Muscle contraction

Weak and strong crossbridges

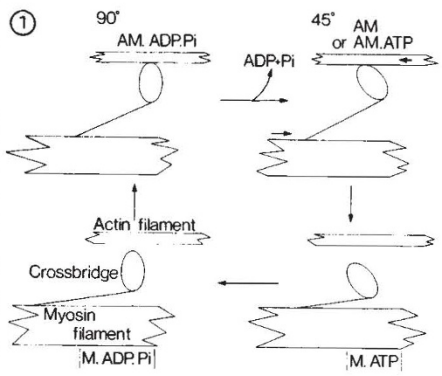
from Malcolm Irving

IN THE most widely accepted model of muscle contraction the actin filaments are pulled along by the cyclical action of crossbridges projecting from the myosin filaments. In this model, crossbridges are thought to attach to actin roughly at right angles to the filament axis (the so-called 90° state) and then to swing round in a power stroke that moves the actin filament by about 120 Å (refs 1,2). Binding of ATP is believed to cause detachment of the crossbridge; the ATP has to be hydrolysed before the crossbridge can rebind to actin and repeat the cycle[3]. This model was an attractively simple explanation of mechanochemical coupling in muscle. But it is now being suggested that crossbridge detachment is not an obligatory consequence of ATP binding[4], that the idea of the 90° state needs major revision [4,5] and that the power stroke is much shorter than 120 Å (ref.5). In contrast, T. Yanagida *et al.* elsewhere in this issue[6] present an argument for a power stroke larger than 600 Å (see box). Where does this leave the crossbridge theory?

A cartoon of the original model is shown in Fig.1, where the crossbridge is drawn as a 'ball-on-a-stick'. The elongated ball is the 'head' domain of myosin (M), containing the ATP and actin binding sites. Starting at the lower left of the reaction cycle, a head with bound ADP and phosphate (P_i) binds to actin (A) to produce the complex AM.ADP.P_i. Release of the products of ATP hydrolysis is coupled with the power stroke as the head swings to 45° (AM). ATP binding detaches the head (M.ATP) from actin, the ATP is hydrolysed and the resulting complex, M.ADP.P_i, can rebind to actin in the 90° configuration. This biochemical scheme was suggested by studies in solution on the interaction of actin with isolated myosin heads[3].

E. Eisenberg and T.L. Hill[4] have recently reviewed these solution studies in the light of subsequent experiments using a wider range of conditions; it is now clear that, in solution, ATP binding to the head does not necessarily cause it to dissociate from actin before the ATP is hydrolysed. Rather, when either ATP or ADP and P_i are on the head it is weakly bound to actin, in a rapid equilibrium between attachment and detachment. A simple crossbridge cycle suggested by these newer data is shown in Fig. 2. Here there is no structural difference between the weakly bound AM.ATP and AM.ADP.P_i complexes, which have been depicted with a range of orientations to suggest the possibility that they do not have a sterically unique conformation. The power stroke is still associated with P_i release, and drives the head into the strongly bound AM.ADP and AM states. The difference is that ATP binding now returns the head to the weak binding states rather than detaching it.

At first sight the new model seems to have a fundamental defect: the power stroke is reversed while the heads are still



attached, which must push the actin filaments the wrong way. Why does this not reverse the work done in the power stroke? Recall that a myosin filament has many crossbridges working in parallel, but asynchronously, so that swinging of an individual head will not necessarily be accompanied by movement of the actin filament to which it is attached. The difference must be taken up as conformational strain within the attached bridge. To make the model work, Eisenberg and Hill propose that those heads in the population that are strained the 'wrong' way detach more quickly. The general idea of a strain-dependent detachment rate is not new[7] and, indeed, is necessary for the efficient operation of any model of this general type, including that in Fig. 1. Such models can provide a quantitative description of the mechanical and energetic properties of muscle[7-9], but are not critically dependent on the chemical identity of the intermediates in the crossbridge cycle.

Does the biochemical cycle in Fig.2, inferred from solution studies, actually occur in contracting muscle? The answer will require biochemical studies of intact muscle fibres, in which it is difficult to apply the transient kinetic techniques used in solution. Fortunately, it has recently become possible rapidly to release ATP from a photolysable precursor inside muscle fibres[10], providing at least a partial solution to the technical problem.

From the structural viewpoint the model in Fig. 2 is rather poorly defined. One general problem is that if strain in a crossbridge affects its structure then a given biochemical state may not be identifiable with a unique conformation. Nevertheless, there still might be two types of conformation corresponding to the strongly and weakly bound states. H.E. Huxley and M. Kress[5] have now summarized the ultrastructural evidence from contracting muscle and demonstrate

A crossbridge too far . . . . . ?

AN interesting new view of the crossbridge power stroke is presented by T. Yanagida, T. Arata and F. Oosawa on page 366 of this issue. They have estimated the length of the power stroke from the maximum velocity of filament sliding in crab muscle, in which the sarcomeres are long enough for the velocity of fluorescently labelled actin filaments to be measured with a light microscope. The normal transverse connection between adjacent actin filaments — the Z line — was removed by selective proteolysis, leaving single sarcomeres with a normal array of myosin filaments but with actin filaments that were now free to move independently. On addition of ATP in the presence of calcium, all the actin filaments started to slide with a velocity of about 5 μm s^{-1}. The rate of ATP hydrolysis in the same conditions was about 1 s^{-1} per myosin molecule, which corresponds to about 80 s^{-1} per actin filament.

Yanagida and his colleagues argue that as viscous drag would very quickly attenuate actin filament momentum, each filament must have at least one crossbridge pulling on it at any instant. So if one ATP molecule is hydrolysed per crossbridge cycle, the rate of cycling of active crossbridges could not be higher than 80 s^{-1}. To achieve a filament velocity of 5 μm s^{-1} the length of the power stroke under these conditions would therefore have to be at least 5/80 μm or 625 Å.

This estimate is not only strikingly larger than those obtained by other methods (see accompanying article) but also than the largest dimension of the crossbridge head (190 Å) or the actin monomer (70 Å). If the power stroke really is greater than 600 Å, some drastic rethinking of the swinging head crossbridge model would be required. The paradox might be most simply resolved, and a short power stroke retained, if the condition that one ATP molecule must be hydrolysed per cycle of crossbridge attachment and detachment did not hold during rapid filament sliding against little or no resistive force. This could occur, for example, if the number of weakly bound, rapidly attaching and detaching crossbridges increased during sliding as the degree of overlap between actin and myosin filaments became progressively greater. This might make sliding energetically favourable without committing such crossbridges to ATP hydrolysis.

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