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THEORETICAL APPROACH TO MUSCLE CONTRACTION

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Summary: A mechano-chemical approach to the choice of characteristic variables for the description of the cross-bridge states in active muscle is proposed. A small number of mechanically significant states of the cross-bridge should be postulated to obtain an informative model of the cross-bridge contractile cycle. There exist two simplest models which are capable to describe a variety of experimental data on muscle contraction. In the "kinetic" model /V. I. DESCHEREVSKI , *Biorheology* 7, 147 (1971)/ two mechanically significant states of the cross-link are postulated in which it develops constant positive ("pulling" state) and negative ("hindering" state) forces independent of the velocity of contraction. In the alternative model suggested by CHAPLAIN and FROMMELT and independently by BURAVCEV only one mechanically significant state is postulated in which the cross-link develops a positive force linearly decreasing with the speed of contraction. Near the steady-state conditions both models are mathematically equivalent, but under sharply non-stationary conditions their behavior differs essentially. Transient responses of muscle to step-like change allow to decide between the models. It is concluded that the steady-state velocity of unloaded

contraction cannot be limited by the cross-link inherent "friction", as results from the second model, but it can be limited by a hindering force of potential nature such as postulated in the "kinetic" model. The relation between the postulated significant states of the cross-bridge and its actual molecular transitions in active muscle is discussed.

The sliding-filament concept gives the most valid scheme of striated muscle contraction. Its basic principles may be formulated mathematically. The states of the myosin cross-bridge in active muscle are described adequately by two kinds of variables: discrete and continuous ones. Discrete variables are applicable for the description of the myosin interactions with actin, ATP, ADP and so on, i. e. for the description of various "chemical" states of the cross-bridge. Its mechanical state, for example the angle position and the distance to the action receptor site, is characterized by continuous variables.

With such chemo-mechanical approach to the choice of characteristic variables, the cross-bridge dynamics in active muscle is described by the set of partial differential equations for distribution functions of the cross-bridges of every "chemical" type with respect to the mechanical variables.

To analyse the set of equations of such a type, some additional assumptions should be introduced to concretize the number of the significant "chemical" states of a cross-bridge, the dependence of the transition rate constants and the force developed by the cross-bridge in every state upon the mechanical variables. The number of the parameters arising in this case is proportional to the number of postulated significant states. Accordance of a theory with the experimental data available is of little value if it has many adjusted parameters, hence the simplicity of the model should be regarded as an important criterion of the proper choice of significant states.

The well known model of A. HUXLEY /9/ may be regarded as the first

attempt of such type of approach to the description of muscle contractile properties. The "kinetic" model /5/ of striated muscle contraction developed by us within the limits of the formulated scheme differs from HUXLEY's model in starting assumptions and in simpler mathematical treatment. Its significant features were formulated earlier as a "gas" model of muscle contraction /6/. It is postulated that there are two significant "chemical" states of the myosin cross-bridge, free and attached ones, and two significant "mechanical" states for an attached cross-bridge, "pulling" and "hindering" ones. In the first state the cross-bridge develops a constant positive force +f and in the second - constant negative one -f. Transition from the first to the second state takes place when the filaments have slid a distance δ in the positive direction since the moment of the cross-link formation. In the "pulling" state the probability of the cross-link splitting is low, in the "hindering" one - many times higher. Under such assumptions the kinetics of cross-bridges in contracting muscle is described by two ordinary differential equations:

$$\frac{dn}{dt} = k_1 (\alpha - n - m) - \frac{v}{\delta} n \quad (1)$$

$$\frac{dm}{dt} = \frac{v}{\delta} n - k_2 m \quad (2)$$

where α is the whole number of myosin projections in a half of the sarcomere, which are capable to make simultaneously cross-links, n and m are numbers of "pulling" and "hindering" cross-links, k_1 and k_2 are the rate constants of cross-link formation and splitting. The velocity of filament sliding v is governed by the muscle force $f(n-m)$ and by the magnitude P and inertia I of the load as results from the NEWTON's law:

$$\frac{dv}{dt} = \frac{1}{2N I} [f(n - m) - P], \quad (3)$$

where N is the number of sarcomeres in a muscle fibre. The series elasticity of muscle and viscous resistance of sarcoplasm to filament sliding can be taken into consideration as the load properties.

The dynamics of tetanised muscle contraction under various conditions was described by the "kinetic" model /5, 7, 8/. HILL's characteristic and energetic equations /13/ and his data on the heat production rate /14/ follow automatically from the steady-state solution of the set of equations (1 - 3).

The calculated rates of force development and redevelopment after quick release coincide with JEWEL's and WILKIE's data /15/. Mechanical energy production by insect flight muscles and skeletal muscles of vertebrates under driven length oscillations are given analytically¹⁾ and correlate with experimental data /3, 16, 17/. The theory predicts oscillating transient responses to the load change. These oscillations have been registered by us under predicted conditions and their active nature has been demonstrated /2/.

The oscillations of increasing amplitude and double-frequency oscillations observed by us may be explained in terms of the theory.

It should be concluded that this simple model is in accordance with a large number of experimental data on muscle dynamic processes with inherent time range of 10⁻²- 1 sec. This allows to consider the proposed kinetic scheme as the first approach to the molecular nature of the elementary contractile cycle.

¹⁾To describe the stretch of active muscle under external force, it is necessary to introduce a "superpulling" state into which the cross-link passes after displacement for a distance in the negative direction from its starting position.

In this connection the question may arise of whether it is possible to simplify the model in the scope of the scheme under consideration and what relation exists between the postulated significant states of the cross-bridge and its actual molecular transitions in active muscle.

There is little doubt that both attached and free states of cross-bridges do exist in active muscle and are significant for its mechanical behavior. So, to simplify the model we should consider only one significant mechanical state of the cross-link instead of two. The model of such a type has been suggested recently by CHAPLAIN and FROMMELT /4/ and independently by BURAVCEV /1/. In this model an attached cross-bridge develops only positive force the magnitude of which linearly decreases with the speed of contraction. The cross-bridge gets free after displacement for a distance . CHAPLAIN and FROMMELT have demonstrated that this model is in a good accordance with the energy and heat production data on isotonic steady-state contraction. BURAVCEV has calculated both isotonic and isometric contractions, some transient responses and contraction under driven length oscillations. It may be concluded that this "reduced" model is capable of describing about the same number of experimental data as the "kinetic" model does.

It may be useful to find the reasons of such dynamic likeness of these two models and possible points of their discrepancy. It should be noted that the "reduced" model cannot be regarded as a simpler one because it contains just the same number of adjusted parameters as the "kinetic" model. Under steady-state conditions these two models are mathematically equivalent.

Under other conditions their mathematical likeness is determined by the relative values of the parameters k₁ and k₂ in equations (1-2). Really at q = k₂/k₁ » 1 equation (2) may be regarded as a "fast" one in equation set (1 - 3)

(this may be shown by an appropriate substitution of the variables). It means that for the "slow" processes (in comparison with $1/k_2 \sim 5 + 7$ msec) Eq (2) is equivalent to the corresponding steady-state expression: $m = vn/k_2$. So, Eq (1) gives:

$$\frac{dn}{dt} = k_1 (\alpha - n) - \frac{n}{\delta} v, \quad (4)$$

where $\delta = q/(q+1)$. For the muscle force we have

$$f(n - m) = nf \left(1 - \frac{v}{v_m}\right), \quad (5)$$

where $v_m = k_2$ is the steady-state velocity of contraction without a load.

The dependence of force related to one cross-link on the velocity of contraction coincides with that postulated in the models proposed by CHAPLAIN - FROMMELT and by BURAVCEV. The kinetic equation by BURAVCEV coincides with (4). In the equation by CHAPLAIN and FROMMELT in addition to (4) the cross-link splitting independent of filaments sliding is taken into consideration²⁾ (in the notations of these authors $\delta = I_k v_{cbm} / (v_{cbm} - I_k u f_{cbm})$). In the "kinetic" model $q = 2 + 4$, so that the "reduced" model can show similar behavior near the steady-state. However, under sharply non-stationary conditions their behavior differs essentially. In the "reduced" model there is no possibility for filament sliding with the speed exceeding that of unloaded steady-state contraction. In the "kinetic" model the speed of filament sliding for a distance δ can be limited only by viscosity of the sarcoplasm in the region of the filament overlap or by inherent time of the cross-link conformational rearrangement. The latter is taken to be small in comparison with $1/k_2$, hence

²⁾This process is rather slow and taken into consideration in the "kinetic" model in the regimes with partial activation of the contractile system when k_1 becomes small and the speed of contraction is very low /5, 8/.

the transient speed can exceed the maximal steady-state one. An investigation of fast transient regimes can give an answer to the question of whether the steady-state speed of unloaded contraction is limited by the inherent cross-link "friction" or by a "hindering" force of the potential nature. This question is closely associated with the problem of the energetic structure of the cross-link actual conformational states. As the cross-bridge is small in size, it must intensively fluctuate and its mechanical characteristics such as force, friction, and displacement have the meaning of time average values (time interval of averaging is taken to be small as compared with contractile processes). The averaged force characteristics postulated by CHAPLAIN and FROMMELT /4/ and by BURAVCEV /1/ will take place if the cross-link at filament sliding passes a number of relatively stable (separated by high energetic barriers) positions with progressively decreasing energy. The force characteristics postulated in the "kinetic" model /5, 6/ suggests that either the barriers between the states with progressively lowering energy rise before the cross-link splitting or there is only one high energetic barrier, namely, for the cross-link splitting.

Transient responses of active muscle to step-like length changes obtained by HUXLEY and SIMMONS /10, 11/ with high time resolution may be interpreted in terms of the inherent cross-link "friction" /12/, but the latter seems to be too small to limit the steady-state velocity of unloaded contraction. This means that some kind of "hindering" state of the cross-link should really exist. It is of interest also that the average force of an individual cross-link does not depend on its displacement over a wide range /12/, this being in accordance with the assumption made in the "kinetic" model with respect to the constancy of the cross-link "pulling" force /5, 6/.

HUXLEY and SIMMONS gave a very attractive interpretation of their own results in terms of the theory of rate processes /12/. The first application of this theory to individual cross-bridge action was given by VOLKENSTEIN /18/. However, considerations of such a type will probably have an illustrative character as long as the number of the cross-bridge stable positions and their energetic structure remain a matter of choice. Some information on this problem can probably be obtained by investigating the "averaged" parameters of the "kinetic" model under various physico-chemical conditions of the contractile system performance.

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