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MUSCULAR CONTRACTION

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SUMMARY

A molecular theory of muscular contraction, based on the trigger action of the cross bridge between actin and myosin, is postulated. The formation of the cross bridge is followed by a transconformation in contractile protein producing work and liberating heat. The process possesses a mechanochemical character and utilizes the energy liberated by dephosphorylation of ATP. The equation of A. HILL for tension dependence of muscle power is derived from the theory of reaction rates. The equation of A. HILL is meaningful after elementary treatment; the physical meaning of the constants in these equations is explained. Quantitative analyses are corroborated by the experimental data.

INTRODUCTION

The theory of muscular contraction explains the mechanism of this process in accordance with three groups of facts: structural data obtained by investigations using electron microscopy, roentgenography and low-angle scattering of X-rays, thermomechanical measurements and biochemistry. The theory is partially complicated by excessive amounts of experimental data which already exist.

Structural data demonstrate that shortening of the muscle is determined by the sliding action of actin and myosin filaments and that actin and myosin interact only through cross bridges connecting the projections of H-meromyosin with the active sites of actin[1–4]. Models based either on coiling of the filaments of contractile proteins or on the combination of coiling and sliding (*e.g.* ref. 5, the review in ref. 6) are of no value; electron microscopy shows no coiling, and no structural foundation exists for important roles of any forces except those determined by the formation and breakdown of cross bridges. Therefore, the hypothesis based on the long-range electrostatic interaction between actin and myosin is unfounded[7], which is also true for the hypothesis concerning the role of surface tension between these proteins suggested by EIDUS[8]; 5 years later the same idea in a more naive qualitative form was published by GAMOW[9]. Structural investigations show that actin and myosin are in contact only through cross bridges. Models based on continuous contacts contradict both biochemical and thermomechanical data.

The thermomechanical properties of striated muscle were investigated by A. HILL[10]. The shortening muscle produces work and liberates heat. The rate of work and heat production is expressed by

$$\dot{E} = PV + \alpha V \tag{1}$$

where P is the applied tension, V is the rate of muscle shortening, α is heat liberated by shortening per unit of length. The first experiments of A. HILL demonstrated that α is a constant independent of P; later it was shown that

$$\alpha = 0.16\, P_0 + 0.18\, P \quad \text{(ref. 11)} \tag{2}$$

where P_0 is the tetanic tension, *i.e.* the maximal load supported by muscle without its lengthening. It follows from (1) and (2) that

$$\dot{E} = (1.18\, P + 0.16\, P_0)V \tag{3}$$

A. HILL obtained also the experimental equation

$$\dot{E} = b'(P_0 - P) \tag{4}$$

Independently A. HILL obtained the experimental characteristic equation describing the P dependence of V

$$(P + a)V = b(P_0 - P) \tag{5}$$

where b is a constant practically equal to b'.

Constant a is

$$a = 0.25 - 0.30\, P_0 \tag{6}$$

If b equals b', hyperbolic Eqn. (5) must follow from (1) and (4). As α is not a constant equal to a, Eqn. (5) cannot be directly deduced from (1) and (4). This discrepancy is not explained.

According to Eqn. (5), the rate V becomes maximal if $P = 0$. Thus,

$$V_{max} = b\frac{P}{a} \tag{7}$$

and from Eqn. (5),

$$V_{max} = 0.25 - 0.30b \tag{8}$$

The relation (8) is derived from the experiment independently from Eqn. (5).

Value P_0 depends on the sarcomere length and is not constant during muscle shortening[12,13]. P_0 is small if the sarcomere length is big; P_0 increases and becomes maximal if the sarcomere is shortened until 2.0–2.5 of its minimal length and then decreases. The maximum of P_0 corresponds to the maximal overlapping of actin and myosin filaments; the number of active cross bridges increases during the process of shortening. The decrease in P_0 at small sarcomere lengths can be explained by the deformation of protein filaments. A. HILL's equations are valid in the region of maximal P_0, corresponding to the plateau on the curve $P_0(L)$ where L is the sarcomere length. This region of L values corresponds to the length of muscle *in situ*.

Biochemical data show that shortening of muscle is stimulated by the transfer of Ca^{2+} from sarcoplasmic reticulum into sarcoplasm. The muscular work is determined by the dephosphorylation of ATP produced by the ATPase activity of myosin. Muscular contraction can be considered as a mechanochemical process: transformation of energy of macroergic bonds of ATP into mechanical work.

NATURE OF THE CONTRACTION PROCESS

It is concluded that the chemical transformation of ATP resulting in muscular work occurs in direct relationship with the formation and follows breakdown of myosin–actin cross bridges. Shortening must result from a pushing or pulling effort; this effect on the organization at a molecular level can be explained by suggesting a conformational change in contractile protein. This transconformation cannot be localized from existing data. It can occur in the H-meromyosin projection as suggested by DAVIES[14], in L-meromyosin along the myosin filament according to the model of A. HUXLEY[15] and DESHTSHEREVSKY[16], in actin or in both actin and myosin.

Transconformation of the protein can possess the character of a phase transition. ENGELHARDT[17] first attempted to explain muscular contraction as a phase transition process. He thought that the shortening was a result of melting of protein crystals. Later these ideas were developed by PRYOR[18] and by FLORY[19,20]. In discovering that under the action of ATP sharp shortening of the glycerinized muscle fibers begins only at a definite concentration of the ethylene glycol–water mixture, HOEVE AND FLORY[21] and HOEVE *et al.*[22] indirectly supported this idea with experimental data.

Recently T. HILL[23,24] proceeding from his works on the phase transitions of linear systems, has considered contraction of the sarcomere as a first-order phase transition between two states of protein filaments, both without and with cross bridges[25]. The first state corresponds to elongated sarcomere without the overlapping filaments of myosin and actin; the second state corresponds to the shortened sarcomere where the filaments overlap. The applied load hinders the phase transition whose condition can be written

$$f_0 L = \Delta H - T\Delta S \tag{9}$$

where f_0 is the load P_0 per one cross bridge, L is the distance between two neighboring bridges and ΔH and ΔS are the differences of the enthalpies and entropies of two states. This theory does not include the chemistry of the process, the role of ATP reduces to the small change of ΔH and ΔS.

Later T. HILL[26] rejected this theory mainly because f_0 (*i.e.* P_0) is not constant but rather depends on the sarcomere length.

It seems to be impossible to explain the muscular work on the basis of thermodynamic equilibrium. It is necessary to solve the problem kinetically.

The first kinetic model including all facts listed above, was put forward by A. HUXLEY[15] (see also ref. 29). This theory considers the kinetics of formation and breakdown of bridges; using special assumptions it leads to the equations which give quantitative results in agreement with those of A. HILL if the constants are suitably chosen.

Recently this theory was greatly improved by DESHTSHEREVSKY[16]. Simplifying the model, he obtained simple expressions for rates of sarcomere shortening and of formation and breakdown of the cross bridges. Eqn. (5) of A. HILL can be directly obtained from the stationary solution of the problem, considering three classes of cross bridges: free, closed and developing active force, and closed and developing hindering force.

The theory[16] suggests that the energy of transconformation is equal to $f_0 L$, where L is the interval along the filament where the bridge develops an active force.

The production of heat is introduced with an extra constant.

The theory of DESHTSHEREVSKY is essentially macroscopic as all three stages of the cyclic process, the formation of the bridge, its transition from the straining into hindering state and the breakdown of the bridge, are considered as irreversible. The values of rate constants for the formation and breakdown of the bridge have to be determined experimentally; they are not expressed through molecular parameters.

Recently T. HILL[26] and T. HILL AND WHITE[27,28] have also improved the theory of A. HUXLEY but they have not developed the calculations in such a simple and clear form as before[16].

However, it is possible to approach the problem from another side. We have to agree with H. HUXLEY[1], who wrote that the equations of A. HILL express "some characteristic property of the fundamental processes involved in contraction, and their simplicity suggests that there ought to be some very simple way of visualizing these processes". It can be shown that the second equation of A. HILL follows from simple physical considerations concerning the behavior of a single cross bridge.

THE LOAD DEPENDENCE OF POWER

Without contradicting experimental facts, assume that the following events occur in the sarcomere: (1) initiation of cross bridge formation, probably as a result of the binding of Ca^{2+} to the H-meromyosin projection or to the active site of actin; (2) formation of the cross bridge; (3) transconformation caused by this act, followed by production of work f_0L and liberation of heat q_0; (4) simultaneous breakdown of the cross bridge; suggesting that the formation of the cross bridge acts as a signal for a mechanochemical elementary act. The cross bridge is a trigger system.

The particular model which agrees with assumptions (1)–(4) was described by DAVIES[14].

As a result of all four events, energy

$$\varepsilon = f_0L + q_0 \tag{10}$$

is liberated.

The change of state of the trigger system can be described by the energy curve shown in Fig. 1. Here 1 is the state of the cross bridge and of the transconforming protein connected with it before events (1)–(4); 2 is the state after these events. l is the length of the chemical bond, or chelate bond, connecting the H-meromyosin projection with the active site of actin.

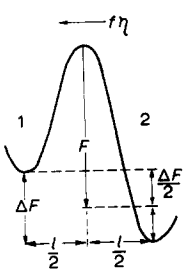

Fig. 1.

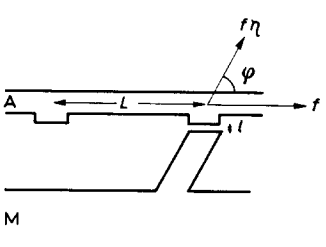

Fig. 2.

The external force f per one bridge hinders its formation, *i.e.* hinders the trigger system. The force is directed along the actin or myosin filament and therefore is directed under an angle ϕ to the bridge (Fig. 2). The acting force is equal to $f\eta$, where $\eta = \cos\phi$.

The rate of energy liberation according to the theory of rate processes can be written

$$\dot{E} = \varepsilon \frac{kT}{h} (e^{-F_+/kT} - e^{-F_-/kT}) \tag{11}$$

where F_+ and F_- are the free energies of activation for the direct and backward process and h is the Planck's constant[30]. These values are equal to

$$F_+ = F - \frac{\Delta F}{2} + \frac{fl\eta}{2} \tag{12}$$

$$F_- = F + \frac{\Delta F}{2} - \frac{fl\eta}{2}$$

It follows from (11) and (12) that

$$\dot{E} = \varepsilon \frac{kT}{h} e^{-F/kT}\, 2 \sinh \left(\frac{\Delta F - fl\eta}{2kT}\right) \tag{13}$$

Expression (11) suggests the microscopical reversibility of the process.

The basic assumption is that if $f = f_0$, the process does not occur. f_0 is the critical force making the transconformation impossible. $\dot{E} = 0$ if

$$f_0 l\eta = \Delta F \tag{14}$$

Eqn. (13) can be rewritten as

$$\dot{E} = \varepsilon \frac{kT}{h} e^{-F/kT}\, 2 \sinh \frac{(f_0 - f)l\eta}{2kT} \tag{13a}$$

and if

$$(f_0 - f)l\eta \ll 2kT \tag{15}$$

$$\dot{E} \cong \varepsilon \frac{l\eta}{h} e^{-F/kT} (f_0 - f) \tag{16}$$

Eqn. (16) coincides with the second equation of A. HILL (4) if the constant b (per one bridge) is equal to

$$b' = \varepsilon \frac{l\eta}{h} e^{-F/kT} \tag{17}$$

It follows from condition (14) the expression for the critical force

$$f_0 l\eta = \varepsilon - T\Delta S \tag{18}$$

and according to (11)

$$f_0 = \frac{T\Delta S - q_0}{L - l\eta} \tag{19}$$

In a chemical process

$$q_0 - T\Delta S = \Delta H - T\Delta S = \mu \Delta n \tag{20}$$

where $\mu\Delta n$ is the change in the chemical potential produced by the dephosphorylation of one molecule of ATP. We get

$$f_0(L - l\eta) = -\mu\Delta n \tag{21}$$

Work is produced by the change of the chemical potential.
The rate constant

$$k = \frac{kT}{h} e^{-F/kT} \tag{22}$$

has to be considered as the rate constant of the initiation, of the activation of the bridge formation.

QUANTITATIVE ESTIMATIONS

We have to establish whether condition (15) is fulfilled.

Tension is supported in every half of the sarcomere. The number N of cross bridges in a volume equal to 1 cm^2 multiplied by half the sarcomere length (1.1 μ) is equal to $6 \cdot 5 \cdot 10^{12}$ (refs. 1 and 2). Experimentally $P_0 = 3.0$ kg/$cm^2 = 3 \cdot 10^6$ dynes/cm^2. One cross bridge produces tension $f_0 = P_0/N = 4.6 \cdot 10^{-7}$ dyne. The bond length $l = 2 \cdot 10^{-8}$ cm. The value η is not known. H-Meromyosin projections are directed under right angles to the myosin filaments[31], but according to PEPE[32,33] (see also ref. 34), bridge formation is followed by the bending of these projections. $\eta = 0.5$, $f_0 l\eta = 4.6 \cdot 10^{-15}$ erg $= 2\ kT \cdot 0.055$. Therefore condition (15) is fulfilled.

The heat of shortening is 350 g·cm per cm^2 per cm of shortening. The transconformation in one bridge corresponds to the shift per L cm. If $L = 5 \cdot 10^{-7}$ cm (the distance between two neighboring sites of actin), $q_0 = 3.4 \cdot 10^5 \cdot L/N = 2.6 \cdot 10^{-14}$ erg and $f_0 L = 23 \cdot 10^{-14}$ erg. Thus $\varepsilon = f_0 L + q_0 = 25.6 \cdot 10^{-14}$ erg.

According to (8), constant b is equal to 4.0–3.3 V_{max}. The maximal shortening rate of frog sartorius at 0° is 1.33 L_0/sec, where L_0 is the initial muscle length. In our case, $L_0 = 1.1\ \mu$, half of the sarcomere length. Therefore, $V_{max} = 1.5\ \mu$/sec and $b = 4 \cdot 10^{-5}$ cm/sec. Putting this value and the estimated values of ε and $l\eta$ into (17), $F = 14000$ cal/mole.

If the temperature increases 10° (from 300 to 310°K) b must increase 2.1 times. Experiments show a 2.05-fold increase[10].

It has to be mentioned that the value of F is not very susceptible to the changes of l and η.

Putting into (19) the values of f_0, L, l, η, q_0, $\Delta S = 12.5$ cal/mole·grade.

According to (19) the value of f_0 is practically independent of temperature and increases upon heating only for 3–4% per 10°. This result also agrees with the experiment.

The liberated energy $\varepsilon = 2.6 \cdot 10^{-13}$ erg per bridge corresponds to 40% of the energy of the macroergic bond of ATP if it is assumed equal to 10000 cal/mole.

Thus the theory suggested here does not contradict the experiment. The second equation of A. HILL follows from the behavior of every formed cross bridge independent of the kinetics of formation and breakdown of an ensemble of cross bridges in the sarcomere.

It has to be emphasized that the thermodynamical condition (19) and conse-

quently (21) differs from that of T. HILL (9). The difference of sign is due to fundamental assumption of the theory suggested here; the external force influences only the trigger system, *i.e.* the formation of the bridge. The work of every bridge, if it is formed—does not depend on this force.

KINETIC AND CHARACTERISTIC EQUATIONS

Cross bridges do not act synchronously and in every moment the shortening of muscle is produced by some effective number n of bridges, which is smaller than the maximal one n_0. Therefore tension P produced by the muscle is smaller than P_0. If $P = P_0$ all bridges take part in the shortening.

It is reasonable to suggest the linear dependence of n on f or P. If $f = f_0$, $n = n_0$; and if $f = 0$, $n = n_0 r$, *i.e.* the number of bridges acting in an unloaded muscle. Thus

$$n = n_0 r + n_0(1-r)\frac{f}{f_0} \tag{23}$$

However, n depends on the shortening rate. If the rate of relative motion of the protein filaments v is high, all cross bridges have insufficient time for their formation, and n has to be small. In the steady state, the ratio n/n_0 is expressed by the probability of bridge formation, *i.e.* the probability of interaction of the sites moving with relative rate v. Let x be the distance between sites M and A along the filament. The probability of their interaction is $w(x)$. The probability $\mathrm{d}w$ of the interaction in the next moment $\mathrm{d}t$ is $(1-w)k(x)\mathrm{d}t$, where $k(x)\mathrm{d}t$ is the probability *a priori* of bridge formation during time $\mathrm{d}t = \mathrm{d}x/v$. Equation[5]

$$\dot{w} = (1-w)k(x) \tag{24}$$

results with the solution

$$w = 1 - \mathrm{e}^{-\lambda/v} \tag{25}$$

where

$$\lambda = \int_{-\infty}^{+\infty} k(x)\mathrm{d}x \tag{26}$$

We can approximately state

$$\lambda \cong \frac{l\eta}{h}\,\mathrm{e}^{-F/kT}\,(f_0 - f)L \tag{27}$$

and if $\lambda/v \ll 1$ then

$$\frac{n}{n_0} = w \cong \frac{\lambda}{v} \cong \frac{l\eta}{h}\,\mathrm{e}^{-F/kT}\,(f_0 - f)\,\frac{L}{v} \tag{28}$$

The kinetic equation describing the relaxation towards the steady state is

$$\dot{n} = \frac{1}{\tau}(n_0 w - n) \tag{29}$$

where τ is the time of relaxation. Putting into (29) the value w from (28),

$$\dot{n} = \frac{1}{\tau}\left(n_0 \frac{l\eta}{h}\,\mathrm{e}^{-F/kT}\,(f_0 - f)\,\frac{L}{v} - n\right) \tag{30}$$

Generally Eqn. (30) is nonlinear, as τ, n_0 and v can depend on the sarcomere length and therefore on time. Perhaps this equation can be used for the investigation of nonstationary processes, particularly such as the rapid autooscillations of the flying muscles of insects.

Comparing Eqns. (28) and (23),

$$\left(\frac{r}{1-r} f_0 + f\right) v = \frac{f_0 L}{1-r} \frac{l\eta}{h} e^{-F/kT} (f_0 - f) \tag{31}$$

or

$$(a + f)v = b(f_0 - f) \tag{5}$$

where

$$a = \frac{r}{1-r} f_0 \tag{32}$$

and

$$b = \frac{f_0 L}{f_0 L + q_0} \frac{1}{1-r} b' \tag{33}$$

The characteristic Eqn. (5) of A. HILL is thus obtained. Putting v calculated from (31) into (28), always $v > \lambda$ except $f = f_0$ when $v = \lambda$.

The characteristic equation can be also obtained directly from the condition of the constant v, corresponding to steady state. Thus

$$nf_0 - n_0 f - n\beta v = 0 \tag{34}$$

where nf_0 is the stress produced by the sarcomere, $n_0 f$ is the external load and $n\beta v$ is the force of effective friction. From (34) Eqn. (5) is obtained in the form

$$(a + f)v = \frac{f_0 r}{(1-r)\beta} (f_0 - f) \tag{35}$$

Comparing (35) and (31) the friction coefficient is

$$\beta = \frac{rh}{l\eta L} e^{F/kT} \tag{36}$$

The kinetic Eqns. (29) and (30) can be rewritten. Putting into (30)

$$f = f_0 \frac{\frac{n}{n_0} - r}{1-r} \tag{23a}$$

for the steady state

$$\frac{n}{n_0} = w = \frac{b}{b + v} \tag{37}$$

and it follows from (29) that

$$\dot{n} = \frac{1}{\tau} \left(n_0 \frac{b}{b + v} - n\right) \tag{38}$$

If $v = 0$, $n = n_0$; if $v = v_m = b(1-r)/r$, $n = n_0 r$. The parameter r has the sense of minimal probability corresponding to $v = v_m$

$$r = w_m = \frac{b}{b + v_m} \tag{39}$$

The value of r can be estimated with the help of the empirical relation (8). Thus $r = 0.23$.

Putting the values f_0L, q_0 and r into (29), $b = 1.17b'$. The contemporary state of experiment does not allow b' to be quantitatively distinguished from b. There exists, however, a physical difference between these constants. b' contains the heat of shortening, but b is a purely dynamical constant containing only the work of shortening:

$$b' = (f_0L + q_0)\frac{l\eta}{h}e^{-F/kT} \tag{17}$$

$$b = f_0L\frac{l\eta}{h}e^{-F/kT}\frac{1}{1-r} \tag{33}$$

The second equation of A. HILL and the characteristic equation include the constants which are physically different although nearly equal.

According to the theory suggested here, the heat of shortening must depend on the number of acting cross bridges in the same way as the work. In other words, the heat of shortening has to be proportional to n/n_0. This result contradicts the old data of A. HILL[10] but agrees with his new data[11]. We get the value of the heat of shortening

$$q = q_0\frac{n}{n_0} = q_0\left[r + (1-r)\frac{f}{f_0}\right] \tag{40}$$

or

$$q = \frac{q_0}{f_0}\left[rf_0 + (1-r)f\right] \tag{40a}$$

If $f = f_0$, $q = q_0$, if $f = 0$, $q = q_0r$.

Putting q_0, f_0, r, L into (40) we get

$$\frac{q}{L} = 0.03\,f_0 + 0.10\,f \tag{40b}$$

Multiplying this expression by 2.6, we obtain an expression which can be compared with (2)

$$\alpha = 0.08\,P_0 + 0.26\,P \tag{41}$$

instead of

$$\alpha = 0.16\,P_0 + 0.18\,P \tag{2}$$

The cause of the difference between these two expressions cannot be established as more exact experimental data are lacking.

If $P = P_0$ both expressions give $\alpha = 0.34\,P_0$.

FURTHER DEVELOPMENT OF THE THEORY

If $f > f_0$ the muscle does not shorten but rather is elongated. The rate of elongation is not described by the equation of A. HILL for the shortening and is expressed by a different constant. It is clear that the activation energy for this process must be different from the activation energy of the initiation.

The relaxation of the muscle has to be considered as a result of withdraw of

the Ca^{2+} from the sarcoplasm. The effective value of $\mu\Delta n$ per one bridge must become smaller; therefore f_0 decreases. Every cross bridge supports a continuously decreasing tension. The chain of events initiated by the formation of the cross bridge is broken down from the beginning. These qualitative considerations have to be used in the quantitative theoretical investigation.

This theory must be experimentally supported. Sufficient knowledge about conformational changes occurring in the actomyosin system of muscle does not exist. A detailed experimental study of these processes is necessary.

Perhaps muscle contraction is a cooperative phenomenon, suggesting that the events occurring in different cross bridges are interdependent. The quaternary structure of the helical F-actin suggests its allosteric properties, *i.e.* the interdependence of active sites. We know nothing about similar properties of myosin.

The suggested theory does not include cooperativity. The first attempt to include it occurs in the second part of the paper[16]. The problem has to be further investigated. Perhaps studying cooperativity will explain the difference between the Eqns. (32) and (2).

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