Excitation-Contraction Coupling and Digitalis

THE PRIMARY task of heart muscle is to develop force and shorten at regular intervals. The action potential is the initial step in triggering contraction of the heart, and it may also be an important regulator of contraction strength. The process that links this membrane electrical event to the contraction is given the broad name of excitation-contraction coupling. The more we have increased our understanding about the events leading to muscle contraction, the more we can see that excitation-contraction coupling is not a simple event, but is a complex sequence of steps. This complexity is important because it endows the process with the flexibility to adjust strength of contraction over a wide range. At the same time, the complexity leads to two other characteristics that are less desirable. It makes the process more susceptible to dysfunction, so that abnormalities of excitation-contraction coupling could play an important role in failure of the heart in disease states. And the complexity has also made excitation-contraction coupling difficult to study experimentally. Nevertheless, a number of recent observations in skeletal and in heart muscle provide the basis for improved understanding of this important regulator of contraction.

If one arbitrarily divides the entire active muscle process into three parts, one can identify excitation as the action potential, contraction as the process of force development and shortening, and the steps in between as coupling. The action potential results from a sequential alteration of permeability of the cell membrane to ions in the extracellular solution. The dominant events are movement of sodium ions into and potassium ions out of the cell, but other ions participate in ways not yet entirely settled. Of special importance to our discussion is the possible transmembrane movement of calcium ions. Physiologists have succeeded in showing that some properties of the action potential, including the change in membrane resistance and the inward flow of sodium ions, are not directly related to triggering contraction. The most clearly defined event that correlates with contraction is simply depolarization of the surface membrane.1

Actual force development and shortening are the results of interaction of the proteins actin and myosin. This interaction requires ATP, and is regulated by at least two other proteins—tropomyosin and troponin. In the presence of tropomyosin and less than 10⁻⁷M calcium ions in the myoplasm, troponin inhibits the actin-myosin interaction, permitting the muscle to be relaxed. The inhibition is removed when calcium ions bind to troponin. An increase of free calcium ions in the myoplasm, which can be bound to troponin, may be considered the final link in excitation-contraction coupling. The major question about coupling is how membrane depolarization makes calcium ions available for binding to troponin.

Membrane depolarization could lead to an increase in the concentration of intracellular calcium ions either by a release of calcium from an intracellular store or by a change in the membrane permeability to calcium, so that it enters from outside the cell. In skeletal muscle it seems clear that calcium ions must be maintained in an intracellular store, from whence they can be mobilized again and again for repetitive contractions. This conclusion is partly based on the fact that the skeletal muscle cell can continue to contract and relax when the extracellular calcium ion concentration is very low. For many reasons, we can suggest that most of the intracellular calcium in skeletal muscle cells is stored in the terminal cisternae of the sarcoplasmic reticulum, which are membrane-lined sacs located just beneath the cell membrane that lines the transverse tubular system.

The source of the calcium used for contraction in heart muscle is not so clear. Contraction in heart cells depends strongly on the presence of calcium ions extracellularly but the relationship is a complicated one.2 The cellular exchange rate of isotopic calcium is greater in heart muscle than in skeletal muscle, and it is changed by factors altering contraction strength. However, the amount of calcium entering the heart cells with each beat, judged by isotopic tracer studies, appears to be too
small to activate the contractile proteins directly. A distinction probably should be made regarding the instantaneous effect of extracellular calcium ion on a single contraction and its effect after prolonged exposure of a beating muscle to that calcium ion concentration.

The apparently small influx of calcium per beat may be reconciled with the dependence of contraction on extracellular calcium ion concentration by the concept that heart muscle depends primarily on an intracellular pool of calcium, but that this pool is quite labile. Contraction strength for an individual beat would depend on the amount of calcium in the pool and the fraction of the pool that is released by the action potential. The amount in the pool would also vary from beat to beat, depending on the loss and gain of calcium by this pool.

One of the most important recent observations in excitation-contraction coupling of mammalian heart muscle is the identification of a transient membrane current that may be calcium ion movement. This current has been seen under voltage clamp conditions in atrial and ventricular muscle and Purkinje fibers. It depends on the presence of calcium ions in the external solution and is blocked by manganous ion, which blocks calcium currents in crustacean skeletal muscle. In order to distinguish the current from sodium ion movement (which would lead to a current in the same direction), sodium ions are removed from the solution or the sodium channel is blocked by tetrodotoxin. In both cases the current associated with calcium remains. This presumptive calcium current rises to a peak by about 40 msec after the membrane is depolarized beyond the threshold for this current, and it then decays over several hundred milliseconds, much like the time course suggested by mechanical measurements for "active state" in heart muscle. The magnitude of the current is increased by exposure to sympathetic amines.

If this current indeed represents entry of calcium ions from the extracellular solution, it might directly activate contraction. The amount of calcium needed is not entirely certain but it is in the range of 50–60 μmoles per kg muscle for full activation. The currents measured by several laboratories are smaller than this, but not so small as to rule out direct activation. The size of this current is graded by the magnitude and duration of voltage steps and by the frequency of depolarizations. So far, a one-to-one correspondence between the size of the current and its associated contraction has not been found. This failure may be for technical reasons. The current is small, and imperfections in spacial uniformity of voltage control could alter its magnitude. In addition, other currents—sodium and chloride currents—are changing at the same time, and this overlap makes quantitation difficult. On the other hand, the current could be both a partial source of the activating calcium ion and a trigger for release of intracellular stores of calcium. This effect of calcium as a trigger for release of calcium from the sarcoplasmic reticulum has already been demonstrated for skeletal muscle under some conditions. One would not expect a one-to-one correspondence of the current with force of contraction if this were the case, because the intracellular source would make available variable amounts of calcium under different conditions.

This "activating current" is probably a key step in excitation-contraction coupling in heart muscle. Its characterization is likely to provide the means for unravelling the entire ionic and molecular events leading from excitation to contraction. However, there are a number of problems facing the investigators working with this current. As already mentioned, achievement of a sufficiently uniform voltage clamp in heart cells is tedious and difficult. Each investigator is obligated to demonstrate the quality of clamp control in his hands under the conditions of his experiments. Second, the increase in calcium ion concentration in the cell alters its chemical driving force for movement of calcium across the membrane, so that calcium permeability is difficult to estimate from measuring membrane currents. Indeed, compartmentalization of calcium within the cell may exaggerate this problem. Since a rise in intracellular calcium ion cannot yet be directly measured in heart muscle, as it has in barnacle muscle and squid axon, tension must be used as a physiologic indicator of myoplasmic ionized calcium concentration. However, the quantitative relationship between tension and calcium ion concentration is not known and may be quite nonlinear.
It is possible that the activating current seen in the voltage clamp is not the result of calcium ion movement from the extracellular space at all. If the calcium ions were bound or sequestered in the sarcoplasmic reticulum, and were released into the myoplasm on activation, this would represent a large addition of positive charge to the myoplasm. The current would still be measured in the voltage clamp because it would be counteracted by the offsetting current of the voltage clamp circuit, keeping the transmembrane potential at the set value. Yet the calcium ion movement would be from the sarcoplasmic reticulum—an intracellular structure—rather than the extracellular space. This discharge of calcium could be provoked by a voltage shift across the sarcoplasmic reticular membrane or by a threshold quantity of calcium, and might resemble a graded action potential of the sarcoplasmic reticular membrane. The sarcoplasmic reticular space would be hyperpolarized as a consequence of loss of calcium, and some other positive ions, such as hydrogen, potassium or sodium ions, would presumably be taken up. Calcium ions might enter the space from the extracellular solution through the special junction between the sarcolemma and the terminal cisterna. Such a mechanism for producing the activating current would make it exceedingly difficult to study quantitatively, since neither the concentration of calcium ions in or bound to the sarcoplasmic reticulum nor its transmembrane potential can be measured.

As discussed in a recent review in this journal by G. A. Langer, the mechanism of action of digitalis is closely associated with excitation-contraction coupling, and may involve the calcium regulatory system. The best explanation for digitalis action now available is its effect on intracellular sodium ion concentration and the consequent effect of the sodium ion on calcium ion influx. However, it is also quite possible that digitalis changes the activating current. Such a mechanism could bring together some of the mechanical and electrical effects of digitalis into one common step. Digitalis could change activating current by modifying the membrane’s permeability to calcium. But it could also change the current by alteration of the amount of calcium available for release from the intracellular pool.

Whatever the effect of digitalis on the activating current, it seems clear that studies of this current will occupy the attention of physiologists for some time. And the current may indeed be the event that is most likely to deserve the name excitation-contraction coupling. If its physiologic role can be defined, an excellent tool will be available to examine directly the question of whether diseases of the myocardium depress function by effects on excitation-contraction coupling.

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Circulation. 1973;47:5-7
doi: 10.1161/01.CIR.47.1.5
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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