for Na can be shown to be rather small.13, 31, 32 Accordingly, the net inward diffusion of NaCl resulting from the sudden increase of Na permeability sets up a diffusion potential tending to make the intracellular face of the cell membrane positive with respect to its extracellular face. This reversal of sign of the electrical potential difference across the membrane means that for a given thin section of the membrane the advancing front of the net inward diffusion of NaCl is made up of positively charged Na ions, dragging behind them, by the force of electrostatic attraction, the relatively impermeant Cl ions. NaCl now diffuses inward through the cell membrane as a dipole, the positive pole (the Na ion) leading and the negative pole (the Cl ion).
following. Since the membrane at the beginning of the action potential has been altered to be many times more permeable to Na than to K, the outward diffusion of KCl at this time contributes comparatively little to the observed potential difference. Figure 8 is a comparison of the resting steady state and the first portion of the action potential with respect to the dependence of the electrical potential difference on the external Na concentration. The figure shows that in the resting state, when the membrane is relatively impermeable to Na, the potential difference remains unaffected by large changes in the external Na concentration. By contrast, during the early part of the action potential there is a marked dependence on the Na concentration, as indicated by the closeness with which the slope of the observed potential difference approaches the slope of the theoretical line \( V_m = -61.5 \log ([Na]/[Na]_o) \) for a membrane uniquely permeable to Na. The important differences in the permeability of the cell membrane in the resting state, during the early part of the action potential and during repolarization are summarized in table 1.

The spike of the action potential (fig. 7), corresponding to the increase in permeability to Na just described, is of short duration. The repolarization phase that ensues may again be analyzed in terms of “downhill” and “uphill” transport. Considering first the “downhill” processes, we see that the electrical potential difference can be caused to shift toward its resting value (intracellular solution negative) in either of two ways. A version of the increased Na permeability to the relatively low value prevailing in the resting state would reduce the net inward NaCl diffusion and therefore also the associated diffusion potential that makes the intracellular solution positive. Alternatively, even if the Na permeability remains high, a transient increase in the K permeability above that obtaining at the beginning of the action potential would give rise to a net outward diffusion of KCl. As described earlier, such a net outward KCl movement would generate a diffusion potential tending to make the intracellular solution negative with respect to the cell exterior. The studies of Weidmann suggest that the repolarization phase includes both a decrease in Na permeability and a transient net outward movement of K. A partial decrease in Na permeability appears to occur before the end of the spike, but the evidence as to whether the observed net outward KCl movement is due to an increased K permeability is inconclusive. Weidmann suggested in addition an explanation for the prolonged plateau phase of slow repolarization. During this phase the electrical potential difference is temporarily maintained at a value intermediate between its steady state value and the value at the time of the maximal depolarization (maximal intracellular positivity) at the end of the spike. The plateau is interpreted as resulting from an adjustment of the
Na and K permeabilities such that the diffusion potential set up by the inward net NaCl diffusion is temporarily approximately equal to the diffusion potential of opposite electrical sign generated by the net outward diffusion of KCl. Experimental evidence to support this hypothesis has so far proved difficult to obtain. The definitive determination of the magnitude and time sequence of the changes in cation permeability during repolarization, and their exact correlation with particular segments of the action potential remain as challenging unsolved problems.

"Uphill" transport during the repolarization phase includes the extrusion from the cell of Na that has entered during the period of increased Na permeability, and the uptake by the cell of K lost in any net outward K movements that may have occurred. The comparatively short duration of these transient permeability changes, as well as the relatively low membrane permeability to Cl, probably keeps cellular Na accumulation small and limits cellular K loss. Nonetheless, the Na gain and K loss must be reversed by transport against the electrochemical gradient. For this reason the portions of the action potential associated with restoration of the steady state should be sensitive to interference with the active transport mechanism, whether by oxygen lack, metabolic inhibitors, or digitalis glycosides. It is not known at what point in the repolarization sequence "uphill" transport processes become active, or whether restoration of the steady state is complete at the time the electrical potential difference has returned to its resting value.

The transient net ion movements associated with the action potential should be accompanied by net water movements, and therefore by changes in cell volume. Moreover, complexities in the structure of the cell membrane and in the biophysical properties of the extracellular regions of heart muscle raise the possibility of non-uniform ion distributions localized near the cell surface. When methods for the experimental measurement of such distributions are developed, it is
to be expected that the elementary scheme presented here may require modification.

Summary

The electrical potential difference across the cell membrane of heart muscle cells is a diffusion potential arising from the interaction of fixed charges within the membrane pores with NaCl and KCl diffusing into and out of the cell. The magnitude and sign of this potential difference depend on the relative permeabilities of the membrane to K, Na, and Cl. The resting membrane is predominantly permeable to K, while the action potential is characterized by a transient increase in Na permeability. An intracellular solution of high K concentration and low Na concentration is separated by the cell membrane from an extracellular solution having a low K concentration and a high Na concentration. These concentration differences are maintained by active transport processes that utilize the energy derived from cellular metabolic reactions to transport Na and K "uphill" against electrical and concentration gradients.

References


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Appendices

1. The electrical potential difference across a membrane may include, in addition to the diffusion potential described above, a contribution from so-called Donnan potentials due to fixed charges at the boundary of the membrane with the solutions on either side. In order to simplify the present discussion, such Donnan potentials are considered negligible.

2. The use of the K concentrations in this equation is an approximation. To be exact, the concentration terms [K] should be multiplied by a factor, γ, called an activity coefficient, the product γ [K] being defined as the activity of K in the solution. The activity may be thought of as an effective concentration, i.e., as that fraction of the total K concentration which is effective in producing an electrical potential difference. At the concentrations encountered in tissue fluids, the activity of ions is always less than their concentration. The usual flame photometric determination of K and Na [K] measures concentrations. The K and Na activities of solutions may, however, be measured directly with special K and Na glass electrodes, just as the activity of hydrogen ion is conventionally measured with a pH glass electrode.

3. In deciding for a given biological membrane whether the transport of a charged particle like the K ion is an “active,” “uphill” or energy-consuming process rather than a “passive,” “downhill” or spontaneous process it is necessary to take into consideration not only the gradient of concentration but also the gradient of electrical potential. Thus, movement of K from an extracellular concentration of 5 mM into a cellular solution at a concentration of 200 mM is “uphill” with respect to the concentration gradient; since the cellular solution is at a negative electrical potential compared with the extracellular solution, the transport into the cell of positively charged particles like the K ion is, however, “downhill” with respect to the gradient of potential. When both concentration and potential gradients are considered together for the simultaneous movements of K and Na, it appears likely that both these ions are actively transported in mammalian heart muscle. Throughout this paper the conventional assumption that the Cl ion is passively transported is followed. A consequence of this assumption is that in the steady state at 37°C the distribution of Cl ions between the intracellular and extracellular solutions can be predicted from the electrical potential difference across the cell membrane by the relation, $V_m = -61.5 \log ([Cl^+]/[Cl^-])$. For a discussion of the validity of this assumption, see Page.7

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4. An approximation commonly used to express these relative contributions is the equation developed by Goldman\textsuperscript{38} and by Hodgkin and Katz.\textsuperscript{39} If movements of Cl may be assumed to be passive, this equation takes the form,

\[ V_m = -61.5 \log \frac{P_K [K]_i + P_Na [Na]_i}{P_K [K]_o + P_Na [Na]_o} \]

in which \( V_m \) is the electrical potential difference across the cell membrane at 37°C. \([K]_i\) and \([Na]_i\) are the intracellular K and Na concentrations, \([K]_o\) and \([Na]_o\) the corresponding extracellular concentrations, and \(P_K\) and \(P_Na\) the permeabilities of the membrane to K and Na, respectively.

5. Changes in the apparently small electrical potential differences across cell membranes of excitable tissues may alter the permeability of the membrane to ions because the short distances across which such potential differences exist set up relatively large forces. The force acting on a charged particle in the membrane is called an electric field and may be approximated by the electrical potential difference divided by the thickness of the membrane. For an electrical potential difference of 100 mV across a cell membrane 100 Å in thickness this calculation gives a force of 100,000 volts per centimeter. In an electric field of this magnitude positively charged molecules within the substance of the membrane will tend to move toward the negatively charged face of the membrane and negatively charged molecules will attempt to migrate to the positively charged face. Since the charged molecules making up the substance of the membrane are fixed, they are prevented from moving in these directions. Such molecules, however, may have a certain amount of freedom to rotate about an axis. This freedom permits them to orient themselves so that their fixed charge groups tend to point toward the face of the membrane toward which they would migrate if they were free to move. Variations in the electrical potential difference may alter this orientation of fixed charges, suggesting a possible mechanism for permeability changes.

If our feeling constantly puts the question why, our reason shows us that only the question how is within our range; for the moment, then, only the question how concerns men of science and experimenters. If we cannot know why opium and its alkaloids put us to sleep, we can learn the mechanism of sleep and know how opium or its ingredients puts us to sleep; for sleep takes place only because an active substance enters into contact with certain organic substances which it changes. Learning these changes will give us the means of producing or preventing sleep, and we shall be able to act on the phenomenon and regulate it at pleasure.—CLAUSE BERNARD. \textit{An Introduction to the Study of Experimental Medicine}. New York, The Macmillan Company, 1927, p. 82.
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