Proc. Nat. Acad. Sci. USA
Vol. 71, No. 9, pp. 3343–3344, September 1974

The Mechanism of Muscle Contraction

(mechanochemical coupling/meromyosin subfragment 2)

ALBERT SZENT-GYÖRGYI

Marine Biological Laboratory, Woods Hole, Massachusetts 02543

Contributed by Albert Szent-Györgyi, May 28,1974

ABSTRACT Muscular contraction is essentially the shortening of the S_2 subunits of heavy meromyosin, integrated to macroscopic motion by the thick and thin filaments.

According to our present knowledge the main contractile proteins of muscle are myosin and actin which, *in vitro*, form the complex actomyosin (AM). The actin filaments, in muscle, have attached to them tropomyosin and troponin. The slender myosin molecule is about 1400 Å long and is built of two fragments, the "light" and "heavy" meromyosin (*LMM* and *HMM*). The latter consists of a long and thin "stalk" (subfragment 2, S_2) and a globular "head" (subfragment 1, S_1). The HMM S_2 is actually a double spiral of two polypeptide fibers attached at one end to the LMM, each peptide carrying a globule, S_1 at the other (1).

AM is strongly hydrophilic. Threads prepared from it contain 97% water. At a proper ionic concentration its micelles show two major changes under influence of ATP: they contract and become completely hydrophobic, anhydrous. Thus, under influence of ATP, suspensions of AM "superprecipitate," while threads contract. If the micelles within the threads have a random orientation, then their contraction causes the thread to contract in all directions, that is, shrink, become shorter and thinner. If the micelles are arranged parallel to the axis, then, under influence of ATP, the threads become shorter and thicker without losing volume, behaving thus similarly to contracting muscle.

There are reasons to believe that these changes, shortening and dehydration, reflect the elementary changes taking place in contracting muscle. The analogy between muscle and AM was brought still closer by the development of glycerination and the introduction of the psoas fiber (2), and the demonstration that *rigor mortis* is essentially a lack of ATP (3). It was natural to expect that muscle would be found to be a bundle of AM threads built of micelles, ordered parallel to the axis.

It came as a shock when the electron microscope revealed muscle to consist of "thick" myosin and "thin" actin filaments, which did not shorten on contraction, but only slid alongside one another. Initially no connection was seen between the two. Later, H. E. Huxley (4) showed them to be connected by "bridges." It is generally believed that these bridges are the HMM S2-s of the myosin molecules, which attach themselves, in contracting muscle, to the "actin" of the thin filaments. H. E. Huxley believes that the sliding and tension are brought about by the tilting action of these heads, their "angling." Contraction in muscle is triggered by Ca^{++}, which binds to troponin (5), which may act cooperatively (6) with tropomyosin.

In all these studies the hydration and dehydration were completely disregarded. The first question on this line has to be: which of the components of muscle is responsible for the binding and release of the great quantities of water? Actin cannot be, because very little actin is needed to make AM hydrate and dehydrate under influence of ATP. Nor can LMM be made responsible, because it does not interact with actin or ATP, and it is this interaction that induces the changes in hydration. This leaves us with HMM, and within the HMM only the helical HMM S_2 could be expected to bind a great amount of water, by cladding itself with a sheath of water which is thrown off on contraction. Such an envelope of strongly bound water would keep the stalk straight in resting muscle, while the loss of the water sheath would allow the S_2 to curl up and shorten.

All this can be put together in a theory of contraction according to which the sliding and tension are brought about by the shortening of the HMM subfragments 2, attached on one end by their "heads" to the actin filaments, and attached to the thick filaments through their junction with LMM.

Thus, the contraction cycle as considered by Huxley (4), Ebashi (5), and Taylor (7) would include a loss of the hydration shell of HMM S_2, associated with the splitting of ATP.

The contraction cycle would thus involve the following events: (*1*) Liberation of Ca^{++} by the sarcoplasmic reticulum and its binding to troponin, which abolishes the repulsion between the actin-troponin-tropomyosin system and the "head" of the HMM, with the ATP molecule bound to it. (*2*) Attachment of the HMM globule to "actin" which activates it as ATPase. (*3*) Splitting of the ATP into ADP and P_i. This splitting makes the HMM S_2 shed its water envelope, whereupon the dehydrated thread curls up, shortens. The shortening of the HMM S_2 pulls the thick and thin filaments alongside one another, causes them to slide. The sliding itself is not the force-generating process. The force is generated by the contraction of the HMM S_2 and the sliding is a secondary consequence. The thick and thin filaments do not shorten. They only integrate the shortening of the HMM S_2s to "muscular contraction," to the macroscopic motion of muscle. (*4*) The contracted HMM S_2s release the actin and re-hydrate and stretch out. At the same time the ADP is rephosphorylated to ATP or is replaced by a fresh ATP molecule. How far this re-phosphorylation plays a role in rehydration is not known. It is possible that this rephosphorylation promotes hydration, but it is equally possible that this rehydration and consecutive

Abbreviations: AM, actomyosin; LMM, light meromyosin; HMM, heavy meromyosin; S_1 and S_2, subfragments 1 and 2 of heavy meromyosin.

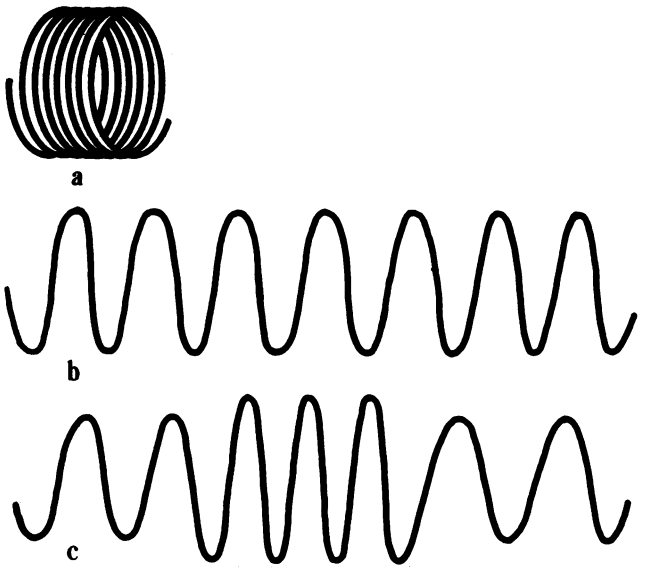

FIG. 1. (*a*) Coil of steel ("Slinky"); (*b*) same coil extended; (*c*) wave of denser coiling.

"stretching out" is spontaneous, and the rephosphorylation is needed only to restore the initial state, setting the stage for a new cycle, making the process repetitive.

This hypothesis may also be related to Kaminer's (8) observations in which muscle, undergoing contracture, loses water in proportion to the degree of contraction. He also found that actomyosin superprecipitates on freezing and thawing. It is believable that the crystallization of water deprives the HMM S_2 of its water envelope.

The assumptions made in this paper are in accord with results of nuclear magnetic resonance measurements that indicate a reduced freedom of motion of water in muscle and an increase in freedom in contraction (9–12). The theory is also in accord with my contention that muscle contraction is "contraction," that is, the shortening of elongated particles, fibers. The above hypothesis opens the question how the splitting of an ATP molecule can induce the destruction of the water envelope of HMM S_2.

The HMM S_2 is a double spiral. A wave of denser coiling can be generated in spirals by giving a sudden push at one end in direction of the axis. Such waves can be demonstrated by the toy "Slinky," which is a densely coiled steel spring (Fig. 1*a*). If the spiral is extended (Fig. 1*b*) and a push is given at one end in the direction of the axis, then a wave of denser coiling is generated which runs along the whole spiral at a high speed (Fig. 1*c*). That such a wave can destroy a rigid envelope, as the hydrate envelope of the HMM S_2 subfraction is supposed to be, can be shown by extending Slinky and then providing it with a rigid envelope by dipping it into molten sealing wax, which soon solidifies. This coat does not allow Slinky to coil up. By giving the extended coil a push at one end, a wave of denser coiling is generated which, in its passage, destroys and throws off the coat, allowing Slinky to coil up and shorten, contract. It is believable that such a wave is generated by the splitting of ATP by the HMM's head. The fission of ATP is a "molecular explosion" and by the kicking off of the phosphate a recoil may be generated, which gives a push to the fiber and generates a wave of denser coiling that then runs along the whole length of the S_2 subfragment and destroys its water envelope, allowing the S_2 spiral to coil up and shorten.

Such waves generated in fibers by the splitting of ATP could be responsible for protoplasmic streaming, which hitherto found no satisfactory explanation. In a straight fiber a push given from one side could generate a sinusoid wave, while in a coiled fiber the push given coaxially could generate a wave of denser coiling. Both would drive the surrounding fluid in the direction of the axis. Similar considerations hold for membranes.

The experiments with Slinky were performed by Miss C. Felker, to whom my thanks are due. This research was sponsored by an award of the Muscular Dystrophy Association.

1. Lowey, S., Goldstein, L., Cohen, C. & Luck, S. (1967) *J. Mol. Biol.* **23**, 287–304.
2. Borbiro, M. & Szent-Györgyi, A. (1949) *Biol. Bull.* **96**, 162–167.
3. Szent-Györgyi, A. (1949) *Biol. Bull.* **96**, 140–161.
4. Huxley, H. E. (1969) *Science* **164**, 1356–1366.
5. Ebashi, S. & Endo, M. (1968) *Progr. Biophys. Mol. Biol.* **18**, 123–183.
6. Bremel, R. D., Murray, J. M. & Weber, A. (1972) *Cold Spring Harbor Symp. Quant. Biol.* **37**, 267–275.
7. Taylor, E. W. (1972) *Annu. Rev. Biochem.* **41**, 577–616.
8. Kaminer, B. (1962) *J. Gen. Physiol.* **46**, 131–143.
9. Bratton, C. B., Hopkins, A. L. & Weinberg, J. W. (1965) *Science* **147**, 738–739.
10. Cope, F. W. (1969) *Biophys. J.* **9**, 303–319.
11. Hazlewood, C. F., Nichols, B. L. & Chamberlain, N. F. (1969) *Nature* **222**, 747–750.
12. Damadian, R. (1971) *Science* **171**, 1151–1153.