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Actin as the generator of tension during muscle contraction

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ABSTRACT **We propose that the key structural feature in the conversion of chemical free energy into mechanical work by actomyosin is a myosin-induced change in the length of the actin filament. As reported earlier, there is evidence that helical actin filaments can untwist into ribbons having an increased intersubunit repeat. Regular patterns of actomyosin interactions arise when ribbons are aligned with myosin thick filaments, because the repeat distance of the myosin lattice (429 Å) is an integral multiple of the subunit repeat in the ribbon (35.7 Å). This commensurability property of the actomyosin lattice leads to a simple mechanism for controlling the sequence of events in chemical–mechanical transduction. A role for tropomyosin in transmitting the forces developed by actomyosin is proposed. In this paper, we describe how these transduction principles provide the basis for a theory of muscle contraction.**

The central problem of muscle contraction is to account for the mechanism of force generation between the thick and thin filaments that constitute the sarcomere (1–6). In Huxley's analysis (3, 5, 6), the proportionality of isometric tension to the overlap of thick and thin filaments, as well as the other mechanical properties of muscle, are neatly explained with so-called independent force generators that are presumed to be distributed uniformly along the overlap zone. In most models, the individual force contributions of these generators are summed up by some relatively inextensible structural element to which each generator has a single point of attachment. In the case of the classical rotating cross-bridge model of force generation, thin filaments themselves serve the role of the inextensible structural elements. In this note, we propose an alternative model in which repetitive length changes in segments of actin filaments, induced by myosin heads, generate forces that are summed and transmitted to the Z disc by tropomyosin.

The impetus for this model came from observations that actin in profilin–actin crystals is organized around a ribbon motif (r-actin), which we interpret to be an untwisted, extended form of the helical filamentous form of actin (h-actin) (7). In the transformation of actin from the helical to the ribbon form, the actin subunits undergo a 13° rotation as the segment extends by 8.25 Å per subunit. It is presumed that the actin–actin intersubunit contacts are largely maintained during this transformation.

The conclusion that r-actin and h-actin are related structures is based on a number of observations. First, growth of the r-actin form in the profilin–actin crystals appears to depend in a precise way on subtly shifting the competition for actin monomers away from h-actin formation toward entry into the growing crystal lattice. This strongly suggests that the same actin–actin bonds are used in both r-actin and h-actin. Second, x-ray diffraction shows clearly that crystals can be transformed into semicrystalline fibrous assemblies by replacing the bathing medium with solutions known to induce h-actin formation. Third, the zigzagging appearance and overall width of r-actin closely resemble the wide view of h-actin seen by electron microscopy (8), while the narrowness of the edge-on view (9) and fiber diffraction data (10) seriously limit the orientational possibilities for the monomer in the helical fiber. Fourth, fluorescence energy measurements enabled the locations of nucleotide and cysteines to be triangulated with respect to the filament axis, establishing the monomer orientation (11).

Description of the Model

The Mechanism of Tension Generation. The hydrolysis of ATP on myosin heads is known to provide the free energy that drives the chemical–mechanical transduction. We propose that binding of myosin in the ADP·P_i state induces the formation of r-actin from h-actin (Figs. 1 and 2). Tension then develops as the direct result of segments of actin ribbons contracting to the helical state one monomer at a time. Thus, the Gibbs free energy of a segment of an actin filament is proportional to the number of monomers that have not yet made the transition from the r-state to the h-state. Consequently, the free energy of an r-actin segment is proportional to its length, and the force (the derivative of Gibbs free energy with respect to length) is independent of the segment length. The segment therefore does not behave as a Hookean spring. A segment of progressively contracting actin is "on" and generating a constant tension between two points of attachment; it is "off" when it has returned to its fully helical ground state.

To qualify as an acceptable independent generator model, a mechanism of skeletal muscle contraction must provide explanations for four experimental phenomena (3, 5, 6): (*i*) isometric tension is proportional to the degree of overlap between thick and thin filaments (17, 18); (*ii*) stiffness is also proportional to filament overlap (19); (*iii*) recovery of tension following a quick release scales to overlap with a time course independent of overlap (18, 20); (*iv*) speed of shortening is independent of overlap for an isotonic contraction (21, 22).

Tension Proportional to Overlap. In the sarcomere, the regular array of myosin heads projecting from thick filaments uniformly subdivides actin into independent segments, each capable of developing a constant force as it contracts. If provision is not made for an inextensible element to sum the individual force contributions, the maximal force felt at the Z line would only be as great as that produced by any single segment of the thin filament, and tension would be independent of overlap. In skeletal muscle, adjoining tropomyosin molecules form a continuous rope-like structure through a head-to-tail association strengthened by troponin T (23, 24). We propose that tropomyosin is the inextensible parallel component that sums the individual forces being developed over the length of an actin filament in the overlap zone and transmits them to the Z disc.

Tension is developed by a helicalizing segment of an actin filament having two points of attachment: to tropomyosin on

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Abbreviations: r-actin, ribbon form of actin; h-actin, helical form of actin.

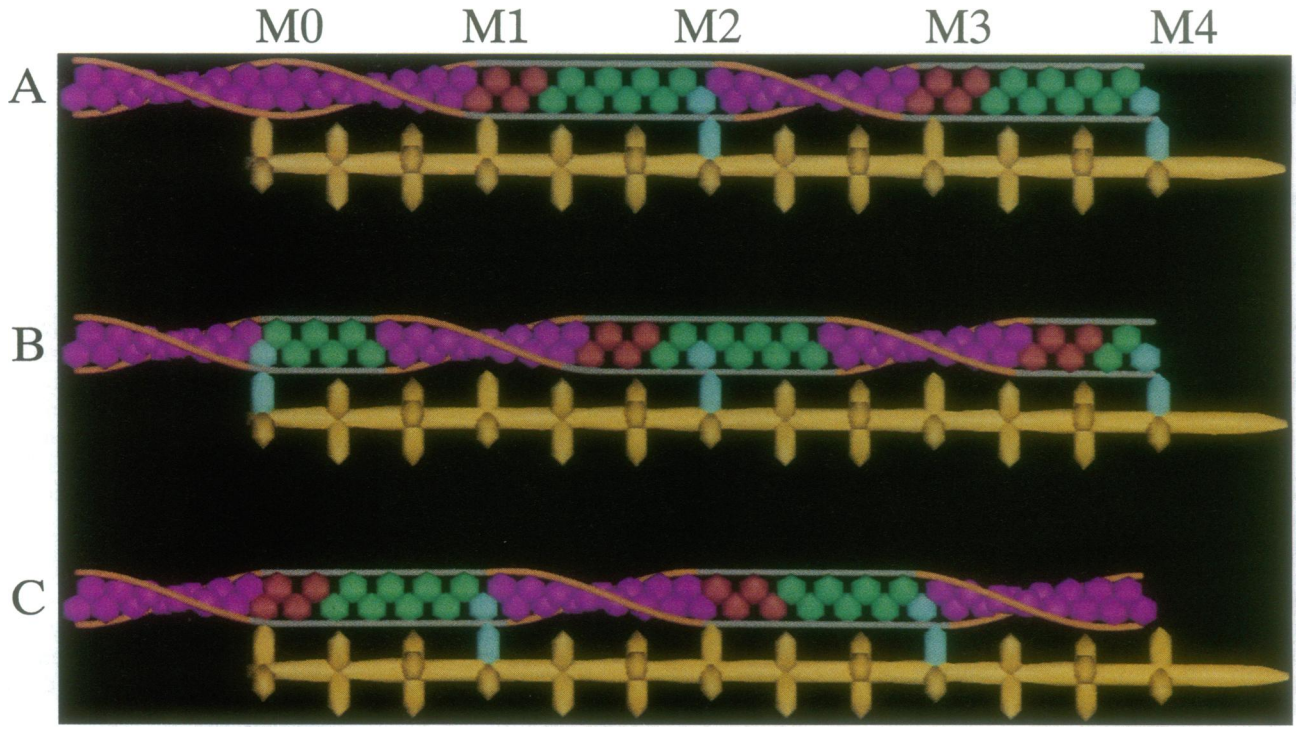

FIG. 1. Isometric contraction. We propose a mechanism in which a segment of an actin filament that is undergoing a length change is attached at one end to an inextensible tropomyosin and at the other end to an adjacent myosin filament through a myosin head. This diagram illustrates that, for such a mechanism, tension will be proportional to overlap during an isometric contraction. In this mechanism, the myosin ATPase is regulated by the continued propagation of helical waves along actin filaments. The developing torque at the helicalization front is a critical factor in breaking the actomyosin bond. The actin on-rate is controlled by the coordinated delivery of actin monomers having the correct orientation for binding. The number of actin monomers is unchanged from *A* to *C*. (*A–C*) Successive snapshots of the continuous process occurring at the peak of an isometric contraction as it is thought to occur at the entrance to the overlap zone. An actin filament is shown as it interacts with the heads, M0, M1, M2, M3, and M4, of a myosin filament. Other myosin heads are shown, but they are unable to interact with the actin filament because they are unfavorably oriented; these other heads are, however, able to interact with other actin filaments that are in a favorable orientation. Similarly, the actin filament that is shown is capable of interacting with myosin heads on other myosin filaments (not shown) in the three-dimensional array of filaments. The Z-line attachment (not shown) is to the left. Four states of the actin monomer are indicated by colors: purple, helical form (h-actin); blue, myosin-bound state; green, ribbon state (r-actin); red, a monomer that is one of a group that is in transition between r-actin and h-actin. Two states of tropomyosin are also indicated: orange, the state bound to h-actin via the seven actin binding sites (12–16); gray, the unbound state running parallel to r-actin and bypassing the bound, tension-bearing, myosin head. Two states of the myosin heads are indicated: yellow, the detached state that is hydrolyzing ATP; blue, the tightly bound, tension-bearing state. The actin–tropomyosin link is broken when a myosin head binds tightly to the actin. In *A* and *B*, as the r-actin segments between M1 and M2 and between M3 and M4 begin to helicalize, forces are developed that pull on the heads toward the Z line. As helicalization proceeds toward the right (i.e., toward the center of the sarcomere), a constant tension is maintained between M2 and the translocating tropomyosin–actin attachment site to the left. The same events are taking place simultaneously between M3 and M4. For each monomer that is undergoing the transition from h-actin to r-actin between M0 and M1, another is changing from r-actin to h-actin between M1 and M2. A fixed ratio is therefore maintained between the number of monomers in the ribbon state (including those in the red state) and those in the helical states. The essential point is that the force developed between the Z line and M4 is twice that generated by the actin–myosin interaction between the Z line and M2. Tension proportional to overlap is possible because the unbound parts of the tropomyosin molecules (gray) bypass the contracting parts of the system, including the tightly bound myosin heads. This ensures the independence of the force-generating ribbon segments. Note that there is always a fixed ratio of r-actin to h-actin in the overlap zone over a length of two unit cells (i.e., 2×429 Å). The rate at which helical attachment sites move along the overlap zone toward the center of the sarcomere depends on the load, being maximal for lightly loaded fibers shortening at high velocity and slowest for isometrically contracting fibers.

one end and to a myosin head on the other. Thus, contracting actin segments pull on tropomyosin while being anchored via cross-bridges to thick filaments. A useful analogy is a tug-of-war in which each person (ribbon segment) pulls independently on the rope (tropomyosin) by digging their heels into the ground (myosin). The tension on the rope is the sum of the individual forces.

As illustrated in Figs. 1 and 2, the attachment site to tropomyosin corresponds to the set of seven consecutive h-actin monomer binding sites defined by sequence analysis (12–14), crystallography (15), and molecular genetics (16). Constant tension will be maintained without slack in tropomyosin as long as the attachment site to the actin filament binds one monomer on the helicalizing end for each one lost on the ribbonizing end as it slides toward the M line. The unattached portions of the tropomyosin molecule running in parallel to r-actin bypass the r-actin-bound bridges. This ensures that the total force relayed to the I band is proportional to the number of active ribbon segments attached to tropomyosin. In terms of our tug-of-war analogy, the rope does not wrap around the feet of the individuals.

Stiffness Proportional to Overlap. In our model, tension development will result in elastic distortions of the attached cross-bridges. To a good approximation, all of the myosin heads bearing tension are bent to the same extent, because the forces on them are constant, independent of the amount of r-actin between the two points of attachment. Thus, fiber stiffness is a simple linear function of overlap, as shown by experiments for both isotonic and isometric contraction (19, 25).

Behavior After a Quick Release. It is well known that tension in an isometrically contracting muscle fiber can be reduced to zero by a quick release that amounts to a shortening per half sarcomere of a little less than 40 Å (19). In the

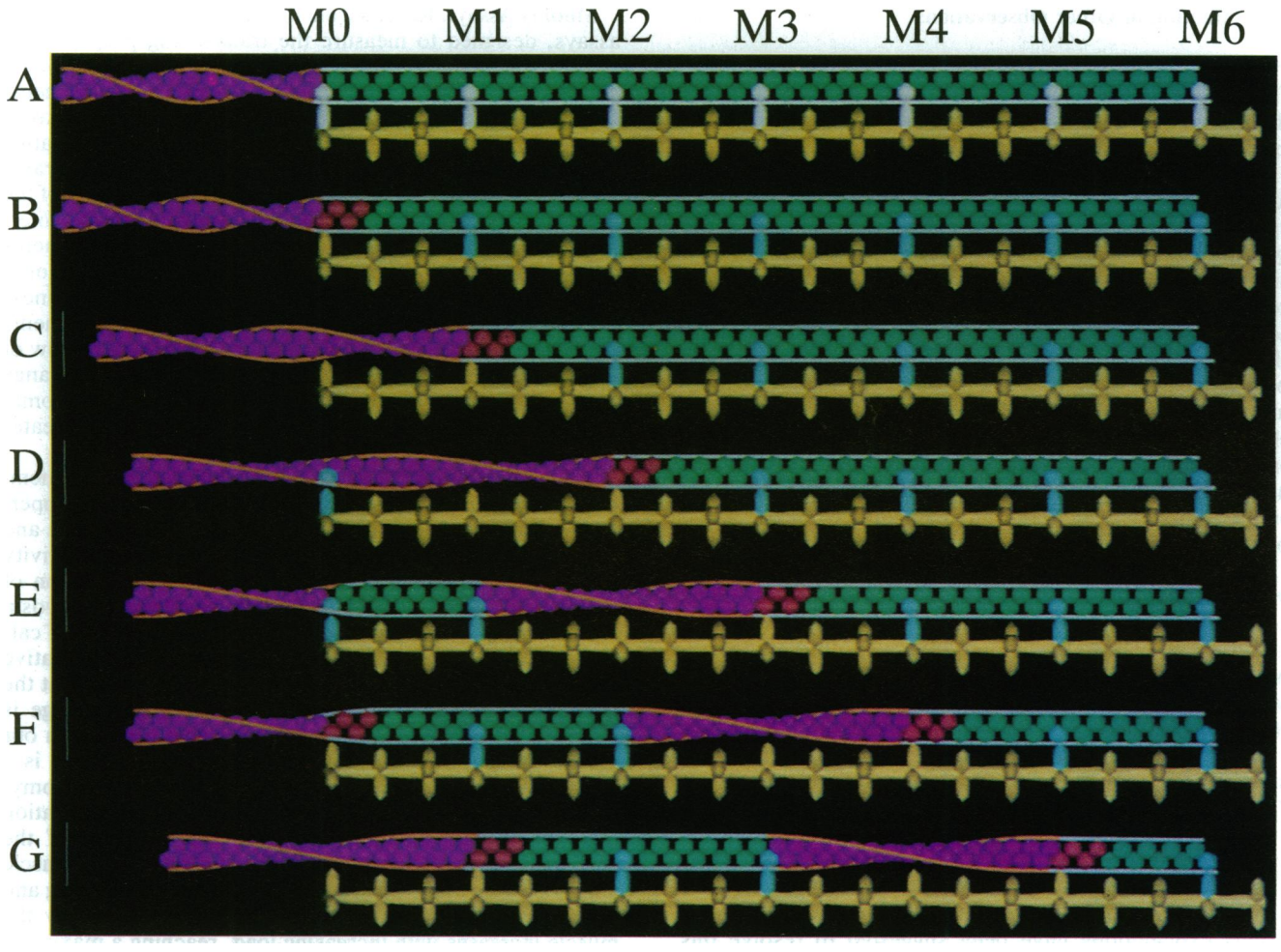

FIG. 2. Development of a contraction. Diagram showing how transformation from r-actin to h-actin leads to contraction. The number of actin monomers shown is constant from *A* to *E*. (*A*) Relaxed state in which ribbons, in the absence of Ca^{2+}, are held by weakly interacting myosin heads (white). The reason that r-actin is thought to be the predominant form of actin in the relaxed state is to be found in the strength and sharpness of the 215-, 143-, and 71.5-Å meridional reflections in the x-ray patterns. After stimulation, in the presence of Ca^{2+}, myosin heads (blue) bind strongly to the actin ribbon and helicalization begins at the entrance to the myosin lattice, where the first myosin head (yellow) has detached (*B*). Stiffness, proportional to the number of tightly bound myosin heads, thus develops in advance of tension. As helicalization proceeds from M0 toward M1, three and a half h-actin monomers are drawn in from the I band. Actin monomers in red represent the transition state that develops at the boundary between h-actin and r-actin. (*C* and *D*) The process has progressed toward the center of the sarcomere. Note that the Z disc has been pulled to the right by three and a half monomer units in *C* and by seven monomer units in *D–F*. In *D*, the head M0 has hydrolyzed ATP and rebound to a targeted h-actin monomer. Tropomyosin at that location detaches as a consequence of myosin binding. The cooperative release of tropomyosin accompanies the development of the ribbon toward the right (*D* and *E*). For every actin monomer that is released from tropomyosin, another is rebinding further along the thin filament at the point where helicalization is taking place. The ribbon between M0 and M1 develops by an induced rotation and stretching of each actin monomer toward the right. Three and a half h-actin monomers slide by M1 until an r-actin monomer arrives that has the correct orientation to bind myosin head M1 (*E*). This event initiates ribbon formation of the units between M1 and M2. Progressive helicalization of the ribbon segment between M0 and M1 begins at the same time. (*F* and *G*) Further progression of the contraction. In modeling this process, the orientation of the actin monomers bound to the Z disc is assumed fixed as is the orientation of the monomer bound to M2. As a consequence, in *C* and *D* a negative supercoil forms at the I-band end of the filament as the ribbon between M1 and M2 helicalizes. It is reversed as the ribbon forming between M0 and M1 restores the twist in h-actin between M1 and M3 (*E*).

model proposed here, the tension is generated by contraction of short segments of ribbons anchored to the thick filaments by the myosin heads, while pulling on the tropomyosin molecules. Therefore, in a quick release, the elastically bent heads can all return in parallel to their local energy minima, relieving the developed tension. It is a remarkable fact that isometric tension returns almost to its previous value after a quick release (of <40 Å) with a time course independent of overlap. Our model accounts for this because very little happens to the uncontracted portions of r-actin between the two points of attachment during the release. The time to recover tension is thus determined by how long it takes the helicalizing segments to rebend the parallel array of elastic bridges by an amount somewhere between 31 and 39 Å (19).

Velocity of Shortening Independent of Overlap. Two coordinated processes, ribbonization and helicalization, are continually taking place along thin filaments. These orchestrate the cyclic attachment/detachment of catalytic myosin heads. The velocity is independent of overlap (21, 22) because the progressive helicalization along r-actin requires that any section of actin does not contract until the preceding section has done so (see Fig. 2). The velocity of shortening is evidently equal to the rate of helicalization itself and thus should be simply related to the time course of tension recovery following a quick release (see above). Therefore, under the assumptions of the present model, the quick release data of Huxley and Simmons (18) yield a velocity of shortening in the range of 40 Å per 1–2 msec, which is in agreement with the measured value of 2 μm/sec.

Reexamination of Other Observations

The attraction of this model is that it explains at least as many of the classical phenomena as the rotating cross-bridge model while also accounting for a number of other perplexing observations as described below.

X-Ray Diffraction Data. Since the high radius projections from the myosin thick filaments seen in electron micrographs repeat on a 429-Å lattice, the changes during contraction of layer lines in the inner part of the x-ray pattern indexing on this spacing are usually considered as only reflecting myosin cross-bridge movements (26, 58). Our model suggests a radically different interpretation because it raises the possibility that actin in the ribbon state can take on the longitudinal spacings (429 Å) of myosin (transformation of an incommensurate to a commensurate lattice). Consequently, in the relaxed state, for example, the intensities of the 143-Å and the forbidden 215-Å meridional reflections are stronger and sharper than for contracting muscle because r-actin is reinforcing an actomyosin lattice having a unit cell of 429 Å and contributing additional scattering material at these spacings.

A key prediction of this model is that the intensity of the 59-Å reflection, characteristic of the subunit repeat along helical actin, must increase during a contraction as helicalization takes place. The failure earlier to detect intensity changes in this reflection had been the basis for ruling out large structural changes in actin filaments during contraction (26). Recently, however, it has become technically possible to detect rather large changes in the 59-Å reflection, especially during the early rapid phase of tension development (27–29).

Remarkably, these intensity changes are not accompanied by a shift toward the meridian, the expected diffraction effect if the more massive myosin heads are binding to the outer surface of undistorted filamentous actin (marking). Although various explanations have been suggested to resolve this paradox, in our view the increased intensity in the 59-Å reflection is simply a consequence of the increased proportion of helical relative to ribbon actin as contraction develops from the relaxed state.

Huxley *et al.* (29) has pointed out the importance of accounting for the puzzling weakness of the 360- to 385-Å actin-based layer line during contraction. This reflection is observed to be some 30 times weaker than expected (29) from the classical rigor diffraction pattern. We suggest that the x-ray intensity of this spacing is weak because segments of ribbon are interspersed with helical segments, reducing the coherence of the scattering from the filaments.

Length–Tension Measurements. Creep-free length–tension data, when subjected to a least-squares analysis under the hypothesis of the sliding filament model, reveal considerable variation in the magnitude of the thin filament overlap (30). The observed value of ± 0.21 μm per half sarcomere is 20% of the nominal length of actin filaments. Indeed, it is consistent with the value 0.17 μm per half sarcomere for actin length changes calculated earlier from the relationship between stiffness and shortening speed based on measurements of the time course of tension development (31). It was noted that this high level of filament length variation was inconsistent with the tight limits (0.25%) placed by x-ray diffraction on changes in actin subunit spacings. However, the latter was based only on the existence of the helical form of actin and, as we have argued above, the x-ray patterns themselves may require reinterpretation in light of the possible presence of r-actin. Our model raises the question of whether these experiments are revealing misalignment of filaments, variation in the number of actin monomers per thin filament, or true length variations in a population of thin filaments having a fixed number of subunits.

Motility Assays. Results from the newly introduced motility assays, designed to measure the transducing properties of actomyosin independently of sarcomeric context (32–35), are consistent with the ideas presented here. Actin filaments polymerized from monomers containing a single cleaved peptide bond, for example, while still capable of activating the myosin ATPase and forming rigor links, failed to translocate in these assays (36), suggesting that the integrity of the monomers is essential for relative sliding. Similarly, interference with the conformational flexibility of actin filaments by the introduction of chemically crosslinked actin monomers into filaments reduces relative sliding (37). The unexpectedly long power strokes measured in these experiments (38, 39), no longer easily explicable in terms of the throw of a single myosin head, might be indicating the maximum range over which ribbonization extends in a field of randomly oriented myosin heads. (This will be discussed in greater detail elsewhere.)

The Actomyosin ATPase. Solution studies of the biochemistry of myosin ATPase point to the importance of cooperative effects in actin filaments in activating the enzyme and to a role for tropomyosin in potentiating this cooperativity (40–44). In the model presented here, the transmission of mechanical energy along thin filaments regulates the myosin ATPase by clocking the attachment and detachment of catalytic heads. Therefore, the model suggests an alternative explanation for the Fenn effect (6)—the observation that the heat production of a muscle for a given length change is independent of the load present during that change. In our model, the developing twist of a helicalizing filament is a critical determinant of the reaction that breaks the actomyosin bond during a contraction cycle—i.e., helicalization overcomes the activation barrier in the breaking of the actomyosin bond by ATP. Increasing the load on the muscle would slow down helicalization and thereby the binding and hydrolysis of ATP, even though tension developed by the muscle increases with increasing load, reaching a maximum in the isometric state where the rate of helicalization is at a minimum. Furthermore, in the lattice, the ATPase rate is optimized because the coordinated delivery of precisely oriented (targeted) actin monomers determines the on-rate.

This model raises questions concerning the exact chemical role of the actin nucleotide. Protein intermediates containing an acylphosphate are found in other transduction systems incorporating an ATPase and operating on the same millisecond time scale as muscle contraction, such as signal transduction in bacteria (45) or ion translocation systems (46). Although there is no evidence that a phosphate is transferred from myosin to actin during the product release step, studies on the *in vitro* polymerization of actin (47–49) have provided results consonant with the idea that an actin·ADP·P_i state can be formed. Alternatively, myosin·ADP·P_i stimulates ADP–ATP exchange on the actin filament (50–52) with subsequent hydrolysis of the actin-bound ATP to reestablish r-actin. Thus, the enigmatic hydrolysis of ATP seen in the polymerization reaction of actin might have a natural role in muscle contraction in the regeneration of metastable r-actin during a cycle of transduction. Clearly, the existence of a second ATPase would have important implications for interpreting the Fenn effect. The question has received a great deal of attention without having been conclusively answered for the case of sarcomeric contraction under tension (53–57).

Conclusion

We have proposed a mechanism for tension generation in the actomyosin system based on repetitive length changes in actin filaments. In this model, myosin heads induce the length changes and bear the tension of contracting segments of actin anchored to them.

Independent segments of actin pull on tropomyosin molecules, which transmit the summed force to the Z disc. The unique feature of this actomyosin chemical–mechanical transducer is that the Gibbs free energy is a linear function of actin filament extension. It allows a straightforward account for many of the classical mechanical features of muscle contraction. The transduction process is perhaps best pictured as helical waves propagating along actin ribbons toward the center of the sarcomere during a contraction, regulating the cyclical attachment and detachment of myosin heads.

We are deeply grateful to Sir Andrew Huxley for his considerable efforts in helping us to understand the critical issues of muscle contraction. His advice has been invaluable. This should not, however, be taken to mean that he accepts our model as a valid possibility. Walter Kauzmann has taken a great interest in our work over the years. He suggested that we consider tropomyosin as a candidate for the force summator required by our model. We thank him for sharing his insights with us and for his constant encouragement. We also want to thank Sir Aaron Klug for constructive criticisms of our model and for encouragement. Arvid Mostad, Michael Rozycki, and James Myslik provided thoughtful discussion. Stephen Miller produced the computer program for generating the figures. This work was supported by grants to C.E.S. from the National Institutes of Health (GM44038) and to U.L. from the Swedish Cancer Foundation and the Swedish Natural Science Research Council.

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