Excitation-Contraction Coupling and Control of Cardiac Contractility

EARLY WORK ON MUSCLE led to the discovery of the chemical basis for muscular contraction: The contractile protein actomyosin was discovered, ATP was established as the energy source for contraction, and the enzymatic activity required for utilization of ATP was localized to a portion of the actomyosin. Recent advances may offer insight into the control of muscular contraction, that is, the way in which contractile activity is turned on and off and how its intensity is graded.

The basic mechanism of muscular contraction can be studied in the test tube. It is well known that if ATP is added to a protein suspension of actomyosin in the presence of magnesium and calcium shortening of the actomyosin occurs. These constituents are all present in intact resting muscle, but their interaction which leads to contraction does not occur until the cell is excited by an electrical or nervous stimulus. The question of so-called excitation-contraction coupling can be asked in two ways: How is muscle maintained in a state of rest despite the presence of all of the ingredients for contraction? And what, upon excitation, induces the change from rest to activity?

Recent studies on skeletal muscle have provided an answer to the first half of the question. Although the amount of calcium in the cell is considerable, the concentration of ionic calcium in the immediate environment of the contractile protein is extremely low, approximately one tenth that required for contractile activity. This is the result of the presence of intracellular organelles called "relaxing factor vesicles," which sequester calcium. These tiny vesicles possess a limiting membrane (analogous to a cell membrane) across which calcium is actively transported from cell cytoplasm into the interior of the vesicle. The calcium required for contraction is thus not available to the resting muscle, though it is anatomically very close by within vesicles distributed in proximity to the contractile protein. Since the ionic calcium surrounding the actomyosin is insufficient for contraction, it follows that the penultimate event in the activation of contraction must be a local increase in ionic calcium. It has been postulated that this is effected by a sudden release of calcium from the vesicles, though there is no direct evidence in support of this. The current hypothesis is that excitation of the muscle leads to a sudden release of calcium from the vesicles, thus permitting contraction to occur. This is followed by resumption of calcium uptake by the vesicles so that relaxation ensues.

Although local increase in the concentration of ionic calcium appears to be necessary for activation of contraction in heart muscle as well as in skeletal muscle, at least part of
the activating calcium enters the cardiac cell from the external medium rather than from the intracellular vesicles. It should be understood that the extracellular ionic calcium concentration is more than 1,000 times that in the cell interior, that chemical forces, therefore, strongly favor movement of calcium into the cell, but this is prevented by the cell membrane through which calcium cannot diffuse freely. When cardiac muscle is stimulated, the permeability of the cell membrane to calcium increases transiently so that extracellular calcium can diffuse into the muscle. This calcium is essential for contraction in the heart; none occurs in the absence of extracellular calcium. Furthermore, the magnitude of the contractile response appears to depend on the amount of calcium which enters during the period of membrane depolarization. This amount can be increased when the external calcium concentration is increased\(^6\) or when the duration of depolarization is prolonged\(^7\); either intervention leads to an increased contractile response. Completion of the contraction cycle with a return to the resting state must be accompanied by removal of the calcium which entered the cell. This requires an active transport system in the cell membrane which returns the activating calcium to the extracellular fluid.

The foregoing is not meant to suggest that the relaxing factor vesicles are unimportant in heart muscle. They are present in heart muscle and may play an essential role in excitation-contraction coupling, particularly since the amount of extracellular calcium which enters during excitation is only a fraction of the total thought to be necessary for full activation of the contractile protein.\(^8\) However, the point to be emphasized is that in the heart the vesicle system alone is not sufficient: Influx of extracellular calcium is required, and the magnitude of the influx influences the strength of the ensuing contraction.

The contrast between skeletal and heart muscle is now apparent. In skeletal muscle the activating calcium is thought to be released from specialized intracellular vesicles and is reaccumulated by them in each contraction-relaxation cycle. The muscle is a self-contained unit which can cycle independently of the external medium. In fact, contractions can be evoked in bathing media containing negligible amounts of calcium.\(^9\) The function of the relaxing factor vesicles and their membranes across which the intracellular calcium movements occur are doubtless critical for normal skeletal muscle function. On the other hand, in heart muscle the cell membrane itself also plays a critical role, since at least part of the activating calcium crosses this membrane from extracellular fluid to cell interior and is subsequently pumped out again to complete each cycle. Furthermore, not only is extracellular calcium essential for activation, but changes in extracellular calcium concentration cause changes in the strength of contraction. It is apparent that excitation-contraction coupling and gradation of contractile response are closely related in cardiac muscle.

One would, therefore, expect to find mechanisms in the intact animal for regulating cardiac contractile force by altering the amount of calcium that enters the cell during activation. Cardioglobulin, a plasma protein system which increases contractility of isolated cardiac muscle, may qualify for this role by releasing its protein-bound calcium into the cell.\(^10\) The system may be important for maintenance of normal cardiac contractility.\(^11\)

Regulation of contractile response through the amount of calcium entering the cell during activation could be accomplished in other ways. For example, there could be control of the extent of increase in cell membrane permeability to calcium occurring during excitation. Disturbances in control mechanisms, leading to impaired regulation of myocardial contractility, may be the basis for certain types of congestive heart failure. The importance of cell membrane and relaxing factor vesicles in excitation-contraction coupling provides a new frame of reference.
for the study of these unsolved clinical problems.

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References

The Value of Hypothesis

Now I do not regret these hypotheses, or even the titles of the papers; because they have set people (including myself) thinking and devising new experiments. That indeed is the chief purpose of hypotheses. I have long believed, and am still inclined to believe, that all theories of muscular contraction are wrong. But they have been very useful in stimulating new research. In fact many of the best theories are self-destructive, by provoking fresh inquiry and leading to new facts which they cannot explain. The only useless theories are those that cannot be tested and can "explain" everything.—Archibald Vivian Hill: Trails and Trials in Physiology. Baltimore, The Williams & Wilkins Co., 1965, p. 362.
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