The Contractile Structure of Cardiac and Skeletal Muscle

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Previous findings that have led to the 'sliding-filament' model for striated muscle are reviewed, together with some recent observations on isolated filaments produced by a new procedure. The basic structure of the contractile apparatus in skeletal and in cardiac muscle appears to be identical. The relation between certain special features of cardiac muscle and its structure is discussed.

I SHOULD LIKE first of all to review very briefly the picture we now have of the fine structure of striated muscle. This will be very familiar to many people here, but I hope to mention one or two new pieces of evidence to maintain their interest. It will be useful to set out this picture again, I believe, since many of its features are established with a rather high degree of certainty and have been accepted by its original opponents; it is therefore likely to be both profitable, and fairly correct to think of muscles in these terms when trying to explain their various properties. The features I shall describe appear to be common to both cardiac and skeletal muscle.

Review of Structural Observations

The starting point in describing the fine structure is the well-known appearance of the cross striations in these muscles, illustrated in figure 1. This shows the characteristic alternation of dark and light bands along each of the myofibrils, the dense A-bands, and the less dense I-bands. The I-bands are bisected by the dense Z-line, and the A-bands often show a less dense zone in the center, known as the H-zone. The myofibrils are also composed of longitudinal filaments, and, when very thin sections are examined (fig. 2), it becomes evident that it is the arrangement of the filaments that gives rise to the pattern of striations, as Dr. Jean Hanson and I suggested on the basis of light-microscope observations and the earlier electron micrographs.1 There are 2 types of filaments present, organized into a series of overlapping arrays along each fibril, arrays of thicker filaments forming the A-bands and arrays of thinner filaments being present in the I-bands. The thinner filaments extend into the A-bands but at rest length do not quite reach to the center, leaving there, as a result, the somewhat less dense H-zone. The thick filaments have a diameter of about 100 Å and lie in a hexagonal array about 450 Å apart; they are each about 1.5 microns long, the length of the A-band. The thin filaments are about 50 Å in diameter and extend approximately 1 micron on either side of the Z-line. At resting length, each sarcomere (Z to Z) is about 2.3 microns long, so the width of the H-zone is approximately 0.3 micron.

Cross-bridges extend between the thick and thin filaments. Each thin filament is connected to each of its 3 neighboring thick filaments by a bridge every 400 Å along the length of the overlap region, giving it a total of about 54 bridges at resting length. The total number of bridges in 1 cc. of muscle is of the order of $5 \times 10^{14}$. It is very plausible to suggest that the bridges provide a means by which chemical and mechanical interaction can take place between the arrays of filaments.

Muscle fibrils can be disintegrated mechanically in the presence of agents that weaken the forces of attachment of the cross-bridges. When this is done, the structure breaks down into (1) isolated thick (100 Å diameter) filaments, nearly always 1.5 microns in length, showing projections reminiscent of the cross-bridges seen in intact muscle;

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328 Circulation, Volume XXIV, August 1961
Figure 1

Low magnification electron micrograph of thicker section of rabbit psoas muscle showing a number of myofibrils near the edge of a fiber. A-band dense; I-bands less dense and bisected by Z-line. × 27,000.

(2) isolated thin (50 Å diameter) filaments, sometimes 1 micron long and sometimes apparently broken into smaller lengths; (3) groups of thin filaments still joined onto a Z-line, forming an "I-segment" about 2.0 microns in length; and (4) occasional groups of thin and thick filaments lying side by side and seemingly joined together by cross-bridges. These various structures are illustrated in figures 3, 4, and 5; their appearance provides a new form of confirmation of our previous conclusions. They also provide a new type of experimental material, both for electron microscopy and perhaps for biochemical studies also.

Now let us consider the composition of the filaments. At present there are very strong reasons for believing that the thick filaments contain all the protein myosin that is present in the muscle, while the second principal structural protein, actin, occurs in the thin filaments. Solutions known to dissolve out myosin from the muscle selectively
will dissolve out the thick filaments,¹,² leaving the array of thin filaments behind, a process that can be observed in the light microscope as the disappearance of the dense A-bands. Subsequent extraction of actin dissolves away most of the material of the thin filaments. These observations have been put on a quantitative basis by the use of the interference microscope.³ ⁴ The amount of material in the A-bands, arising from the presence of the thick filaments, very closely approximates the amount of myosin present, and the amount of material removed from the A-bands is quantitatively equal to the amount of myosin that could be extracted from the same type of preparation by large-scale biochemical techniques. More recently, Perry and Corsi⁵ have shown that the selective removal of actin and tropomyosin removes the I-band material, leaving the A-bands (and all the ATPase activity and hence presumably the myosin) intact.

The changes that take place in this structure during changes in the length of the muscle can be investigated by light-microscope observations as changes in band-pattern. These show⁶ ⁷ that during stretch and during shortening, active or passive, the two sets of filaments slide past each other, there being no substantial overall change in the length of any of the filaments until it is brought about by steric factors in more pronounced degrees of shortening (e.g., when sarcomere length decreases below the length of the A-bands). When the actin filaments have come together in the center of the sarcomere, further shortening seems to cause them to slide past each other, giving the double overlap effect illustrated in figure 6.

These observations, and others, lead us to think that the system must function in the following way. In the resting state, the cross-bridges, which are projecting parts of the myosin filaments, do not attach to the actin filaments, which are therefore free to

Figure 2

*High magnification picture of thin section of rabbit psoas muscle showing arrangement of thick and thin filaments. × 150,000.*
slide past them easily. This accounts for the high extensibility and relative plasticity of resting muscle. When the muscle is active, the cross-bridges can attach to specific sites on the actin filaments for a brief period of time, during which a relative force and, if the muscle is allowed to shorten, a relative movement are generated between the 2 types of filament, in some way at present unknown. The bridge then detaches and is free to form another attachment further along the actin filament if movement has taken place. Each bridge will perform a number of such cycles while the muscle is active (about 5 during a single twitch), the energy required for the process being liberated by the splitting of the substrate (probably ATP) by the ATPase of the myosin. When activity is over, the bridges cease to attach to the actin, enzyme activity comes to an end, and the muscle returns to the resting, relaxed state. When the muscle passes into rigor (a condition characterized by the absence of ATP), the cross-bridges become permanently attached to the actin filaments and the muscle is rigid and inextensible, for the filaments are not able to slide past each other.

**Important Features of the Model**

Reviews of the large amount of biochemical and physiologic data available concerning striated muscle and the structural model that has been described have already been published in extenso. Here we will mention briefly only 3 particular points that seem worth while to emphasize.

1. The system can develop a range of different tensions depending upon the number of cross-bridges that are active simultaneously. For a given load, the system shortens with a particular velocity of shortening (rather than, say, a particular acceleration), such that the number of bridges actively developing tension is just sufficient to bear the load. The rate-limiting factor in the system is the rate at which unattached bridges can become attached again and develop tension; as a given active site on the

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*Figure 3*

Isolated thick filaments, 1.5 μ in length, prepared by blending glycerinated muscle in the presence of a relaxing agent (EDTA + ATP). Specimen prepared for electron microscopy by negative staining technic. X 30,000.

actin moves past the bridge, there is a certain length of time available for this process to take place: the faster the movement, the less the chance of attachment to a particular site, and the lower the tension at any given moment of time. Thus, when shortening under a particular load, the system will settle down to an equilibrium velocity at which the rate of formation of new links is just equal to the rate of opening of formed links that have already exerted their pull on the actin filament.

2. Energy release by the enzyme site is activated by the attachment of the cross-bridges to the actin filament. Thus the
number of fully active sites is controlled by the tension in the muscle, and the rate at which those sites repeat their cycles of activity is controlled by the velocity of shortening. The system therefore has the possibility of behaving economically, i.e., releasing more energy for a given distance of shortening when it is shortening against a larger load. This is a very important feature of the behavior of real muscles. One can see in a general way how such a system might give rise to the type of behavior characterized by the Hill equation:

\[(P + a)V = (P_0 - P)b\]

where \(P\) = actual load; \(P_0\) = isometric tension; \(V\) = velocity of shortening; \(a\) = constant (heat of shortening); and \(b\) = constant. The left side of this equation gives us the total rate of energy release required to do external work and produce shortening heat (assuming that maintenance heat can be accounted for separately). The right side contains the term \((P_0 - P)\), which is proportional to the number of unattached bridges. If the attachment of such bridges is the rate-limiting step, as we have assumed, then the model could quite naturally give rise to this equation. A more elegant and complete account of the mechanical and thermal properties of striated muscle in terms of a particular version of the sliding filament model has been given by A. F. Huxley.9

3. It is not necessary to postulate that each cross-bridge generates a pull over a distance comparable to that separating successive cross-bridges between a given pair of thick and thin filaments, or between successive active sites on the actin filaments. All that is necessary is that the actin filament shall be drawn along such a distance between 2 successive operations of a given cross-bridge, and this movement can equally well be achieved by small movements—say of 5 \(\AA\)—produced successively at 10 other cross-bridges. As any given actin filament has...
about 54 bridges directed toward it in each half of the A-band, this can be achieved quite easily, still leaving the possibility for up to 5 bridges to be acting in parallel at any given moment, to permit the variation in tension and rate of energy release with velocity of shortening that we have already described.

**Special Features of Cardiac Muscle**

Although the essential features of the contractile structure and its behavior appear to be the same in cardiac and skeletal muscles, there are a few points at which differences occur that may be significant. Probably the most obvious one is the presence of very large numbers of mitochondria in cardiac muscles, as compared to skeletal muscle, no doubt associated with the ability of the heart to function continuously over very long periods of time without intervals for recovery.

The second feature is the comparatively small diameter of heart-muscle fibers (as small as a few microns) compared with those of skeletal muscle, which are most commonly 50 to 100 microns in diameter. The latter are usually provided with quite an abundant reticulum, i.e., a system of internal membranes in each fiber, and these are believed to be concerned in relaying the signal for contraction into the interior. Such a reticulum is either very sparse or seemingly absent in many of the heart-muscle preparations that have been examined, a point of difference that, in view of the apparently different membrane properties of cardiac muscle, deserves further study.

Another rather puzzling feature of cardiac muscle is the relatively low tension per unit area which it will develop, only about one-tenth that of skeletal muscle according to 2 recent studies. Some of the difference may be accounted for by the greater fraction of the cross-sectional area occupied by mitochondria in the cardiac muscle—perhaps a factor of 2 difference might occur for this reason—but a large factor still remains, and there is no obvious reason from the visible structure to account for it. It may, of course, result from different enzymatic properties of cardiac actomyosin. This is a difficult hypothesis to investigate, as the enzymatic properties of all actomyosins seem to be rather low in comparison with what one would anticipate from the maximum energy output of the muscles from which they were obtained.
A fourth feature of cardiac muscle that distinguishes it from skeletal muscle is the nature of the active isometric length-tension curve, i.e., that showing the increase in tension over resting tension when the muscle is active. In skeletal muscle, this curve exhibits a maximum around resting length (which lies very close to the greatest length at which the muscle develops zero resting tension). As the length of the muscle is increased beyond resting length, the active tension decreases, an effect that has been explained by Huxley and Niedergerke as resulting from the decreased length of the region in which actin and myosin filaments overlap and can form cross-links with each other. The factors that cause the tension to decrease below resting length are unknown. In cardiac muscle, however, the active tension increases as the length of the muscle is increased beyond resting length as defined above, and reaches a peak only after a stretch of about 30 per cent. This effect might be explained if the sarcomeres of cardiac muscle at resting length resembled, either in the extent of overlap or in the factors that produce the decrease in tension at length below rest length, those of skeletal muscle that had shortened by about 25 per cent.

References


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Circulation. 1961;24:328-335
doi: 10.1161/01.CIR.24.2.328

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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