Considerations on muscle contraction

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Abstract

The independent force generator and the power-stroke cross-bridge model have dominated the thinking on mechanisms of muscular contraction for nearly the past five decades. Here, we review the evolution of the cross-bridge theory from its origins as a two-state model to the current thinking of a multi-state mechanical model that is tightly coupled with the hydrolysis of ATP. Finally, we emphasize the role of skeletal muscle myosin II as a molecular motor whose actions are greatly influenced by Brownian motion. We briefly consider the conceptual idea of myosin II working as a ratchet rather than a power stroke model, an idea that is explored in detail in the companion paper.

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1. Background

The following text is largely based on a lecture we gave at the European Congress on Sports Science, in Cologne, July 2001. The lecture had two principal purposes. The first purpose was to provide an overview of the current thinking governing the molecular mechanism of muscular contraction, the cross-bridge theory, while the second purpose was to draw attention to the limitations of the current mechanism, and to propose an alternative way of how muscular contraction might occur. This paper will follow the same format.

Before diving into the foundations of the cross-bridge theory, we should like to point out that the proposed mechanism of muscular contraction has changed completely over the past century. At the beginning of the 20th century, the so-called lactic acid theory was based on the idea that contraction was caused by the lactic acid-induced folding of long protein chains along the muscle fibers. This theory remained the primary mechanism for muscle contraction until the early 1950s.

H. Huxley [17] was the first to suggest that contraction may occur through the relative sliding of two sets of filaments. This so-called “sliding filament theory” was independently confirmed by H. Huxley and Hansen [19] and A. Huxley and Niedergerke [15] using isolated myofibrils and phase contrast microscopy and single fibers and interference microscopy, respectively. The question then became, what makes filaments slide?

2. The 1957 formulation of the cross-bridge theory

In 1957, A. Huxley [13] formulated a theory that proposed how filaments slide past each other. The theory was based on several properties that had been observed in muscle experiments. First, Ramsey and Street [27] performed experiments on single fibers of frog and showed that isometric force reached a maximum at an average sarcomere length of about 2 µm. When increasing the length beyond 2 µm, they found a nearly linear decrease in force, with zero force occurring at about 4.2 µm (Fig. 1). This result suggested that force production might be directly related to the amount of myofilament overlap. Second, Hill [11] reported that the relationship between the speed of shortening and the total rate of energy liberation was a rectangular hyperbola (Fig. 2).
Needham [26] pointed out that Hill’s [11] observation could readily be explained by active sites in a muscle that operate in a cyclic manner, similar to an enzyme causing a chemical reaction. Third, adenosine triphosphate (ATP, Fig. 3) was discovered in muscle extracts [20], and was shown to be hydrolyzed by actomyosin [4]. These findings hinted at the central role of ATP as the fuel for muscle contraction.

In the formulation of the cross-bridge theory, A. Huxley [13] assumed that thick filaments (myosin) had side pieces (M) that were connected via elastic springs to the thick filament (Fig. 4). These side pieces were thought to oscillate about their equilibrium point (O) because of thermal agitation (Brownian motion). Side pieces were assumed to attach to specialized sites (A) on the thin filament. Attachment and detachment of the side pieces was thought to occur in a cyclic fashion, therefore great shortening of the muscle could occur through a series of small steps. Each time a side piece M is attached to a corresponding A site, force is transmitted between the two filaments because of the force in the elastic springs of the M piece, except if M is at its equilibrium position where strain (and force) in the springs was assumed to be zero.

How do we now get directed force from a system as shown in Fig. 4. If we assume that M attaches spontaneously to A, as Huxley did, then one would assume that the probability for a detached cross-bridge to attach to an actin site is equal to the probability of its location (x, Fig. 4). It can be shown that the probability distribution of M’s location undergoing Brownian motion is a Gaussian shape about the equilibrium position. Therefore, a cross-bridge would likely attach to the actin at a location where strain in the springs is relatively low, thus force would be low as well. Similarly, from the structural symmetry of the system, it follows that M would attach to A with equal probability for A being located on the left and right of the cross-bridge equilibrium position.
Therefore, on average, the actin filament would undergo a zero displacement relative to the myosin filament. Obviously, such a system cannot produce directed muscle force and shortening. In order to produce a directed movement of actin relative to myosin (such that muscle shortening and directed force production could occur), Huxley [13] introduced the idea that the rate of attachment \( f \) and detachment \( g \) were dependent on the \( x \)-location (Fig. 4) of the actin attachment site relative to the cross-bridge equilibrium position. These rate constants had to be chosen asymmetrically in the sense that the attachment probability of a cross-bridge had to be greater for positive \( x \)-values (thus, cross-bridge attachment would cause muscle shortening) than for negative \( x \)-values. Huxley’s asymmetrical choice is shown in Fig. 5. No explanation was given as to how this asymmetry may be produced.

If we now consider, as Huxley [13] did, a great number of M–A pairs that have one and the same \( x \)-location at each instant in time, the proportion of attached cross-bridges, \( n(x) \), is a function of time exclusively. By definition of \( f(x) \) and \( g(x) \), the rate of change of \( n(x) \) over time becomes:

\[
\frac{dn}{dt} = (1-n)f(x)-ng(x)
\]  

For a dynamic equilibrium state (i.e., \( \frac{dn}{dt}=0 \)), we find that the number of attached cross-bridges, \( n_{eq} \), is given by the probability of attachment:

\[
n_{eq} = \frac{f(x)}{f(x) + g(x)}
\]  

So far, we have assumed that all cross-bridges have the same value \( x \) at each instant in time, \( t \). However, for a great number of cross-bridges, \( x(t) \) would be distributed (almost) uniformly over the range \([-0.5l_a, 0.5l_a]\), where \( l_a \) is the distance between actin attachment sites. The proportion of attached cross-bridges, \( n(x, t) \), is now a function of \( x \) and \( t \), and the rate of change in \( n(x, t) \) is obtained as the material derivative:

\[
\frac{Dn}{Dt} = \frac{\partial n}{\partial t} + \frac{\partial n}{\partial x} \nu
\]  

where \( \nu \) is assumed to be negative for muscle shortening. The governing differential equation, assuming that the two myofilaments are perfectly rigid, becomes:

\[
\frac{\partial n}{\partial t} + \frac{\partial n}{\partial x} \nu = \left( \frac{1}{l_a} - n \right) f(x) - ng(x)
\]  

Eq. (4) may be solved using the method of characteristic curves [5,35].

3. The 1969 formulation of the cross-bridge model

So far, the cross-bridge head (M, Fig. 4) was thought to be in a single configuration. However, Reedy et al. [30] demonstrated that cross-bridges at rest were about perpendicular to the filament axis, while cross-bridges in rigor were tilted 45° to the perpendicular rest configuration. Based on this information, H. Huxley [18] proposed that the cross-bridge head (subfragment 1) attaches to the thin filament, and force and filament transport would be generated by a tendency of the head to rotate about its attachment point (Fig. 6). Therefore, subfragment 1 was assumed to act as a crank, pulling the thin relative to the thick filament. Subfragment 2, that connects subfragment 1 to the backbone of the thick filament.
filament, acts as a connecting rod, converting the rotary movement of the cross-bridge head into a linear displacement of the filaments. The idea of the cross-bridge power stroke was born.

4. The 1971 formulation of the cross-bridge theory

A. Huxley and Simmons [16] observed that when a muscle fiber is shortened rapidly, force drops virtually simultaneously with the length change, and then recovers in two distinct phases, a quick and a slow phase (Fig. 7). Huxley and Simmons [16] defined the force transients associated with a quick shortening step with two characteristic variables, $T_1$ and $T_2$. $T_1$ was defined as the minimum force achieved during the rapid shortening step. $T_2$ was defined as the force at the end of the quick recovery phase. $T_1$ was found to vary almost linearly with the magnitude of the step, reaching zero force at a step amplitude of approximately 6 nm per half-sarcomere (Fig. 8). $T_2$ remained nearly the same as the isometric force just prior to the length step, $T_0$, for step amplitudes of up to about 5 nm, but then started to become progressively smaller with increasing step amplitude, reaching zero force (i.e., the early, quick recovery was completely absent) at step amplitudes of 13 nm per half-sarcomere and beyond.

The interpretation of these results is summarized in the model shown in Fig. 9. The key features of this theory are that the shortening force response is associated with an elastic element and occurs in steps. The elastic element was associated with the link $AB_1$ ($AB_2$) in Fig. 9, and this elastic link accounts for the virtually instantaneous change in force with shortening (Fig. 10). The quick recovery of force following the shortening step was associated with a rotation of the (still attached) cross-bridge head from a position of small affinity between $M_1$–$A_1$ attachments ($M_1A_1$) to increasingly greater affinities between $M$–$A$ for stable states $M_2A_2$, $M_3A_3$, and $M_4A_4$ (Fig. 9). Rotation of the cross-bridge head through these different attachment states would stretch the elastic link (Fig. 10), and so provide a quick force recovery. For step amplitudes greater than about 13 nm per half-sarcomere, all attached cross-bridges were assumed to have detached, therefore, the quick recovery offered by cross-bridge head rotation was lost, and only a slow force recovery was possible that was governed by the (slow) rate of attachment of the cross-bridges to the actin attachment sites.
Fig. 10. Schematic illustration of the presumed events associated with a rapid release and the following quick recovery of force. (a) The cross-bridge head is in its initial position and the elastic link is stretched. (b) A rapid release has occurred. The cross-bridge head is in the same orientation as in (a) but the elastic link has shortened because of the relative movement of the myofilaments. The cross-bridge force (carried by the elastic link) is smaller in (b) than in (a). (c) The cross-bridge head rotates to a position of lower potential energy, thereby stretching the elastic link and increasing the cross-bridge force without any myofilament movement.

5. Current thinking

In the 1969 and 1971 models of the molecular mechanisms of contraction, cross-bridge rotation plays an important part. This rotation was thought to occur about the attachment point of the cross-bridge to actin. However, in a series of structural studies [28,29], it was suggested that the connection between the cross-bridge head (subfragment S1) and actin does not allow for rotation, but that rotation takes place through a conformational change of the light-chain binding domain about a hinge within the myosin head.

Specifically, the following sequence of events was proposed for muscular contraction (Fig. 11). Starting
from the rigor conformation, Rayment et al. [29] suggested that the narrow cleft that splits the 50 kD segments of the myosin heavy chain sequence into two domains is closed (Fig. 11A, horizontal gap, perpendicular to the actin filament axis). Addition of ATP, and initial binding of ATP to myosin at the active site causes an opening of the narrow cleft between the upper and lower domains of the 50 kD segments. This event, in turn, disrupts the “strong” binding between actin and myosin, but still allows for a “weak” attachment (Fig. 11B). The final ATP binding to myosin causes a closure of the nucleotide binding pocket and a corresponding change of the myosin molecule. Myosin now detaches from actin and ATP is hydrolyzed (Fig. 11C). Rebinding of myosin to actin can now occur, presumably in multiple steps. The gap between the upper and lower domain closes in this process to produce strong binding, and phosphate, P, is released. This event starts the power stroke (Fig. 11D). During the power stroke, the myosin S1 reverses its conformational change induced by ATP binding, the active site pocket is reopened, ADP is released, and the rigor conformation is established (Fig. 11E). The cross-bridge cycle can now be restarted by ATP binding to myosin.

The detailed reactions of myosin S1 with actin and ATP are not known because not all of the rate constants have been determined. However, combining the structural evidence [28,29], the biochemical data measured in solution [2,8,10–22,24,31], and the mechanical data [6,16], it is possible to infer the likely actin–myosin hydrolysis cycle (Table 1). Superimposing the biochemical cycle with a schematic structural model for the hydrolysis cycle (Fig. 12) gives the current thinking of how muscular contraction might occur.

Starting from the top left drawing in Fig. 12, and following the arrows (the likely path of the actin–myosin hydrolysis cycle), we go through the following steps.

The binding of ATP catalyzes the dissociation of myosin from actin [3,32]. When dissociated, ATP is hydrolyzed, and the cross-bridge head goes through a conformational change (the recovery stroke, Fig. 12). Myosin attaches to actin, phosphate is released, and the power or working stroke is initiated. ADP is released, establishing the rigor conformation. ATP then attaches to the myosin head, myosin can now dissociate from actin, and the cycle may restart.

Obviously, there are variations from the above proposed theory of contraction, however Figs. 11 and 12, and Table 1 represent the most accepted thinking at present. An interesting variation of the above ideas was proposed by A. Huxley [14] who suggested the possibility of cross-bridge rotation about its attachment point on the actin filament. Another important aspect of the scheme discussed above is that the rate limiting step of the cross-bridge cycle occurs in the attachment of myosin to actin (Table 1). The remaining steps in the hydrolysis cycle are considered much faster than the attachment rate.

6. Limitations

The detailed mechanical steps of muscle contraction, as well as the details of the actin–myosin hydrolysis cycle are not known. And to cite A. Huxley [14]:

the whole history of muscular contraction during the last half century shows that even when a set of ideas seems to be well established, there is a large chance that it will be overthrown by some unexpected discovery.

With this quote in mind, we should continuously ask ourselves, what are the limitations of the current thinking

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Table 1

<table>
<thead>
<tr>
<th>Actin–myosin hydrolysis cycle (rabbit skeletal muscle). (Adapted from Howard [12], with permission)</th>
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<tr>
<td>(+8 kT)</td>
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<tr>
<td>A·M·T</td>
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M, myosin; T, ATP; D, ADP; P, phosphate; A, actin. The most commonly followed path is shown in bold type. In parentheses are the approximate free energies of the states assuming [ATP]=4 mM, [P]=2 mM, [ADP]=0 μM. The actin concentration is taken to equal 1 mM, its concentration in skeletal muscle (this is fairly arbitrary because the effective concentration in a muscle depends on the accessibility of the actin site to the myosin head). Overall ATPase: $k_{cat}=25$ s⁻¹, $K_{cat}(ATP)=10$ μM, $K_{cat}(actin)=100$ μM (low ionic strength) at 20 °C [2]. The rate constants are based on experimental data taken from isolated S1 and/or myofibrils under roughly physiological ionic strength. The values vary by up to a factor of 10 between laboratories. The constants (K) are dissociation constants and $k_i(k_−)$ is the rate constant in the clockwise (counterclockwise) direction (from Howard [12], with permission).
on muscle contraction, and is the set of well established ideas still the best in view of newly emerging experimental results?

One of the things that has troubled us is the asymmetry of the rate constants in a seemingly perfectly symmetrical model in the 1957 theory (Figs. 4 and 5). Of course, the asymmetry was required, otherwise there would have been no net force and no net sliding of the actin relative to the myosin filament. However, no reason was provided why, from a biological point of view, the rate constants for attachment and detachment of the cross-bridges were asymmetrical. Although, in more recent models, structural arguments for this asymmetry have been proposed, none seems terribly convincing.

Other questions arise from experiments on single molecules. For example, if contraction occurs as schematically proposed in Figs. 11 and 12, one would expect that the relative sliding of actin and myosin during a single powerstroke could be calculated from the angular reorientation and the magnitude of the lever arm. However, it is known that the myosin subfragment 1(S1) has a shorter neck than the double-headed HMM construct. Assuming, as has been done, that the neck region of the cross-bridge acts as the lever arm that determines the step size of a single power-stroke, one would expect a smaller step size from S1 compared to HMM. However, such a difference was not found [25]. Similarly, Yanagida [33] found that step sizes remained about the same for myosin II molecules with normal neck lengths, and molecules in which the neck region was reduced to 20% of its normal length. Furthermore, Yanagida [33,34] found that myosin II had a step reversal in about 10% of all steps observed. These results, although preliminary, cannot be readily explained by a power stroke model of muscle contraction.

As a microscopic molecular motor, the myosin head operates at energy levels that are just a little greater than the random thermal energy of the surroundings. These thermal baths are essential for the process of the chemical reactions. The myosin head is exposed to these thermal forces that arise from collision with molecules in the surrounding fluid. Because of the random occurrence of these collisions, in terms of direction and magnitude, the cross-bridge head will undergo a random diffusion, or Brownian motion. In the detached state, the myosin head moves more or less freely, and therefore, undergoes a free Brownian motion. In the attached state, the random diffusion is limited by the force field of the actin filament. The transition between the two diffusive modes is driven by the chemical reaction of ATP hydrolysis. Therefore, the movement of the cross-bridge head has to be stochastic in nature and must be described by a reaction–diffusion equation. Note that thermal diffusion was part of the cross-bridge theory from its conception [13].

At first glance, it may appear that Brownian motion could be quite disruptive and may greatly affect the efficiency of events such as muscular contraction. However, contrary to this intuitive thinking, it appears that the myosin head can extract work from the thermal bath if the system is far from equilibrium and if there is a structural asymmetry in the geometry of the system. A system that extracts work under these two conditions is known as a thermal ratchet. We will investigate these systems in much more detail in the following paper on ratchet-type mechanisms of molecular movement.

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**Fig. 12.** Schematic illustration of the current thinking of the cross-bridge cycle, including a best estimate of the rate constants of the reactions (adapted from Howard [12], with permission).
specifically as they apply to contraction in skeletal muscles. Ratchet-type mechanisms can work without the assumption of asymmetry of the rate constants, an assumption that is essential for the power-stroke cross-bridge model. In the following, we would like to illustrate the role of noise in a system that is far from equilibrium with a simple example. The goal of this example is to show the difference between a system in which force is produced by a power stroke and one in which the system extracts work from the Brownian motion.

Imagine a microscopic “being” at a starting point A of a road, who wants to reach a point B further along the road. Assume that the road has two parallel lanes: One lane has wind locally, but the average wind along the road. Assume that the road has two parallel lanes: One lane has wind locally, but the average wind along the lane is zero. In the second lane, there is no wind. The microscopic “being” is not allowed to walk on the lane without wind. There are two strategies to reach point B. The first strategy consists of walking forcefully in the windy lane. The second strategy consists of staying in the lane without wind and watching the windy lane. Every time the wind is in the required direction, the microscopic “being” jumps into the windy lane and takes advantage of the direction of the wind. Every time the wind is in a direction opposite to the one the “being” wants to go, our macroscopic friend jumps to the quiet lane. Loosely, the first strategy is analogous to the power stroke theory in which the energy is used directly (“pay as you go”); and the second strategy is analogous to the ratchet theory in which the energy is used for the switching strategy itself.

Ratchet-type mechanisms are thought to be part of many molecular motors [1]. In the companion paper, we explore ideas about how a ratchet mechanism may explain the workings of skeletal muscle myosin II and actin, i.e. muscular contraction and force production.

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