Cross-bridge cycling theories and high-speed lengthening behavior in frog muscle

Dear Sir:

Recently, Harry et al. (1990) and Morgan (1990) have studied experimentally and theoretically the behavior of active frog muscles undergoing stretches at speeds up to and exceeding 2 V_{max}. Their conclusions concerning the validity of the cross-bridge cycling theories are severe and they suggest that the P-V relationship for negative velocities up to $\approx -2\ V_{max}$ can be explained on the basis of intersarcomere dynamics. Their interpretation is extremely interesting, but their conclusion that cross-bridge cycling theories cannot explain the *P-V* relation for $V < 0$ must be revisited.

Harry et al. (1990) have used the Huxley (1957) model and some modified models. Thus, they have considered that the cross-bridges are the force generators. In my laboratory, we have used for more than 10 years a theoretical formalism independent of the mechanical role(s) of the cross-bridges (see Morel, 1990 and references therein). Therefore, I consider it useful to try to apply this approach to the present problem. I shall use below my usual notations. Eq. 11 in Morel (1990) becomes here, for $V^* < 0$:

$$\bar{n}^*(V^*/V_{max}) = \frac{\Delta h^*}{\sigma^*}\frac{f^*}{f^* + g^*} - \frac{s_o V_{max} f^*}{2\sigma^*(f^* + g^*)^2}\frac{V^*}{V_{max}}\left(e^{z^*}\frac{V_{max}}{V^*} - 1\right). \quad (1)$$

In this equation, I have considered the symbol "*" for all the parameters, except V_{max}. This choice corresponds to the fact that the movements of the myosin and actin filaments are reversed with respect to the "natural" movement. Since the actin filaments are polarized, it is extremely probable that the structural and kinetic parameters are in fact different in the two directions of sliding. According to Eq. 17 in Morel (1990), we deduce the rate of turnover of a cross-bridge:

$$r^* = \frac{\Delta h^*}{\sigma^*}\frac{f^* g^*}{f^* + g^*} + \frac{s_o V^*}{2\sigma^*}\left(\frac{f^*}{f^* + g^*}\right)^2\left(e^{z^*}\frac{V_{max}}{V^*} - 1\right). \quad (2)$$

Note that for a "natural" shortening ($V > 0$) we have:

$$r = \frac{\Delta h}{\sigma}\frac{fg}{f + g} + \frac{s_o V}{2\sigma}\left(\frac{f}{f + g}\right)^2\left(1 - e^{-z}\frac{V_{max}}{V}\right). \quad (3)$$

In my previous models, I have written:

$$E_{isot} = m_f \omega \epsilon r = m_f \omega \epsilon \frac{\Delta h}{\sigma}\frac{f}{f + g} + \frac{m_f s_o \omega \epsilon V}{2\sigma}\left(\frac{f}{f + g}\right)^2\left(1 - e^{-z}\frac{V_{max}}{V}\right). \quad (4)$$

Now, it is well known that $E_{isot} = E_{isom} + (P + l)V$ (Fenn effect). By comparison, we obtain (see Eq. 1 in Morel, 1990):

$$P + l = \frac{m_f s_o \omega \epsilon}{2\sigma}\left(\frac{f}{f + g}\right)^2\left(1 - e^{-z}\frac{V_{max}}{V}\right). \quad (5)$$

Although the energetics of a stretched muscle is not well known, I suggest to also write from Eq. 2 here and by analogy with a "natural" movement:

$$P^* + l^* = \frac{m_f^* s_o \omega^* \epsilon^*}{2\sigma^*}\left(\frac{f^*}{f^* + g^*}\right)^2\left(1 - e^{z^*}\frac{V_{max}}{V^*}\right). \quad (6)$$

The sign + in the exponential term is related to the fact that $V^* < 0$. The value of $P_o + l$ is given by Eq. 2 in Morel (1990):

$$P_o + l = \frac{m_f s_o \omega \epsilon}{2\sigma}\left(\frac{f}{f + g}\right)_o^2. \quad (7)$$

By dividing Eq. 6 by Eq. 7 we get:

$$\frac{P^* + l^*}{P_o + l} = \frac{m_f^*}{m_f} \times \frac{\omega^*}{\omega} \times \frac{\epsilon^*}{\epsilon} \times \frac{\sigma}{\sigma^*}\frac{[f^*/(f^* + g^*)]^2}{[f_o/(f + g)_o]^2}\left(1 - e^{z^*}\frac{V_{max}}{V^*}\right). \quad (8)$$

This equation can also be written:

$$\frac{P^*}{P_o} = \frac{1 + l/P_o}{1 + l^*/P^*} \times \frac{m_f^*}{m_f} \times \frac{\omega^*}{\omega} \times \frac{\epsilon^*}{\epsilon} \times \frac{\sigma}{\sigma^*} \times \frac{[f^*/(f^* + g^*)]^2}{[f_o/(f + g)_o]^2}\left(1 - e^{z^*}\frac{V_{max}}{V^*}\right). \quad (9)$$

Let us now put:

$$A^* = \frac{1 + l/P_o}{1 + l^*/P^*} \times \frac{m_f^*}{m_f} \times \frac{\omega^*}{\omega} \times \frac{\epsilon^*}{\epsilon} \times \frac{\sigma}{\sigma^*} \times \frac{[f^*/(f^* + g^*)]^2}{[f_o/(f + g)_o]^2}. \quad (10)$$

Eq. 9 becomes:

$$\frac{P^*}{P_o} = A^*\left(1 - e^{z^*}\frac{V_{max}}{V^*}\right). \quad (11)$$

In this equation, there are two unknown parameters, A^* and z^*. When V^* tends toward -0 Eq. 11 leads to $P_o^*/P_o = A^*$. Now, Harry et al. (1990) have indeed found that for $V \approx -0$, there is a "jump" in the tension, corresponding to $P_o^*/P_o \approx 1.5$. I deduce that $A^* \approx 1.5$. For $V^*/V_{max} \approx -2.2$, they have also found $P^*/P_o \approx 1.2$, leading consequently to $z^* \approx 3.54$. Thus, owing to the scattering of the experimental points, Eq. 11 describes with a good accuracy the experimental behavior, with $A^* \approx 1.5$ and $z^* \approx 3.54$. I think it is now important to go deeper into the reasoning. In Eq. 10, l/P_o is a corrective factor of the order of 0.16–0.17. I shall assume that the same is true for l^*/P^*, leading consequently to $(1 + l/P_o)/(1 + l^*/P^*) \approx 1$. It is also probable that $m_f^*/m_f \approx \omega^*/\omega \approx \epsilon^*/\epsilon \approx 1$. As concerns

$[f^*/(f^*+g^*)]^2/[f_o/(f+g)_o]^2$, Morel (1990) has shown that $f_o/(f+g)_o \approx 1$ and this term is probably close to unity. Therefore, we have:

$$A^* \approx \sigma/\sigma^*. \tag{12}$$

Because $A^* \approx 1.5$ and because I have usually taken $\sigma \approx 6$ nm, I deduce that $\sigma^* \approx 4$ nm. I conclude that the major parameter involved in the $\approx 50\%$ "jump" in the isometric tension for $V^* = -0$ is a reduction in the spacing between the actin-binding sites. This is not unexpected, owing to the polarity of the actin filaments, which probably present a disymmetry in their properties. A reversal in the direction of the velocity would compress the actin monomers in the direction of $V^* < 0$. This phenomenon may be related to the fact that Morel (1990) has suggested that even for $V > 0$, the behavior of the actin filaments (and probably also the cross-bridges) may depend upon the velocity. As concerns z^*, we have found above $z^* \approx 3.54$, against $z_1 = 0.150$ (Morel, 1990). Now we have $z_1 = 2\Delta h_1\,(f_1 + g_1)/s_oV_{max}$ and because a constant value of z^* is suitable, we have also $z^* = 2\Delta h_1^*\,(f_1^* + g_1^*)/s_oV_{max}$. I deduce that $\Delta h_1^*(f_1^* + g_1^*)/\Delta h_1(f_1 + g_1) \approx 3.54/0.150 = 23.6$. I conclude that we may have $\Delta h_1^* > \Delta h_1$ and $(f_1^* + g_1^*) > (f_1 + g_1)$: the structural and kinetic properties of the cross-bridges also undergo a "jump" for $V^* = -0$.

As a general conclusion, I think I have shown here, by using my mathematical treatment of the cross-bridge cycle, independent of the mechanical role(s) of the cross-bridges, that the behavior of a muscle for "natural" contractions is related to the cross-bridges and/or actin (Morel, 1990) and that lengthening of a muscle, as that described by Harry et al. (1990) is also largely related to these structures, although the phenomena analyzed by Morgan (1990) may noticeably modulate the response of the muscle. Finally, Harry et al. (1990) and Morgan (1990) have definitely shown that when the cross-bridges are assumed to be the force converters, the theories cannot explain the experimental behavior. I have shown here that when no assumption is done as concerns the force generation, provided only the cross-bridges attach to and detach from actin, the theory can explain the experimental behavior. This dichotomy may be related with the fact that the cross-bridges are not the force generators, which has been my position for about 15 years.

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