SOME QUALITATIVE CONSIDERATIONS ON THE MECHANISM OF STRIATED MUSCLE CONTRACTION

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In the current literature on muscle contraction there are a number of important facts which seem subject to unification once a few plausible assumptions have been made about the molecular nature of the contractile system. This paper calls attention to some of these possibilities, in the hope that even purely qualitative considerations may be of value in formulating a satisfactory scheme for the process of contraction.

The fact — demonstrated electron microscopically by HALL, JAKUS, AND F. O. SCHMITT[1] — that there exists in the muscle fiber during all states of activity a permanent (presumably) protein structure, plus the RAMSEYS'[2] demonstration that the tension developed on stretching a resting muscle is very low (the manifested tension actually being due to the sarcolemma), rather compels the idea that excitation of a fiber involves, among other events, a great increase in the amount of transverse bonding between neighbouring contractile elements — let us say "chains" — which are otherwise able to slide by one another giving rise to no tension whatsoever. This notion has been hinted at by various authors, but stated perhaps most explicitly by H. B. BULL[3]. Let us elaborate somewhat on this picture, and visualize the contractile network in the manner of Fig. 1. The transverse membranes which provide points of anchorage for the chains can be thought of as the Z-membranes, the chains themselves as SCHMITT's "filaments", and the cross-bonds as –S–S–, hydrogen, or ionic bonds between residues, but this identification is purely speculative and not essential to the argument. The total number of transverse bonds capable of forming on excitation may be expected to vary in length in the following way. At "rest" length, or perhaps at a little more than rest length, it should be a maximum, for all the chains are extended and in an orderly array. At greater than rest length, there should be a linear decrease in the possibility of transverse bond formation because we are visualizing the chains as partially slid past one another. In our naive scheme, transverse bonding should become impossible at about twice rest length. If we suppose that a very sparsely cross-bonded chain is able to snap free from the system at its non-anchored end, we must conclude that the number of un-snapped chains, that is, the number still participating in the contractile system and contributing to the tension, decreases linearly with length beyond rest length. But this means that the *tension* developed on excitation should decrease linearly with length beyond rest length, and that at about twice rest length it should fall to zero; all these conclusions are in accord with experimental observation[4]. The situation at lengths less than rest length is probably much more complicated, for in addition to a diminished possibility of cross-bonding (as expressed by, say, the number of bonds per unit length of chain

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axis) due to kinking and disordering, such factors as the screening of electrostatically attracting groups and reduction in effective force components may also result from the rotation* of chain "links" into a plane normal to the chain axis. Since all these factors act to reduce the tension manifested at the "ends" of the system, it is not surprising to find experimentally that the tension also falls (a little more steeply than linearly) with shortening from rest length[4]. Thus, our model is not inconsistent with the facts embodied in the length-tension [τ (L)] diagram of the fiber. It may also be mentioned in passing that the interpretation just given for lengths greater than rest length is in accord with certain vibrational experiments of F. BUCHTHAL *et al.*[6]. These authors have described a "plasticity" or a decrease in stiffness of a muscle subjected to imposed vibrations, as indicated by the fact that, at any one length, successive vibrations have a progressively greater amplitude (see especially their Fig. 1). This phenomenon is the more marked the greater the length, and could be interpreted in the present terms by saying that in successive vibrations more and more units are snapped away from the effective system. Still another observation in harmony with these ideas is the inability to obtain the β x-ray diffraction pattern by stretching living, resting muscle[7]. According to our simple model, no stretching force is really being applied under such conditions. On the other hand, if such a muscle is dried, allowing some cross-bonding between the chains, then stretching does become effective and the β-pattern does appear.

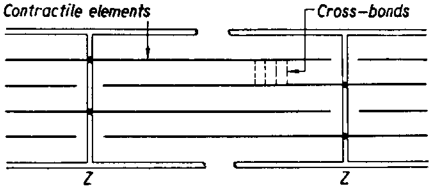

Fig. 1. Schema to show the suggested mechanical relations between Z-membranes, contractile elements and sarcolemma; the latter is shown as split to indicate that the contractile elements can run through more than one sarcomere. Upon excitation it is supposed that cross-bonds form between the extended elements of the resting state.

Keeping the foregoing ideas in mind, let us now turn to another well explored but still controversial field, specifically, to the question as to whether the energy released by the metabolic processes is employed in contraction or relaxation. Evidence bearing on this issue has been ably[8, 9] as well as widely, discussed, and the brief review which follows is only a convenient background for the reconciliation of views to proposed.

If we admit that the dephosphorylation of adenosine triphosphate (ATP) is the chemical reaction directly linked with the contractile protein structure, and if we concede that the behavior *in vitro* of myosin solutions bears a genuine resemblance to events *in vivo*, then what might be termed the "chemical" evidence weighs heavily on the side which maintains the free energy is expended in relaxation. DAINTY *et al.*[10], ENGELHARDT[11], SZENT-GYÖRGYI[12], AND SHEN[13] have all recorded sudden, contractionlike changes (loss in birefringence, in anomalous viscosity, or shortening of gel threads) in myosin upon contact with ATP. But these may be best ascribed to what appears to be a function of ATP other than that of supplying energy, namely, that of "tripping the locks" on the extended myosin structure (see, for example, BULL[14], the recent work of MOMMAERTS[15], and the suggestion of BAILEY AND PERRY (cited[16] as forthcoming work) regarding the stabilization of actomyosin in the extended state); the illuminating fact, perhaps most evident in the work of DAINTY *et al.*[10], is that the properties which are associated with the extended protein of resting muscle *return* hand-in-hand with the

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* That such rotation occurs is evident not only on structural grounds but also from the marked drop in form birefringence with shortening[5].

dephosphorylation of ATP*. The "physiological" evidence seems to point in the same direction. The following has been emphasized especially by the RAMSEYS[2, 4, 9]: In muscle fibers stimulated repeatedly, contraction proceeds normally until excitation fails; the rate of relaxation, however, is progressively slowed**. A fiber, suspended from one end by a hook and immersed in fluid, will relax downward considerably faster than it will fall under the influence of gravity[8]. RAMSEY[2] believes that this obviously active relaxation cannot be due to the elastic recoil of a bulged sheath, for relaxation is impaired in the δ-state of fibers even though the sheath is unharmed (as attested to by the fact that the resting τ-L diagram is unchanged). Finally, it appears to the author that BROWN's discovery[19] of what he terms the α-process can best be assimilated into an "active relaxation" theory. If the lock-tripping referred to above involves a negative volume change, then the potentiating effect of pressure would be due to a decrease in the activation free energy barrier of this preliminary step in such a manner that an increased number of contractile units will subsequently collapse. To be sure, one could suppose that the pressure aids in "mobilizing" a greater quantity of energy to be used subsequently in contraction, but then one is faced with the necessity of imagining a molecular energy storage device which is capable of "paying out" at a rate enormously slower (since this must occur over the next 0.01 or so seconds) than the known devices are capable of doing.

With the foregoing interpretations in mind, we may proceed to apparent consequences of the active relaxation theory, which consequences, however, collide with a set of fairly well-established facts. In particular, it may seem evident that if unexcited, resting muscle is in a configuration of high potential energy, E, then the length-tension, $\tau(L)$, diagram of excited, contracting muscle should specify all possible energetic exchanges between the muscle system and the external world. More specifically, with reference to final state, 2, and initial state, 1, it should be the case*** that $E_2(L_2)-E_1(L_1) = Q - W$, where Q is the heat absorbed by the system and W is the work which it has performed on the external world. That this simple application of the first law is unwarranted, however, has been demonstrated essentially by FENN[20], although the more recent experiments of A. V. HILL[21] have underscored the point. A muscle tetanized isometrically at L_1 is allowed to contract to $L_2 (< L_1)$ where it again develops isometric tension. When this experiment is carried out with varying loads but constant ΔL, *i.e.*, ΔE = constant, Q turns out to be constant. Since W has been variable, we have here seemingly a contradiction of the expected. When the experiment is carried out with constant load but varying ΔL, Q is proportional to ΔL. This second result does not clarify the contradiction in the first, but strongly suggests the thesis elaborated upon by FENN[8], namely, that there is some internal, apparently conservative, energy storage which on shortening releases amounts of energy proportional to ΔL. (We specify conservative because in the converse experiment ($\Delta L < 0$) there is some evidence that

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* Recently, L. VARGA[17] has attempted to obtain a definite measure for the standard free energy change, $\Delta F°$, of relaxing the myosin network, and has arrived at a value of about + 8000 cal. Although this result is in agreement with the thesis here being propounded, it is felt that the assumption underlying such calculation — that the contractile system consists of units each of which can exist in only two states of contraction — is open to serious question.

** Essentially the same result has been demonstrated quantitatively by SANDOW[18] in whole muscle.

*** Provided no appreciable amount of kinetic energy arises, and in such experiments care is taken to see that it does not.

Q changes sign; at least it does not remain negative as required by an explanation invoking a "friction").

Ramsey[9] has offered a resolution of the foregoing difficulty, adducing his observation that, at least in single fibers, contraction can be initially uneven along the length of the fiber, and that the degree of this unevenness is largely conditioned by the load on the muscle. In other words, under experimental conditions, τ, and hence E, is not a single-valued function of the length, so that in the first-mentioned Fenn-Hill experiment the fact that Δ L is held constant does not guarantee that Δ E is a constant (as we have assumed in arriving at the seeming contradiction). Whereas the possibility of uneven contraction in fibers is established fact, an explanation invoking this phenomenon does not appear entirely satisfactory. One difficulty is that the Fenn-Hill energy balances are drawn over periods of time longer than the duration of the uneven contraction in single fibers; a second is the remarkably good quantifiability of the Fenn effect — certainly not to be expected on the basis of a chance unevenness. We should like to direct attention here to a different resolution, which, although purely qualitative, seems at the moment reasonable and consistent with known facts.

The essential point in the following argument is that the steady tension exerted by a tetanized muscle fiber is not due to the steady pull of, say, an extended polymer network, but is due to the time-averaged impulses of an enormous number of contractile units, each of which is undergoing a succession of minute contraction relaxation cycles (see for example the experiments of Nicolai cited by Fenn[8] on p. 460). A steady flow of energy is therefore required to maintain a tetanus tension, whereas this is not so in the case of the rubber band. This commonplace fact of physiology is the simplest and most forceful reason for concluding that "a muscle is not like an ideal coiled spring", although it is not always the one mentioned. Many experiments carried out by Dainty *et al.* show that the catalytic activity of ATPase, that is, of actomyosin, rises exponentially with disorientation of the protein (Fig. 2). This same fact (in the reverse direction has been mentioned several times by Szent-Györgyi[21] as being responsible for the muscle's knowing "when to shut off its energy supply." In a *steadily* maintained tetanus we may imagine a rather large but incomplete degree of cross-bonding of the contractile chains. The extension-contraction cycle undergone by an individual chain would therefore be between some minimum length, L_{min}, prescribed by the separation of the fixed clamps, and some maximum extension, L_{max}, prescribed largely by the average degree of cross-bonding. The extra energy release would be proportional to $L_{max}-L_{min} = \Delta L(L_{min})$. Now, for lengths progressively shorter than rest length, *i.e.*, decreasing L_{min}, not only is the dephosphorylation rate rising rapidly, but also the diminished possibility of cross-bonding allows a larger Δ L. We may therefore expect an increasing "maintenance heat rate" at shorter lengths; although this finding was not clear from Hill's experiments[21], it was subsequently demonstrated by Brown[23], at least for moderate degrees of shortening. (It must be conceded, however, that this situation is reversed for greater shortening, and also that such measurements are rendered somewhat uncertain by the fact that the mass of muscle

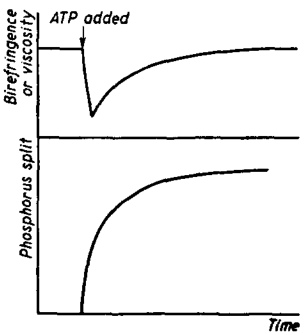

Fig. 2. Correspondence between ATP addition and loss of orientability properties; also the correspondence between dephosphorylation and the restoration of these properties. This figure is schematized from Shen[13].

affecting the thermopile is variable with length, as has been pointed out by RAMSEY (1944). When the muscle is *shortening* it may be reasonably supposed that the degree of cross-bonding is drastically reduced, allowing wider oscillations in length in the cycles executed by individual contractile units. This leads, of course, to an increased energy release in the process of shortening. The *extra* such energy will depend on (a) the amplitude of the oscillations, and (b) the duration of the shortening. We may consider factor (a) to be inversely proportional to the load, m, being lifted, let us say k_1/m, (k_1 = constant), and factor (b) inversely proportional to the velocity of shortening, v, and directly to the distance shortened, l, *i.e.*, $k_2(l/v)$, (k_2 = constant). But HILL[21] has shown that approximately, $v = k_3/m$, (k_3 = constant). Thus, finally, we have for the extra energy released, $(k_1k_2/k_3)l$, which is the essential nature of the FENN effect.

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SUMMARY

Several properties of the "static" tension-length diagram of striated muscle fibers are interpreted on the assumption that on excitation there is a cross-bonding of contractile elements previous to the longitudinal shortening. An attempt is also made to reconcile the FENN effect with the notion that the free energy released by metabolism is used to extend the contractile units. This suggested reconciliation is based on the cross-bonding assumption and on the notion that in a tetanus a contractile unit is undergoing a succession of contraction-relaxation cycles.

RÉSUMÉ

Plusieurs propriétés du diagramme "statique" tension-longueur des fibres du muscle strié sont interprétées en supposant qu'au cours de l'excitation, il existe une association transversale des éléments contractiles, préalable à leur raccourcissement. Une tentative est également faite pour mettre en accord l'effet FENN avec la notion que l'énergie libre dégagée par le métabolisme est utilisée pour l'extension des éléments contractiles. L'accord qui est ainsi proposé est basé d'une part sur l'hypothèse de l'association transversale, et d'autre part, sur l'hypothèse que, au cours d'une contraction tétanique, un élément contractile participe à une succession de cycles de contraction-relaxation.

ZUSAMMENFASSUNG

Mehrere Eigenschaften des "statischen" Spannungs-Längendiagramms quergestreifter Muskelfasern werden unter der Annahme, dass bei Reizung eine Querverbindung kontraktiler Elemente vor der longitudinalen Kürzung auftritt, interpretiert. Ein Versuch wird auch unternommen, um den FENN-Effekt mit der Idee, dass die durch den Stoffwechsel gelieferte freie Energie zur Ausdehnung der kontraktilen Einheiten benutzt wird, in Übereinstimmung zu bringen. Diese vorgeschlagene Übereinstimmung beruht auf der Annahme der Querverbindung und auf der Idee, dass bei Tetanus eine kontraktile Einheit einer Folge von Kontraktion-Relaxationszyklen unterworfen ist.

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