ON THE MECHANISM OF MUSCULAR CONTRACTION

TORMOD FØRLAND
Laboratory of Physical Chemistry, The Norwegian Institute of Technology, N 7034 Trondheim-NTH, Norway

ABSTRACT A thermodynamic analysis is presented for the energy conversion by muscle contraction. During the cyclic processes the major change in energy of the myosin-actin system is due to bond formation between myosin heads and actin. To account for the high efficiency of a working muscle the work done is connected directly to the formation of myosin-actin bond. It is suggested that successively stronger bonds are formed by a stepwise movement of myosin heads over an interval between two troponin molecules on the actin filament. At the end of the interval, where the bond has maximum strength, energy is supplied to break the bond. Here the work is not primarily connected to the 45° rotation of myosin heads as is commonly done. A way of separating the different kinds of energy losses is presented.

INTRODUCTION

It is commonly recognized that the contraction of skeletal muscles is due to a sliding movement of the myosin filaments along the actin filaments whereby chemical energy in the form of ATP is consumed (Huxley and Niedergerke, 1954; Huxley and Hanson, 1954). The interaction between the filaments is created by the cross-bridges extending from the myosin filament. According to the theory by Huxley (1969) the heads of the cross-bridges will first attach to the actin filament in an approximately perpendicular orientation and then, while still attached, undergo a configurational change whereby its angle of orientation on actin is changed, which causes a movement of actin filament relative to the myosin filament. Next the bond to actin is broken and the myosin head can make a new bond to the actin filament. A strong support for the theory are low angle x-ray diffraction data that suggest that in a relaxed muscle the myosin heads are oriented at 90° to the filaments and a repeat distance of 143–145 Å, whereas for a muscle in rigor the myosin heads are oriented at 45° and tilted in the direction of the *z* line and have a repeat distance of 388 Å (Reedy et al., 1965; Holmes et al., 1976).

Basis for Alternative Mechanism

The basis for attempting an alternative explanation of the mechanism in molecular dimensions is the high efficiency of energy conversion (usually up to 40%). Thus, in seeking a mechanism one should consider how energy losses can be avoided, in particular, the energy loss due to attachment of myosin heads to actin. Further, the conditions for converting the scalar energy of ATP into the mechanical vectorial force should be explained on a molecular scale. The addition of $MgATP^{2-}$ to a mixture of actin and myosin filaments causes a sudden and large decline in the viscosity of the solution to the much lower additive viscosity of the two components. With additions of $CaATP^{2-}$ the decline is smaller, and after splitting of ATP the high viscosity is regained (Bendall, 1969). From this and other studies it has been concluded that ATP breaks the actin-myosin bond.

The change in Gibbs free energy per mole due to breaking the myosin-actin bond is ~40 kJ, and the change due to forming the myosin-ATP complex is about −40 kJ (Taylor, 1979). Thus, the larger part of the energy inherent in the ATP has been spent in forming the myosin-ATP bond and a smaller part of the energy is left for other reactions or changes in the myosin head when ATP is hydrolyzed and ADP and P_i are released.

Model

We will assume that the strength of the actin-myosin bond is changing along the actin filament in the interval between two troponin molecules (over a distance of 385 Å). The reasons for this change in bond strength may be partly due to varying steric hindrance due to the tropomyosin molecules and partly due to the orientation of the helical actin filament towards myosin. It is assumed that over part of the 385-Å interval the myosin head gradually forms stronger bonds in the direction of the *z* line. Thus the model of sliding filaments is extended to involve sliding of myosin heads. At the end of the interval the bond has to be broken if the myosin head is to proceed over the next interval (see Fig. 1). In the present model it is assumed that the actin-myosin bond can be broken by ATP at the end of the interval only.

The myosin head tends to move to the end position of the interval. This would be in agreement with the low angle x-ray data from a muscle in rigor where the repeat distance for the myosin head reflection was found to be 388 Å. The essence of the model is that mechanical work is obtained during a stepwise bond formation, and chemical energy is

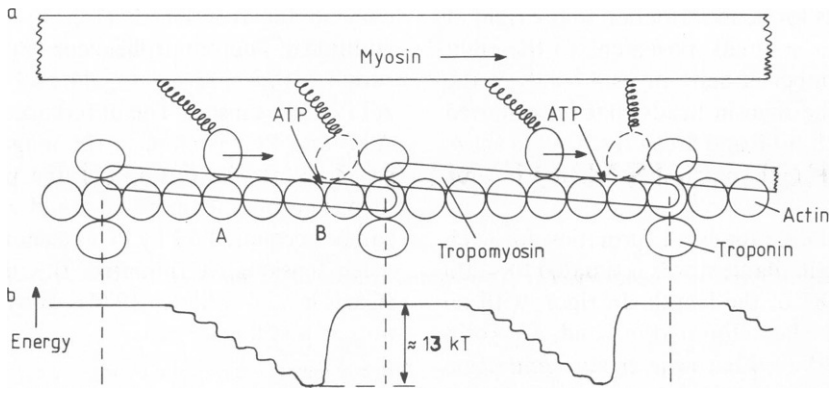

FIGURE 1 (*a*) Schematic model of myosin heads moving along an actin filament. (*b*) Energy of a myosin head during movement along an actin filament.

supplied to break the bond. The model has some similarity to the model of Huxley (1974) in which a 45° rolling movement is suggested for the myosin head attached to actin. More recent work, however, on orientation of spin labels attached to cross-bridges (Cook et al., 1982) indicate that a domain of the myosin head does not change orientation during the power stroke of the contractile interaction.

Mechanical Experiments

"Sudden length change" experiments (Ford et al., 1977) supply information on the mechanism of the actin-myosin interaction. A muscle is stimulated to give isometric tetanic contraction (continuous stimulation at constant length). The tension is measured continuously. The length of the fiber is suddenly changed (e.g., decreased) within 0.2 ms causing the tension to change (e.g., decrease) from a value T_0 to a value T_1. Within ~5 ms the tension is increased to a value T_2, followed by a small decrease and then by a very much slower increase of tension towards the original value T_0.

The ratio T_1/T_0 is approximately proportional to the distance shortened and can be interpreted as an elastic response located at the flexible connection between the myosin head and the myosin filament. The ratio drops to zero for a shortening of 40–60 Å/half sarcomere (see Fig. 2). The ratio T_2/T_0 approaches zero when the shortening approaches 140 Å/half sarcomere. This may be interpreted as the movement of the myosin heads along the globular actin units within an interval of the 385 Å repeat distance where gradually stronger bonds are formed. During this movement some other actin-myosin head bonds must be broken by the action of ATP, a fast reaction (<5 ms). The reactions taking place with the ATP bound to myosin and the reattachment of the myosin head are slower processes. The 140 Å is the maximum distance a myosin head can move after attachment to actin and presumably after a movement whereby the elastic connection between myosin head and myosin filament has been extended, and the total length of the section available for bond formation may thus be close to 200 Å. This means that the myosin head moves in several steps over the distance of 3–4 globular actin units. To conform with the linear part of the T_2/T_0 curve, it can be shown that the number of steps for the movement should be significantly higher than the number (3–4) of globular actin units passed over, which means that bonds between actin and myosin can be formed at different sites of the molecules.

The T_2/T_0 curve has a zero slope for small myosin movements in either direction. Suppose the myosin head can attach to actin only when the strain in the elastic connections is very small. Then there would always be sites available for bonds to myosin to the left of a myosin head like one in position A on Fig. 1. Thus the number of actin-myosin bonds and tension would not change by small movements to the left. Suppose further that some myosin heads under isometric tetanus are close to position B. Even in this state individual myosin heads may change position back and forth and they may reach the position B and react with ATP, which will break the bond to actin. The reattachment is assumed to be a slow process. This means there will be very few myosin heads close to position B, and

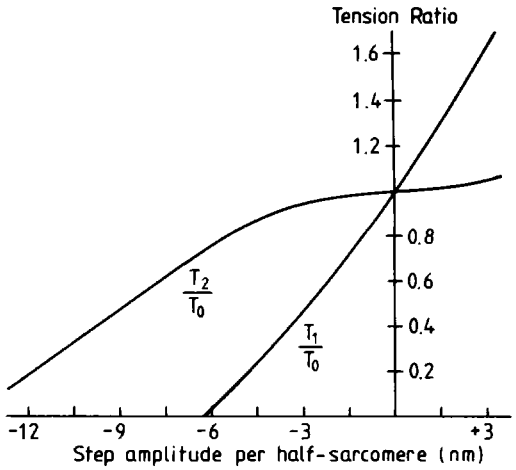

FIGURE 2 Changes in tension during rapid length change with single frog muscle fibers (modified from Ford et al. [1977]).

there will be vacant sites for bond formation to the right of the myosin heads. Thus a small movement to the right should not alter the number of actin-myosin bonds or the tension. After some time myosin heads that have moved close to B may react with ATP and break the bond to actin. This may explain the small maximum in the T_2-time curve.

The total length available for bond formation for each section of 385 Å of a actin filament was estimated to ~200 Å, or a fraction 200/385 of the length. In rigor, with no ATP available to break the actin-myosin bond, a myosin head at position B could even have the elastic connection extended in the opposite direction of that shown in Fig. 1. This would extend the 200 Å length for bond formation by 60 to 120 Å. The myosin head may also possibly bind to another actin filament that may have a more favorable orientation for bond formation. From work on spin-labeled myosin heads Thomas and Cooke (1980) found that in rigor virtually all myosin heads are attached to the actin filament.

Source of Energy in a Muscle

The direct source of energy in a muscle is ATP, which is hydrolyzed to ADP and inorganic phosphate P_i. According to Kushmerick and Davies (1969) the Gibbs free energy change per mole for the hydrolysis under the conditions in a muscle for temperatures in the interval 0–25°C is $\Delta G_{ATP} = -50$ kJ. In the muscle the content of ATP is kept nearly constant by the reaction of ADP with phosphocreatine, PCr:

$$ADP + PCr = ATP + Cr. \quad (1)$$

One may therefore consider phosphocreatine as the source of energy, in particular, since most work and heat measurements refer to phosphocreatine consumed.

The efficiency of energy conversion is usually related to the energy or enthalpy changes of a chemical reaction. From the first law of thermodynamics the change in internal energy, ΔU, of the muscle can be expressed by the supplied heat, q, and work, w:

$$\Delta U = q + w. \quad (2)$$

Since in this case pressure-volume work is insignificant we have

$$\Delta U = \Delta H, \quad (3)$$

where ΔH is the enthalpy change by the hydrolysis of phosphocreatine.

Measurements of q and w have been done for muscles where PCr was the only source of energy in the total process, and the decrease in PCr was also measured. The observed energy change per mole of PCr reacted was (Carlson and Wilkie, 1974): $\Delta U_{PCr} = -46.4$ kJ. Similar but less extensive measurements of heat released under isothermic tetanus have been done on muscles where the enzyme for reaction 1 (Eq. 1) has been poisoned by addition of fluorodintrobenzene (Bendall, 1969). The measurements give $\Delta U_{ATP} = -44.3$ kJ for hydrolysis of 1 mol ATP in the muscle. The difference in ΔU for hydrolysis of ATP and PCr is close to the magnitude of experimental errors. Note that during the first part of tension development in a muscle, more heat and work are produced than can be accounted for by PCr consumption. At a later stage, when tension is terminated, this discrepancy is reversed (Carlson and Wilkie, 1974). Why this takes place in a muscle is still unknown.

Work Performed and Energy Loss

During muscular contraction part of the energy, ΔU, will be transformed to external work and part of ΔU will be lost in the form of heat. The small contribution from energy used for the transport of Ca^{2+} ions is neglected here. We may consider four kinds of energy losses. (*a*) Reactions take place between ATP and the myosin head when the actin-myosin bond is broken and until the myosin head again forms a bond to actin. The energy loss per ATP in these reactions is presumably independent of the velocity of muscle contraction since the myosin head is not in contact with actin.

(*b*) In accordance with the present model, the movements of myosin heads over intervals of actin can be described within the formalism of nonequilibrium thermodynamics. The chemical potential of myosin heads μ_M will decrease over the actin interval, Δl, causing a movement or flux, J_M. When mechanical work is performed (w is negative), the average driving force, $-\Delta\mu_M/\Delta l$, is reduced correspondingly. The force-flux relation can be expressed

$$-(\Delta\mu_M - w)/\Delta l = R \cdot J_M, \quad (4)$$

where $-w$ is the work performed by 1 mol of myosin heads moving over one interval, and R is a resistance coefficient. For the present calculations it is most convenient that R and J_M refer to the movement of 1 mol of myosin heads attached to actin. Then J_M is equal to the myosin-actin relative velocity, v.

Eq. 4 is based on the assumption of local equilibrium and is expected to be valid when the activation energy for each step and the energy difference between steps are not very large in relation to kT. It means that for a net transport of a myosin head by one step there will be several movements back and forth. For very high contraction velocities, when w is zero or close to zero, the linear relation between force and flux may not be valid.

The loss in energy per mole ATP consumed due to the flux of myosin heads on actin is thus expected to be a linear function of contraction velocity

$$-(\Delta\mu_M - w) = (R \cdot \Delta l) \cdot v \quad (5)$$

with the possible exception in the region where w is close to

zero and the loss may increase more rapidly with increasing v.

(*c*) A third type of energy loss is expected from the observed energy consumption in isometric tetanus. The muscle consumes a significant amount of energy (~33 $mJs^{-1}g^{-1}$ for frog sartorius muscle; Bendall, 1969) without performing work. This is interpreted as the breaking and forming of actin-myosin bonds whereby ATP is consumed. According to the present model this occurs only at the end of the 140 Å interval of actin. A support for this assumption is the observed strong decrease in ATP consumption due to slow stretching of the muscle in tetanus (Infante et al., 1964). It seems reasonable to assume that this kind of loss will also exist at low velocities during contraction. One may expect it to decrease rapidly with increasing velocity.

(*d*) A fourth type of loss will come from viscous forces created by the relative movement of actin and myosin filaments. From their measurements Ford et al. (1977) calculated a viscous coefficient in frog muscle fibers to be 3×10^8 ns m^{-2} at velocities ~270 Å/ms. This would give a loss in energy of 0.7 kJ/mol ATP consumed at the highest velocity, 24 Å/ms, in the present calculations. The loss is very small compared with other losses. Here this loss will be included in the second type of loss, even though the two losses are of a different nature.

The energy loss per mole of ATP (or PCr) consumed in frog sartorius muscle is calculated from data given by Bendall (1969). The loss per mole ATP is plotted as a function of contraction velocity in Fig. 3. As shown in the figure, there is a range where the loss is nearly a linear function of velocity. A straight line is drawn close to the curve in this region. There is some degree of uncertainty in drawing this line. The linear relation between loss and velocity may not be valid for the highest velocities, when the load on the muscle is close to zero. The extreme right-hand side of the curve has therefore been given less weight in drawing the line. The deviation from linear behavior may, however, be within the limits of error of the measurements. The intercept of the line at zero velocity gives ~14 kJ for the first type of energy loss. The slope of the straight line gives the loss due to movement of 1 mol of myosin heads attached to actin. This second type of loss is ~1.3 $kJÅ^{-1}$ (ms).

The third type of loss is the difference between the curve for the total loss and the line for the second type of loss. Note, however, that myosin heads involved in this loss mechanism give no loss of the second type. That means that the line for the second type of loss should be lowered, as is indicated by the arrows to a lower curve in Fig. 3. From the distance between this curve and the curve for total loss, one can find the amount of the third type of loss as a function of contraction velocity. The function seems to be of an exponential type, but a more detailed analysis would be premature at this stage.

It was assumed above that the energy loss by reaction 1 (Eq. 1) was very small. From measurements of q and w in muscles with PCr or with ATP as the energy sources, the difference in change of the energy would be $\Delta U_{PCr} - \Delta U_{ATP} = -46.4 + 44.3 = -2.1$ kJ (Carlson and Wilkie, 1974; Bendall, 1969). In the present calculation this energy

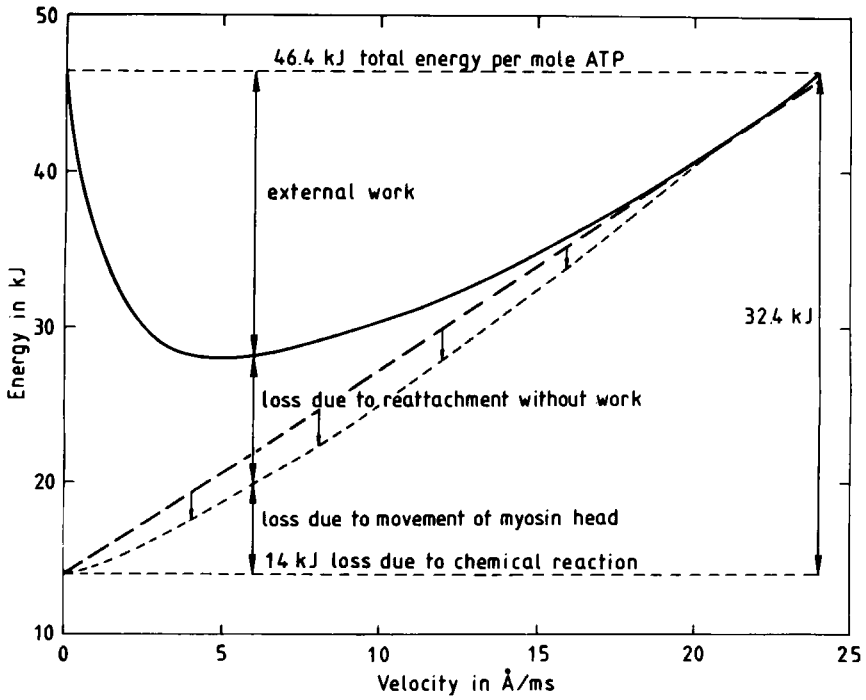

FIGURE 3 Energy losses and external work per mole of ATP consumed by frog sartorius muscle, as a function of contraction velocity expressed as actin-myosin relative velocity.

difference is automatically included in the 14 kJ energy loss. One may expect an energy loss by reaction 1 (Eq. 1) to depend somewhat on the rate of the reaction. Measurements of dU/dT in muscles as a function of contraction velocity (Bendall, 1969) give a close to constant value of dU/dt from the highest velocity $v = 24$ Å/ms to $\sim v = 4$ Å/ms. Then the value drops by a factor of one-half when $v = 0$. Thus if the loss due to reaction 1 (Eq. 1) was taken into account, it would only affect to a small extent the distribution of loss between the first and the third type of loss at very low velocities ($v < 4$ Å/ms).

A crucial point in the above analysis is the drawing of the straight line in Fig. 3. One should search for an independent way of fixing the position of the line. The difference $14 - 46.4 = -32.4$ kJ is the energy change from 1 mol of ATP available for work and loss by movement of myosin heads attached to actin. For low velocities the loss by movement will approach zero. The difference, -32.4 kJ, is therefore energy that can be converted to work. It represents a change in Gibbs free energy and is equal to $\Delta\mu_M$ in Eq. 4.

In a detailed analysis of dissociation constants of complexes of actin, myosin, ATP, and its reaction products, Taylor (1979) suggests that the work-performing transition is from a state AM·Pr** to a state AM. Here AM·Pr** is a complex of myosin and ATP in a refractory state forming a very weak bond to actin, and AM is the actin-myosin complex. The transition involves a change in Gibbs free energy of -34 kJ, which is close to the above calculated $\Delta\mu_M = -32.4$ kJ. Another source of information on $\Delta\mu_M$ is the tension under isometric tetanus discussed later in this paper.

We may summarize calculations of energy changes as follows: (*a*) The loss in energy by the chemical reaction of ATP bound to myosin head: 14 kJ/mol ATP used; (*b*) the change in energy of myosin head moving along an interval on actin: -32.4 kJ/mol ATP used. The loss of energy in this process is equal to 1.3 kJ times the contraction velocity (in Angstroms per millisecond) per mole of myosin heads attached to actin. (*c*) At lower velocities, in particular, an additional loss may be attributed to breaking and forming of myosin-actin bonds without performing work. (*d*) Losses due to viscous forces caused by relative movements of actin and myosin filaments are small compared with other types of losses, <0.7 kJ/mol of ATP used.

Energy Conversion on the Molecular Level

The above macroscopic energy relations may next be connected closer to processes on the molecular level. According to Bendall (1969) one finds for a contraction velocity of 1.25 muscle lengths/s (corresponding to 15 Å/ms in Fig. 3) an energy consumption of 104 $mJs^{-1}g^{-1}$ for frog sartorius muscles. The corresponding mechanical work is 26 mJ. This gives an efficiency of 25% and force of 0.21 kg/cm^2. It may be of interest to relate this force to the consumption of ATP using the present model to see some of its consequences. Note that this is not an independent calculation of the force. The observed efficiency is used in the calculation.

The area covered by a myosin filament in the cross section of a muscle is equal to a hexagon where the edge length is equal to the actin-actin distance. This distance is in the range 220–290 Å depending on the degree of contraction of the muscle. Using a value of 250 Å, the area per myosin filament is $\sim 1.6 \times 10^5$ Å^2. Over a cross section of 1 cm^2, there will then be 6.25×10^{10} filaments. The number of myosin molecules in one filament is ~300, each having two heads. According to Taylor and Weeds (1977) each of the myosin-SI heads can react with one ATP. Over one-half sarcomere and with sufficient actin-myosin overlap there are thus 300 myosin heads that may form cross-bridges and generate force. According to the present model, however, the myosin heads cannot form bonds to actin and exert force over the whole length of the 385 Å repeat distance of actin. The mechanical experiments by Ford et al. (1977) may be interpreted in a way that this takes place over ~140 Å only. This corresponds to a fraction of 0.36 of the 385-Å interval.

The next question is: will all these 300×0.36 myosin heads, which may form a bond and exert force under given conditions, also really form a bond to actin, or are the changes taking place in a myosin head after its reaction with ATP in a previous cycle so slow that some of the myosin heads are not ready for a new bond formation? This would depend on the velocity of contraction.

From the data on frog sartorius muscle (Bendall, 1969) one can see that for a contraction velocity 1.25 muscle lengths/s, or 15 Å/ms, a myosin head will in average travel the distance of 385 Å in 25.7 ms. (At this high velocity the third type of loss is relatively very small.) The total energy, ΔU, consumed per gram of muscle per second at this velocity is 104 mJ. Using a distance between z lines of 2.4 μ, the length of a half sarcomere will be 1.2×10^{-4} cm. This will give the energy consumption per half myosin filament (or for the 300 myosin-S1 heads) by traveling 385 Å in 25.7 ms

$$104 \times 10^{-3} \times 0.0257 \times 1.2 \times 10^{-4} \times 1.6 \times 10^{-11} = 5.1 \times 10^{-18}\ \text{J}. \quad (8)$$

In number of ATP (or PCr) molecules consumed, this corresponds to

$$\frac{5.1 \times 10^{-8}}{46{,}400} \times 6 \times 10^{23} = 66\ \text{ATP (or PCr)}. \quad (9)$$

That means that when the 300 myosin-S1 heads travel over the distance of 385 Å, only a fraction (66/300) of them form a bond to actin (which subsequently is broken). Further, only over a fraction the length (140/385) bonds are formed and force exerted. This means that in our calculation the fraction of myosin heads attached to actin

should be lowered from 0.36 to 0.080 for a velocity of 15 Å/ms.

The force, f, of a muscle per 1 cm^2 may then be obtained by equating the mechanical work performed by a movement of myosin-S1 heads over 140 Å and the chemical energy used times the observed efficiency of 25% for the energy conversion

$$140 \times 10^{-10} \times f \times 9.8 = \frac{46{,}400}{6 \times 10^{23}} \times 300 \times 0.080 \times 6.25 \times 10^{10} \times \frac{25}{100}, \quad (10)$$

which gives $f = 0.21$ kg/cm^2. In the model it is assumed that the actin-myosin bond is broken at the end of a 140 Å interval only. It is further assumed that the bond preferentially forms at the other end of the interval. From the above calculation there is no check of this last assumption. Attachment at intermediate sites could explain part of the 75% energy loss.

Force of a Muscle under Isometric Tetanus

Under tetanic conditions a sufficient number of calcium ions should be presented to activate all sections of actin, and sufficient ATP should be present to prevent rigor. Under isometric conditions no work is performed, but the myosin heads attached to actin will exert a force due to their ability to move along part of the 385 Å interval on actin. It was assumed that only at the end of the interval ATP will break the actin-myosin bond. Thus the myosin heads that are at this position and presumably also those very close to this position react with ATP. After these ATP-myosin head complexes have gone through the process of ATP decomposition, they may again form a bond to actin, etc. Thus energy may be consumed without work being performed.

The number of myosin heads involved in this process will be roughly estimated. The energy consumed under isometric tetanus is ~33 $mJs^{-1}g^{-1}$ corresponding to ~0.8 molecules of ATP consumed per half myosin filament per millisecond. From experiments with sudden change of the load on a muscle under contraction, Podolsky (1960) estimated the time needed for a myosin head to go through a complete cycle to be at least 15 ms. (Experiments at low velocity indicate ~20 ms.) This leads to a number of ~16 of the 300 myosin heads of a half filament involved in the cyclic process. They are assumed to attach at position B (Fig. 1) and will have no significant contribution to the force. This means that according to the present model the energy consumption by isometric tetanus is not connected to the force.

The fraction of myosin heads attached to actin and exerting a force under isometric tetanus was estimated to 140/383 from the mechanical experiments. From the analysis of energy losses (see Fig. 3) it was estimated that an energy of 32.4 kJ per mole ATP was available for mechanical work and losses due to movement of myosin heads and relative movement of the filaments. Under isometric conditions these losses are zero. Thus the efficiency of energy convertion for the myosin heads exerting a force is (32.4/46.4) × 100 = 70%.

The force, f, under isometric tetanus may then be calculated by equating the work and the change in chemical potential of myosin heads, $\Delta\mu_M$:

$$140 \times 10^{-10} \times f \times 9.8 = \frac{32{,}400}{6 \times 10^{23}} \times \frac{140}{385} \times 300 \times 6.25 \times 10^{10} \quad (11)$$

or $f = 2.7$ kg/cm^2. (Assuming no contribution to f from 16 myosin heads close to position B, f will be lowered by 15%.) Values reported are in the range 1.5–3.0 kg/cm^2 for frog sartorius muscle (Bendall, 1969). The force measured depends partly on the freshness of the muscle and partly on unknown factors. Presumably the higher numbers are most reliable.

We can see from Eq. 11 that the factor 140 occurs on both sides of the equal sign. On the left-hand side it means the distance over which work is performed. On the right-hand side it means the length of an interval on actin where actin-myosin bonds are formed. Assuming these lengths to be equal, one obtains a connection between $\Delta\mu_M$ and f under isometric tetanus that contains factors given by the structure of the muscles, and it gives an independent check of the slope of the straight line on Fig. 3. Using the high value $f = 3.0$ kg/cm^3, one obtains: $\Delta\mu_M = -36$ kJ/mol. The fraction of the myosin heads that forms bond to actin under tetanus, 0.36, may be compared with the value 0.20 ± 0.05 obtained by Cook et al. (1982) for rabbit psoas skeletal muscle. The difference may be due to difference in the kind of muscle used. (Assuming detachment of 16 myosin heads close to position B, the fraction 0.36 will be lowered to 0.31.)

There are two geometric factors that have not been considered: there may be a competition between two myosin heads for the same position on the actin filament. On the other hand, during the actin-myosin relative movement a myosin head will at one point have equal distance to two actin filaments and thus a larger probability of bond formation. The two effects are difficult to estimate quantitatively. They work in opposite directions and are not included in the present calculations. Thus there is a need for a calculation of $\Delta\mu_M$ from detailed and accurate thermodynamic data not yet available.

CONCLUSION

The present model for muscular contraction is mainly based on an analysis of energy conversion during the cyclic changes in the state of myosin heads, and it gives a possible explanation for the conversion of scalar chemical energy into a vectorial force. On the basis of the model and data on work and heat produced by a muscle, a separation of the

different types of energy losses has been carried out. The model is in agreement with the measurements of change in tension by sudden length change, and it permits an estimation of the force of a muscle under isometric tetanus.

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