Theory of Muscle Contraction II. Isotonic Contraction

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ABSTRACT: The theory of muscle contraction developed in Part I is extended to non-isometric cases. The basic feature of the approach is the strong viscous coupling of the movement of the counterionic (K^+) layer with the movement of I-filaments. The surface conductance of the K^+ layer governs the flux of H^+ along the I-filaments which in turns regulates the rate of ATP hydrolysis. The energy output of the muscle becomes the function of its mechanical activity. By assuming linear dependence of the K^+ layer's surface conductance on the velocity of shortening Hill's equation has been derived. With a set of reasonably chosen values of the basic parameters of the theory the values of Hill's constants have been computed. The theory has been also shown to provide the observed dependence of the isometric tension on the degree of the myofilamental overlap.

INTRODUCTION

The essential features of the theory evolved in Part I may be concisely reiterated as follows:

1. After an initial hydrolysis of ATP by the myosin ATPase (M) the myosin heads remain in a protonated state. The altered charge state of the heads leads to inhibition of contact with the actins of the neighboring I-filaments. So long as H^+ remains associated with the heads, ADP does not readily dissociate from M, blocking thereby further hydrolysis of ATP.

2. The I-filaments are surrounded by layers of structured water along which protons move by the high frequency jump mechanism. The I-filaments connect the region of overlap of the myofilaments in which H^+ are produced to the Z membrane where the same are consumed in the Lohmann's reaction. The flux of H^+ across the I-band is assumed to be mainly along the I-filaments.

3. The calcium ions, liberated into the sarcomere from SR because of the electrical pulses in the T-system, induce transient contacts of the heads with the actins. H^+ ions move over to the I-filaments in the overlap region and then along the I-filaments toward the Z membrane en route to the transverse tubules. The removal of H^+ from the heads leads to rapid hydrolysis of ATP.

4. The flux of H^+ along the I-filaments is made possible by the charge-compensating movement of the K^+ layer around the tropomyosin molecules (Tm). In case of low surface conductance of this counterionic layer the buildup of a diffusion potential of large magnitude would retard H^+ flux and hinder H^+ movement from the heads to the actins. This in turn would adversely affect the rate of ATP hydrolysis.

5. The electro-osmotic flow of the K^+ layer caused by the surface localized field generated by proton jumps is directed towards the M-line. The K^+ concentration gradient from the H- to I-band causes a reverse flow of the K^+ layer along the A-filaments. The viscous drag of the K^+ layer on the myofilaments generates the contractile force in the sarcomere.

6. The free energy of ATP hydrolysis in the present view is first converted into the electrochemical gradient and ensuing flux of H^+ and then, by means of the viscous coupling of the movement of the K^+ layer with the actins, to the energy output of the muscle in terms of heat generation and work performance.

It follows from the above that the surface conductance of the K^+ layer affects the flux of H^+ and thus also the rate of ATP hydrolysis, i.e. the input of chemical energy. Because of the strong viscous coupling of the movements of the K^+ layer and I-filaments the surface conductance of the K^+ layer must be strongly influenced by the movement of the I-filaments. The acting monomers constitute obstructions for the lateral movement of the K^+ layer; this obstruction will be less if their movements are codirectional and more if the movements are antagonistic. Thus the movement of the I-filaments, that is, the mechanical activity of muscle, must affect the rate of ATP hydrolysis and hence the energy output of the muscle. The objective of this present study is to analyze the dependence of the energy output of the muscle on its mechanical activity arising from the viscoelectrical coupling between the K^+ layer and the I-filament motion and from the electrochemical coupling of H^+ flux with the rate of ATP hydrolysis. In the first section the energy output of a muscle segment of the length of a half sarcomere has been evaluated for constant velocity of the I-filaments v_a. It has been shown that the energy output is larger for shortening and smaller for stretching of muscles compared to the heat generation during isometric contraction. For large values of v_a the energy output of the muscle drops after reaching a maximum. These considerations explain the Fenn effect (Fenn, 1923, 1924), and the findings of Curtin and Davies (1973) and Hill (1964). In Section 2, Hill's empirical equation has been derived by neglecting terms of second and higher order in v_a, i.e., by restricting shortening velocities to small values. It has been shown that with a reasonable choice of the basic theoretical parameters the constrants a and b of Hill's (1938) equation are obtained to the right order of magnitude. In Section 3, the dependence of the isometric tension P_o on the degree of myofilamental overlap has been worked out. The theoretical approach reproduces the observed linear rise for small overlaps and the occurrence of a plateau region around the slack length of the sarcomeres (Gordon, et al., 1966). For the sake of simplicity the treatment in the earlier sections has been confined to muscle length variations around the slack length of the muscle in the plateau region of the tension versus overlap curve.

ENERGY OUTPUT OF MUSCLE

A half-sarcomeric segment of muscle fiber of unit cross-

sectional area is chosen as the structural unit for the quantitative description. The coordinate axis are so defined that the M-line lies in the plane $x = 0$ and the Z membrane is at $x = \lambda$ where λ is the length of the half sarcomere. The I-filaments attached to the Z membrane are pulled by the external load P in the $+x$ direction. The motion of the K^+ layer, v_K, is in the $-x$ direction, i.e., towards the M-line. The velocity of motion of the I-filaments, v_a, is counted as positive when it is co-directional with that of the K^+ layer, as it is during shortening. v_a is related to the velocity of shortening of the whole fiber, v, by the expression $v = Mv_a$ where $M = \ell/\lambda$, ℓ being the length of the fiber. λ will be assumed to vary only slightly around the slack length λ_0 so that the quantities which will occur in the description below can be taken as independent of the degree of overlap. It is further assumed that the fiber is under constant stimulation (tetanus) so that the level of Ca^{2+} is maintained at a constant level. At a sufficient supply rate of ATP a constant Nernst potential ΔV_H will then exist between the ends of the I-filaments in the A-band and the Z membrane.

The H^+/K^+ counterflux equation for the surface of the I-filaments in the half-sarcomeric segment may be written as (compare Eq. 5, Part I):

$$-J_H = J_K = \frac{g_H g_K}{g_H + g_K}\Delta V_H = \frac{1}{g_H^{-1} + g_K^{-1}}\Delta V_H \qquad (1)$$

where

$$g_i = F u_i c_i A_i/\ell_a \qquad i = H^+, K^+ \qquad (2)$$

are the surface conductances of H^+ and K^+. Here A_i are the cross-sectional areas of the surface regions along which H^+ and K^+ migrate and ℓ_a is the length of the I-filaments. Eq. 1 corresponds to an equivalent circuit for the half sarcomere with H^+ and K^+ surface resistances, g_i^{-1}, in series and ΔV_H the source of electromotive force. Because of the viscous coupling of K^+ layer movement with the movement of actins discussed in the Introduction, the surface conductance g_K is a function of the v_a. Before we proceed to work out the functional dependence of g_K on v_a for constant rates of muscle length changes, a few qualitative general statements can be made on the basis of Eq. 1 and the above-mentioned viscous coupling. The current J_H in the circuit will be larger for small values of the K^+ layer resistance. This is the case for shortening since then the actins move in the same direction as the K^+ layer and pose a lesser obstruction in the path of the K^+ layer. From Eq. 1 it follows that the energy output of the muscle $\Delta V_H J_H$ will be greater during shortening against constant load and during twitches in which the muscle is allowed to shorten than in the case of isometric contraction. This is the well known Fenn effect. Curtin and Davies (1973) observed that the muscle energy output during stretches is smaller than that during isometric contraction over the same duration of time. This is explained in terms of the increase in the K^+ layer resistance due to the movement of the actins in the $+x$ direction, opposite to the flow of the K^+ layer and the consequent drop in J_H. They also have found that the tensions generated during stretches were greater than P_o. This is easily understood in the light of the present model for the generation of muscular tension since the viscous drag on the actins is proportional to the difference $v_K - v_a$, i.e., to the relative velocity of the actins with respect to the K^+ layer. For stretching $v_a < 0$ and the viscous drag is greater than for $v_a \geq 0$. Thus the very odd situation presented by the stretching experiments is easily resolved in terms of the viscoelectric coupling model.

The influence of I-filament velocity v_a on g_K will be through the surface mobility u_K and the effective concentration of K^+, $c_{K,eff}$, defined in Part 1. In general these could be complicated functions of v_a. As a first approximation a linear dependence may be assumed:

$$u_K(v_a) = u_0 + s v_a \qquad (3)$$

$$c_{K,eff}(v_a) = c_{K,eff}(0) + t v_a \qquad (4)$$

Then

$$g_K(v_a) = g_0 + p v_a + q v_a^2 \qquad (5)$$

where

$$g_0 = F u_0 c_{K,eff}(0) A_K / \ell_a \qquad (6)$$

$$p = F(tu_0 + sc_{K,eff}(0))A_K/\ell_a \qquad (7)$$

$$q = F s t A_K/\ell_a \qquad (8)$$

If cubic and higher-order terms in v_a are neglected the current J_H in the circuit described by Eq. 1 is

$$J_H(v_a) = \Delta V_H (g_0 t_{Ho} + p t_{Ho}^2 v_a - (\frac{p^2}{g_H + g_0} - q) t_{Ho}^2 v_a^2) \qquad (9)$$

where $t_{Ho} = g_H/(g_H + g_0)$ is the transport number of H^+ for $v_a = 0$. In the case of isometric contraction the energy output rate of the half-sarcomeric segment is

$$\dot{E}^o = \Delta V_H J_H^o = \Delta V_H^2 t_{Ho} g_o \qquad (10)$$

For isotonic shortening against a load $P < P_o$ the visco-electric machine of the half sarcomere performs work along with the generation of heat, and we write for the rate of energy output:

$$\dot{E}(v_a) = \dot{E}^o + a v_a - c v_a^2 + P v_a \qquad (11)$$

where

$$a = \Delta V_H^2 p t_{Ho}^2 \qquad (12)$$

$$c = \Delta V_H^2 t_{Ho}^2 (\frac{p^2}{g_H + g_o} - q) \qquad (13)$$

It will be shown later that, with a set of reasonably chosen basic parameters entering Eqs. 6 to 9, the coefficient of the quadratic term in v_a, c, is positive. The second and the third terms together give the rate of extra heat production during shortening. For small values of v_a there is a linear rise in the rate of extra heat production. For large values of v_a the negative quadratic term leads to a reduction in $\dot{E}$. During stretching of the fiber, $v_a < 0$ so that the rate of energy output is always smaller than $\dot{E}^o$. These results are in accordance with the earlier statements with the addition of the decrease in the rate of energy output of muscle for large velocities of shortening. The decrease in $\dot{E}$ for rapid shortening explains the findings of Hill (1964) according to which the rate of muscle energy output first increases almost linearly in the range of small velocities of shortening and then, after reaching a maximum at about 60% of the maximum speed of shortening ($P = 0$), drops to lower values for larger velocities.

HILL'S EQUATION

For the derivation of Hill's famous empirical equation it is assumed that the velocity of shortening is small and the quadratic term in Eq. 11 is negligible. The rate of extra energy output of the muscle is then

$$\Delta\dot{E}(v_a) = \dot{E}(v_a) - \dot{E}^o = (a + P)\, v_a \qquad (14)$$

Since the rate of extra energy output is zero for $P = P_o$ we can develop $\Delta\dot{E}[v_a(P)]$ in a power series around $P = P_o$ starting with a linear term in $P - P_o$:

$$\Delta\dot{E}[v_a(P)] = b_1(P - P_o) + b_2(P - P_o)^2 + \ldots \qquad (15)$$

$$b_1 = \frac{d\Delta\dot{E}}{dP}(P_o) \text{ etc.}$$

It is easily seen that b_1 is negative since for $P < P_o$ $\Delta\dot{E} > 0$. The earlier assumption of small velocities of shortening implies that the quadratic term in Eq. 15 is also negligible. Writing b_1^+ for the absolute value of b_1 we have

$$\Delta\dot{E}[v_a(P)] = b_1^+ (P_o - P) \qquad (16)$$

If the velocity of shortening v_a in Eq. 14 corresponds to the imposed load P we can eliminate $\Delta\dot{E}$ from the two equations to get:

$$v_a = b_1^+ \frac{P_o - P}{a + P} \qquad (17)$$

Multiplying by the number of half sarcomers along the length of the fiber, M, and putting $b = Mb_1^+$ we get Hill's equation:

$$v = b(P_o - P)/(a+P) \qquad (18)$$

Experimentally Hill's equation describes force-velocity behavior of muscle correctly only in the range of small velocities of shortening. Inclusion of the quadratic terms in Eqs. 11 and 15 would give a better approximation for muscle force-velocity response. Solving the ensuing quadratic equation for v_a and multiplying by M we get

$$V = \frac{M(a+P)}{2c}\left[1 - \left(1 - \frac{(b_1^+(P_o - P) + b_2(P_o - P)^2)4c}{(a+P)^2}\right)^{1/2}\right] \qquad (19)$$

This is amenable to experimental verification.

As the values of a, b and $\dot{E}^o$ are known from experiments it is possible at this stage to relate the basic parameters of the theory with these observables. The experimental data of Curtin and Davies (1973) will be used for this purpose. At the moment no precise values for the basic parameters are known and it is sufficient to establish that, with a reasonable choice of a set of these parameters, the observable quantities are reproduced in terms of orders of magnitudes. The values of the parameters given below refer to the surface values at the I-filaments, as was also the case in Part 1.

$u_H = 0.1$ $\quad u_0 = 10^{-4}$ $\quad (\text{cm}^2\ \text{V}^{-1}\ \text{s}^{-1})$

$c_H = 10^{-8}$ $\quad c_{K,eff}(o) = 0.2\text{x}10^{-5}$ $\quad (\text{moles cm}^{-3})$

$A_H = 4.3\text{x}10^{-3}$ $\quad A_K = 2\text{x}10^{-2}$ $\quad (\text{cm}^2)$ $\quad \ell_a = 10^{-4}(\text{cm})$

By assuming

$$u_K(v_a^{max}) = 5\text{x}10^{-4}\ (\text{cm}^2\ \text{V}^{-1}\ \text{s}^{-1})$$

$$c_{K,eff}(v_a^{max}) = 10^{-4}\ (\text{moles cm}^{-3})$$

the parameters s and t can be estimated as follows. With $M = 1.4\text{x}10^4$ (3-cm-long fiber, slack length of half sarcomere = $1.25\ 10^{-4}$ cm) and $v^{max} = 6$ cm/s, $v_a^{max} = 2.5\text{x}10^{-4}$ cm sec^{-1}. From Eqs. 3 and 4 we get $s = 1.6$ and $t = 0.4$. From the above set of values the following values for the circuit parameters can be computed: $g_0 = 3.8\text{x}10^{-3}$ ohm^{-1}; $p = 8.3\text{x}10^2$ ohm^{-1} s cm^{-1}; $q = 1.2\text{x}10^7$ ohm^{-1} s^2 cm^{-2} $\quad g_H = 4.2\text{x}10^{-4}$ ohm^{-1} and $t_{Ho} = 10^{-1}$. The rather arbitrary choice of A_H made earlier was meant to make t_{Ho} a round figure for computation purposes.

The H^+ Nernst potential $\Delta V_H = 2.3\frac{RT}{F}\Delta\text{pH}$ is roughly 55 ΔpH mV at the experimental temperatures. Taking a pH value of 5.5 around the tropomyosin units at the ends of the I-filaments in the overlap region and a pH of 7.0 in the region of the Z-membrane we have a proton motive force, ΔV_H, of 82.5 mV across the I-filaments.

As the first quantity of interest, the rate of heat production during isometric contraction is evaluated using Eq. 10 and is found to be $2.6\text{x}10^{-6}$ J/s. This may be compared with the rate of release of free energy of hydrolysis of ATP in the same half-sarcomeric segment of muscle of 1 cm^2 cross-sectional area. In Part 1 the rate of hydrolysis of ATP in such a segment was evaluated as $1.4\text{x}10^{-10}$ moles/s. By taking $\Delta G_{ATP} = 7$ kcal/mole, the rate of input of chemical energy in the segment is $4.1\text{x}10^{-6}$ J/s. This means that for isometric contraction the power output $\Delta V_H J_H$ of the equivalent circuit accounts for about 60% of the energy released by the hydrolysis of ATP. This is a result of utmost importance not only in the context of the theory of muscle contraction but also for the mode of action of ATPases in general.

Next it may be confirmed that the velocity of the K^+ layer in isometric contraction given by the relation: $v_K = u_0\ t_{Ho}\ \Delta V_H/\ell_a$ agrees with the value $\sim 10^{-2}$ cm/s used for the calculation of isometric tension in Part 1. P_o has therefore the same value of about 14 Newtons/cm^2 of muscle cross-sectional area. The value of a, using the defining equation, Eq. 12, is 5.6 N. This compares well with the experimental value of 5.5 N. b can also be estimated by using the defining equation, Eq. 15, for b_1 by transforming the experimental $\Delta\dot{E}$ (v) curves to the form $\Delta\dot{E}$ (P) and evaluating $\Delta\dot{E}/\Delta P$ for the limit P tending to P_o. This will not be carried out here but it is easily seen that the value of b obtained through this procedure is also close to the experimental value of about 3 cm/s.

DEPENDENCE OF ISOMETRIC TENSION ON OVERLAP

The proton flux builds up gradually in the overlap region by the transfer of H^+ from the A-filaments to the I-filaments via the transient contacts of the cross-bridges and achieves a final value at the end of the A-band. The flux of potassium ions in the overlap region is composed of two parts: a) the charge-compensating flux J_K^+, which must match the flux J_H at every plane cutting the I-filaments perpendicularly and b) the neutral flux J_K^o in which K^+ ions move together with the phosphate ions left behind by H^+. The latter flux enables the electro-osmotic flow of the K^+ layer to continue inwards, in the direction of the M-line, without violating microneutrality or causing hydrodynamic flow problems. However this flux,

J_K^o, cannot be confined to the immediate neighborhood of the tropomyosin molecules and hence cannot transfer any appreciable amount of momentum to the actins. This has to come primarily from the flux J_K^+. At the terminal points of the I-filaments J_H is zero, hence J_K^+ and therefore also $v_K = J_K^+ / A_K c_{K,eff}$ will drop to zero values as one moves deeper into the A-bank to the terminal points of the I-filaments. The viscous drag of the K^+ layer will, accordingly, vary over the length of the I-filaments in the overlap region, rising monotonously from the ends of the I-filaments in the A-band to reach the maximum value at the end of the A-gand and then remaining constant up to the Z membrane. In order to put the above ideas in quantitative terms the profile of J_H in the overlap region has to be found out.

If m is the length of half of the A-band then the overlap $\Theta = m + \ell_a - \lambda$. In this treatment the length of the half sarcomere, λ, will be restricted to the region $\ell_a \leqslant \lambda \leqslant (\ell_a + m)$. The M line is chosen to lie in the plane $x = 0$ and the Z-membrane lies in the plane $x = \lambda$. A second variable $y = x - (m - \Theta)$ is introduced such that $y = O$ coincides with the ends of the I-filaments in the A-band.

In the overlap region $0 \leqslant y \leqslant \Theta$, the increase in J_H from y to $y+\Delta y$ is due to migration of H^+ from A-filaments over the cross-bridges (CB):

$$J_H(y+\Delta y) - J_H(y) = \Delta J_H = J_{CB}\,\Delta y \qquad (20)$$

Here J_{CB} is the H^+ flux over the cross-bridges per unit length of the myofilamental overlap. If ΔV_{CB} is the H^+ Nernst potential across CB and σ_{CB} the conductance of CB per unit length,

$$J_{CB} = \Delta V_{CB}\,\sigma_{CB} \qquad (21)$$

Both σ_{CB} and ΔV_{CB} will be assumed to be constant in the overlap region. From Eq. 20 we have

$$J_H(y) = \int_0^y dy\, J_{CB} = \Delta V_{CB}\,\sigma_{CB}\, y \qquad 0 \leqslant y \leqslant \Theta \qquad (22)$$

For $y > \Theta$ there is no further increase in J_H. Thus

$$J_H(y>\Theta) = J_H(\Theta) = \Delta V_{CB}\,\sigma_{CB}\,\Theta \qquad y > \Theta \qquad (23)$$

J_K^+ has the same magnitude as J_H, therefore,

$$v_K(y) = C\,y \qquad 0 \leqslant y \leqslant \Theta \qquad (24)$$

where

$$C = -\frac{\Delta V_{CB}\,\sigma_{CB}}{A_K\,c_{K,eff}}$$

For $y > \Theta$, $v_K = C\,\Theta$ = constant. As worked out in Part 1, the viscous drag on a stationary actin monomer is $f^{-1}\,6\pi\eta R_a v_K = w\,v_K$. For the calculation of the net viscous force F we define ρ_a as the density of actins in the half-sarcomeric segment of unit cross-sectional area. Then the numbers of actin monomers in the length dy is $dn_a = \rho_a\,dy$. Therefore,

$$F = \int_0^\theta dy\,\rho_a w\,Cy + \int_\theta^{\ell_a} dy\,\rho_a w\,C\,\Theta =$$

$$Cw\rho_a[\Theta^2/2 + \Theta(\ell_a - \Theta)] \qquad (25)$$

For $\Theta = 0$ the tension is nil as far as the H^+ flux via CB is concerned. However, even in such a situation, there can be non-negligible flux of H^+ by means of diffusion across the gap between the tips of the myofilaments. For small values of overlap Θ, Eq. 25 predicts a linear rise in tension due to the $\Theta\ell_a$ term. For large values of Θ we first note that close to the M line the A-filaments are devoid of CB so that Θ can take a maximum value of $m - m_1, 2m_1$ being the length of the A-band without CB. After Θ exceeds this value the first integral achieves a constant value while the term proportional to $\Theta(\ell_a - \Theta)$ decreases after reaching a maximum at $\Theta = \ell_a/2$. Hence Eq. 25 provides the correct description of the tension as a function of the myofilamental overlap (Gordon, et al., 1966).

DISCUSSION

The theory developed so far has successfully covered most of the classical aspects of the phenomenon of muscle contraction. Muscle tension and velocity transients (Civan and Podolsky, 1966; Ford, et al., 1977) can be qualitatively understood in terms of the viscoelectric coupling here discussed. This may be illustrated by giving the explanation of the occurence of the reduction in the recovery of tension after the early fast recovery in a length jump ($\Delta\ell < 0$) experiment. The early phase of rapid recovery is due to the sudden increase in the velocity of K^+ layer as the hurdles posed by the actins are reduced by the codirectional movement of the I-filaments. The associated flux of K^+ depolarizes the diffusion potential so that for some time later v_K becomes less than the value which obtained in the isometric contraction.

There is much scope for improvement and extension of the theory presented here. For example we have ignored the possibility of H^+ migrating to the M-line along the A-filaments after their dissociation from the hydrolytic site. The structural proteins in the M-line contain a substantial amount of creatine phosphokinase and thus also constitute an electrode for the H^+ consuming Lohmann's reaction. If the H^+ flux is also along the A-filaments then the return flux of K^+ to the I-band along the A-filaments will be by the same mechanism as has been described for the I-filaments. One interesting outcome of this scheme will be that if the A-filaments meet the Z membrane the proton motive force will be annulled but not discharged. This could explain the oscillatory mechanical activity of the insect asynchronous fibers. In these fibers the I-band is very narrow so that the above said situation can easily occur. Until all H^+ which are liberated by the Ca^{2+} released during stimulation have reached the Z- and the M-line the proton motive force would continue to sustain oscillations. It is hoped that the present approach will provide the basis for the understanding of other types of muscle and of the contractile and motile systems of non muscle cells in general.

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