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THE ROLE OF IONS IN MUSCLE EXCITATION AND CONDUCTION

RAYMOND E. FULLER, M.D.* and WILLIAM L. MORGAN, JR., M.D.*

The cell membrane is vital in establishing and maintaining an intracellular ion concentration that is different from that of extracellular fluid. Because of membrane selective permeability to ion flow, such gradients exist and are the basis for the electrical potentials generated within the membrane. In specialized tissues, such as nerve and muscle, the additional properties of excitability and conductivity are highly developed. Newer techniques, especially work with radioactive isotopes, have helped in understanding the action of ions in cellular physiology. It is the purpose of this paper to review the more recent theories of the role of ions in muscle excitation and conduction.

THE CELL MEMBRANE

The sarcolemma (cell membrane of muscle fiber) discussed here is not the inert histologic structure which encloses the cell. It is a living dynamic barrier that possesses properties of selective permeability.

The membrane itself is composed of a few layers of protein molecules overlying a thin layer of lipid material. The exact structure of the membrane has not been defined. Some believe it is sieve-like with pores of varying sizes, accounting for its selective permeability. Eyring and Parlin, on the other hand, describe the membrane as being composed of lipid material between layers of simple protein molecules, which are coiled into spirals. These protein spirals sit on either side of the thin lipid layer like upright barrels. In the resting state, the spirals orient themselves so that the positively charged amino end groups are directed toward the negative charge of the cytoplasm, whereas the negatively charged carboxyl end groups are directed toward the extracellular fluid.

The electron microscope reveals an outer reticulum of fine fibrils and an inner structureless membrane, the combined system being 100-200 A° in thickness. Ridges are also seen on the inner surface of the sarcolemma, to which the Z lines attach. Recently Huxley and Taylor have suggested that the transmission of membrane depolarization may be conveyed to the cell interior by means of these lines.

Although the structure of the sarcolemma has not been correlated with its function, the membrane demonstrates three main properties. There is (1) selective permeability to ions and other substances, and it is (2) the site of an electric potential as well as (3) a conductor of the wave of excitation.

It is believed that the sarcolemma obtains energy for its various functions from oxidative metabolism occurring within the mitochondria of the cell.

The membrane selects ions according to their size and charge. It therefore controls the quantity of ion movement (or flux), as well as their direction of flow. The membrane potential which governs this selectivity is in turn dependent on ionic gradients to maintain a resting potential. With a drop in the resting potential selectivity

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is decreased, and the membrane becomes more permeable. This change in potential (depolarization) initiates the contraction of the muscle cell as well as the propagation of the electrical charge along the length of the fiber.

SODIUM AND POTASSIUM FLUX

Deane and Smith found that in man the intracellular potassium ion concentration is 112 mEq./liter of intracellular water and the sodium ion concentration is 37.0 mEq./liter. Comparable concentrations occur in animals. Conway showed that half of the intracellular sodium in frog muscle is interstitial. The other half is located within the fibers as internal fiber sodium and external fiber sodium. The site of the external fiber sodium is thought to be the sarcolemma, where the proteins have a pH similar to plasma and therefore exhibit a preponderance of negative charges. Because of this, the sarcolemma could remove potassium and sodium ions by acting as a resin. Current theory argues that fluxes of sodium and potassium occurring with depolarization and repolarization of the membrane take place only in a limited area about the membrane.

Small ions pass the cell membrane with varying degrees of freedom. The critical size for rapid passage of cations is that of the potassium ion. Thus potassium and rubidium ions enter the cell at appreciably fast rates. Sodium and lithium are slower, because these hydrated ions are larger than the hydrated potassium ion. Potassium travels from 24-100 times more rapidly than sodium, depending on the state of the membrane. Anions such as chloride, bromide, and nitrate enter freely, but bicarbonate ions diffuse very slowly and sulfate ions are practically excluded. Calcium and magnesium may enter the cell by forming un-ionized complexes with organic compounds, but this may not be true when the membrane is depolarized.

THE SODIUM PUMP

For many years physiologists have been fascinated by the distribution of intracellular and extracellular sodium and potassium. Many theories have been postulated to account for the mechanisms involved in these ionic distributions.

The sieve theory of Boyle and Conway assumed that the selective permeability of the membrane was due to pore size alone and not to electrical charges. Therefore the membrane would be more permeable to the smaller potassium ion than the larger sodium ion.

Later, radioactive isotope studies showed that the cell is permeable to a great many so-called "impermeable" ions such as sodium, calcium, magnesium, phosphorous and lactate. The studies of Hodgkin and Horowicz, using radioactive Na^{24} and K^{42} , demonstrated an exchange of intracellular and extracellular cations. The sodium ion exchange was less than the potassium ion exchange in the resting state.

Ussing has tried to explain the above by his "exchange diffusion" mechanism in which a carrier system in the membrane transports sodium into and out of the cell. It is a coupled reaction so that as one ion is carried in, another is carried out. This does not, however, explain the low intracellular sodium. Ling in his "fixed charge hypothesis", has dispensed with the concept of an external membrane and maintains that the relative degree of ionic accumulation within cells depends on

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the comparative energies of adsorption of the various ions onto fixed charges of the intracellular proteins. Ions such as potassium are strongly adsorbed and accumulate to a greater extent than ions such as sodium, with a lower energy of adsorption. Russian authors believe that sodium is less soluble in the cytoplasm than potassium and that this accounts for the lower concentration of sodium in the cell.

The majority of investigators today believe that the basis of the low sodium concentration within the cell is due to two mechanisms: 1) the relative impermeability of the cell membrane to sodium, and 2) an active extrusion of sodium by a pumping mechanism. A sodium pumping mechanism is deemed necessary since sodium must be extruded from the fibers against both a concentration gradient and an electrical gradient.

Conway believes that the sodium pump utilizes a transport mechanism by means of a cytochrome system similar to the hydrogen ion transport in oxidative reactions. Evidence supporting this is that the net extrusion of sodium was completely inhibited by anoxia or cyanide in the immersion fluid. Critics of the sodium pump theory claim it would take a prohibitive amount of the cellular metabolism to supply the pump with energy. Lewis and Ussing had estimated this to be as high as 30%. Keynes, however, found that the sodium pump may only require 10% of energy available from resting metabolism. He also concluded that sodium efflux must be coupled with potassium influx in a cycle carrying a potassium ion in for each sodium ion leaving, thereby reducing total energy expenditure. Other evidence to support this is that low sodium efflux occurs in potassium-free solutions, whereas potassium-rich solutions cause increased sodium efflux with a proportionate increase in oxygen consumption.

Another concept of the sodium pump is that of Parlin and Eyring. According to them, sodium influx at the time of depolarization initiates a period of marked chemical activity forming a metabolite that acts as a carrier to transport excess sodium out of the cell. Sodium pumping therefore results from a union of sodium with this metabolite (P) to form NaP inside the cell. The NaP complex readily diffuses through the membrane and, being more concentrated inside the cell than out, causes a strong outward positive sodium current. The exact nature of the metabolite has not been defined, but Eyring and Dougherty suggest one candidate for the role of pump substance may be histamine.

THE RESTING MEMBRANE POTENTIAL

Classically the resting membrane potential has been explained by the marked difference in concentration between intracellular potassium (K_i) and extracellular potassium (K_o), in a Donnan equilibrium. This distribution of potassium probably occurs in all cells of the body and it reflects the selective permeability of the cell membrane for potassium.

Hodgkin and Huxley postulated that the resting potential is the result of a dynamic type of Donnan system in which the potassium ratio (K_i/K_o) is secondary to the existence of a sodium pump. Grundfest also accepted the importance of the sodium pump and further postulated that the resting potential is generated by the

membrane itself. He believed that the resting potential due to the Donnan system *alone* is not tenable and that it must be due to other mechanisms. Some of the evidence he presented follows: 1) The resting potential is found experimentally to be consistently lower than that calculated on the basis of the Donnan ratio. 2) In nerve isolated 10-18 hours, one observes considerable potassium loss and sodium gain, but the resting potential remains the same. 3) Large alterations in intracellular potassium and chloride by microinjection into the squid giant axon did not affect the resting potential until the membrane metabolic activity was disturbed resulting in a decreased action potential and blocked wave propagation. 4) Similar experiments that varied the external potassium concentration led to an alteration in resting potential only after the occurrence of changes in concentration sufficient to alter membrane metabolism.

THE ACTION POTENTIAL

The action potential is associated with a drop in the resting membrane potential below a critical level. When the resting potential is caused to fall below this level, either by an external current or by depression of certain metabolic activities (i.e., the sodium pump), the membrane becomes much more permeable to sodium, potassium, and chloride and these ions flow in the direction of their concentration gradients.

Nachmansohn and others have presented evidence that acetylcholine may be responsible for the increased sodium permeability of the nerve cell membrane. In the resting state acetylcholine is bound to protein or lipoprotein. They postulate that with excitation acetylcholine is released from the binding site and attaches to receptor proteins in the membrane. This combination would change the configuration of the protein and increase the permeability to allow sodium ion influx.

A relatively large influx of sodium ions produces a positive inward current and is thought to be responsible for the sharply rising action spike in the monophasic tracing and the QRS complex in the standard EKG (Hodgkin & Huxley, Keynes). As seen in the diagram, the action spike overshoots the base line, the overshoot actually being a reversal of polarity within the cell from negativity during the resting state to positivity during the height of the positive sodium influx.

During the descending limb of the action potential there is an outflow of potassium ions which initiates the return of the membrane to the resting state. This positive outward potassium current reduces the positive charge within the cell, therefore helping to restore resting membrane potential and decreases the membrane permeability to sodium. Cardiac muscle differs from skeletal muscle and nerve in that the action potential is from 10-100 times longer (up to 300 msec.). This is probably due to the delayed potassium outflow during the early phases of the action potential and slower sodium efflux with a resultant slower recovery phase. Wilde, by means of radioactive tracer studies, showed that the potassium efflux in the slowly beating turtle heart reached its peak coincident with the end of the T wave. As the action potential terminates, the decreasing membrane permeability to sodium influx and the extrusion of sodium by the pump mechanism complete the restoration of the resting membrane potential.

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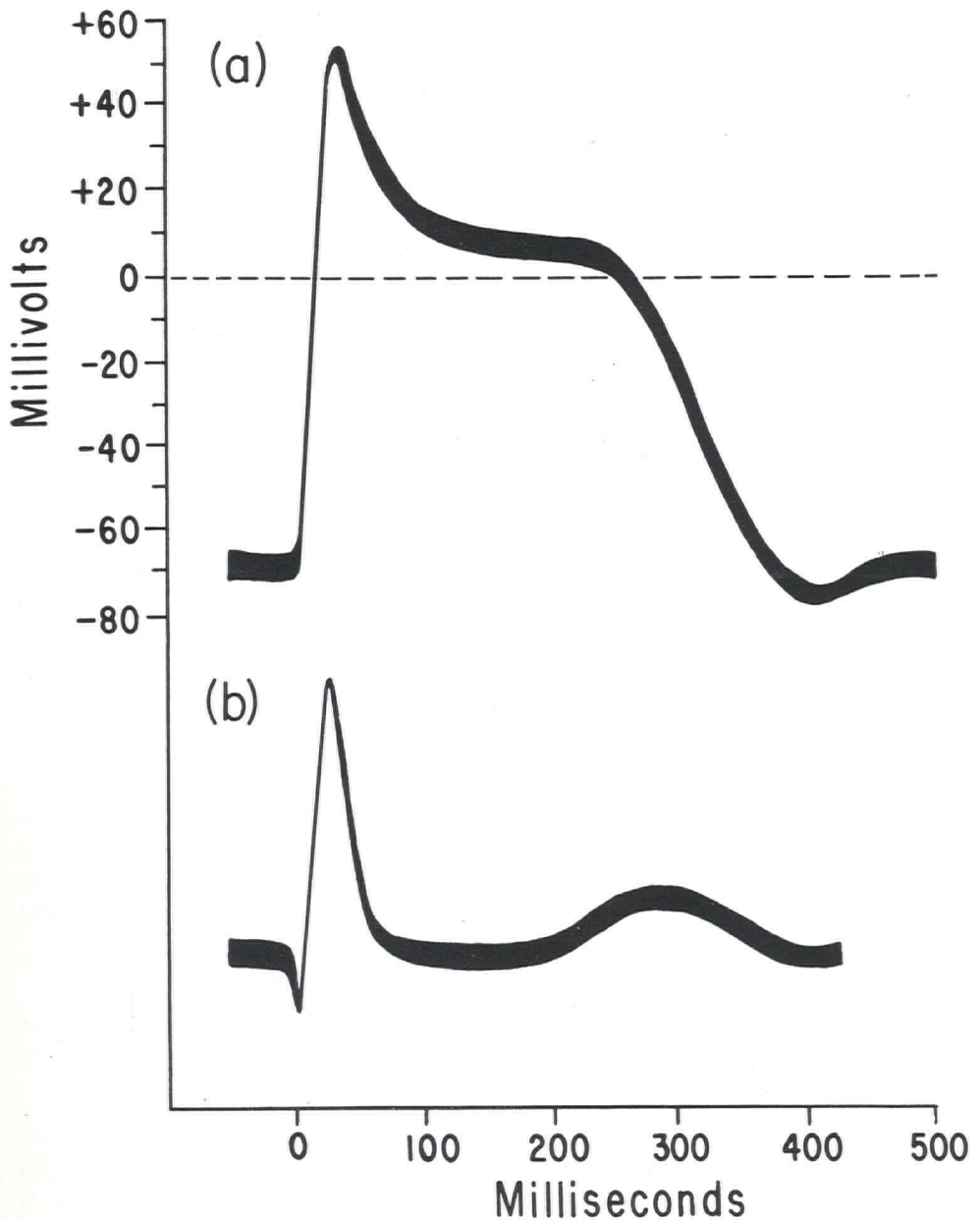


Diagram of a transmembrane action potential (a) as correlated with the standard electrocardiogram (b).

Since the action spike is due to the inward sodium flux, the height of the action potential is dependent on the extracellular sodium concentration. The rising limb becomes lower with decreased concentrations of extracellular sodium. The frog ventricle becomes inexcitable when the extracellular concentration of sodium is reduced to 15% of normal.

As is shown above, the potassium ion plays an important role in the later events of the monophasic action potential and in the generation of the T and possibly U waves of the EKG. At higher extracellular potassium concentrations the action potential is shortened, and the converse applies with below normal concentrations. The effects are twofold: 1) increased external potassium concentration leads to a greater concentration of ions within the cell resulting in a greater potassium efflux during repolarization, and 2) higher external potassium concentrations also cause increased efflux of sodium by coupled ion transport so that the rate of repolarization is increased, thus shortening the duration of the action potential (Keynes).

Calcium antagonizes the effects of potassium. This may be due in part to its influence on membrane permeability. Cardiac rate and excitability are known to be depressed by calcium, vagal stimulation, and acetylcholine. This may be related to their depressing influence on the threshold potential of the membrane at pacemaker areas. In these areas throughout diastole or in presystole there is a gradual reduction (loss) of resting potential until a threshold is reached where rapid sodium influx occurs, thus producing spontaneous depolarization. In isolated frog's heart, Hutter and Trautwein were able to increase the resting potential by vagal stimulation so that the threshold level was not reached, thus producing asystole. Others were able to increase membrane resting potential by as much as 33 mv by vagal stimuli.

Certain compounds stabilize the membrane and "lock" polarization. This results in a cell that does not conduct an impulse but which remains excitable by maintaining its resting potential. Weidmann demonstrated these effects with local anesthetics on Purkinje fibers. In addition to local anesthetics such as procaine and procaine amide, certain antihistamines and quinidine act as blocking agents.

Digitalis profoundly affects the membrane in cardiac muscle, and indeed this may be its principal effect in cardiac tissue. Stutz, et al., found that it did not affect the resting potential but affected the action potential by diminishing the amplitude of depolarization with loss of overshoot and shortened repolarization. Digitalis therefore may affect the fluxes of both sodium and potassium.

ROLE OF THE MEMBRANE PHENOMENA IN MUSCLE CONTRACTION

It appears well established that the intracellular events in muscle contraction are initiated by the depolarization of the membrane. Exactly how this occurs, however, has not been delineated. Several theories postulated are outlined below.

Some investigators believe the flux of sodium and potassium cause an activation of the actomyosin-Mg-ATP complex by liberating bound magnesium which catalyzes the hydrolysis of ATP. The rate of hydrolysis of ATP by actomyosin in situ is determined by the level of free magnesium in the sarcoplasm. With optimal levels of free magnesium the rate of ATP hydrolysis increases with resultant muscle contraction. Relaxation is produced when hydrolysis of ATP is inhibited by the binding of free magnesium to organic compounds, such as the Marsh-Bendall factor.

Another theory can be postulated for the sodium and potassium flux as related to muscle contraction. Sodium stimulates the dephosphorylation of ATP and ADP in the presence of magnesium. This would result in muscle contraction.

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Others have proposed that the entry of calcium during membrane depolarization initiates contraction of the muscle fibers. Microinjection of minute amounts of calcium produces contraction. Bianchi and Shanes have shown by using radioactive Ca^{45} that there is a 30-fold greater influx of calcium during activity than at rest. Calcium is apparently released from binding sites in the membrane during depolarization and enters the cell. It may be that "tubules" seen within the Z lines carry the calcium to the cell interior and the calcium then diffuses longitudinally along the I bands. Hodgkin and Keynes demonstrated that microinjected Ca^{45} did not diffuse through the sarcoplasm and that intracellular calcium was in bound form. An alternate explanation to calcium diffusion would be that influx of calcium creates a chain reaction by releasing calcium held in metastable form along the "tubules" and within the cell.

Despite the recent rapid advances in electrophysiology and microtechniques, only vague outlines of the mechanism of ion transport and muscle contraction are becoming apparent today. Much work remains before a clear understanding of cellular events is at hand.

SUMMARY

1) The muscle cell membrane possesses properties of selective permeability, excitability, and conductivity.

2) The sarcolemma exhibits a resting potential which governs its permeability to ions. This potential in turn is due to the ionic gradients.

3) The high intracellular potassium concentration and the low intracellular sodium concentration is explained by the relative impermeability of the membrane to sodium and the active extrusion of sodium from the cell (sodium pump).

4) The action potential occurs when the cell membrane becomes highly permeable to sodium ions, causing a positive sodium inward current. Repolarization follows with a positive outward current of potassium ions and a decreasing membrane permeability to sodium. The final restoration of the resting potential occurs with the active extrusion of sodium.

5) Several theories have been postulated to relate membrane depolarization to the initiation of muscle contraction.

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