

OF MYOSINS, MUSCLES AND MECHANISMS OF CONTRACTION

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INTRODUCTION

For the past two decades, my research has been focused on the biomechanics of the musculoskeletal system with specific interest in skeletal muscle function and contraction. In the 1980s, I tackled the distribution problem in biomechanics, theoretically and experimentally, and realized that a solution to this problem could only be achieved with a deep understanding of the mechanical properties of muscles. Investigating the force-length and force-velocity relationships, I stumbled over the phenomenon of force enhancement and force depression following stretching and shortening of activated muscles, respectively (Abbott and Aubert 1952), and realized that these history-dependent properties could not be explained within the framework of the sliding filament (Huxley and Niedergerke 1954; Huxley and Hanson 1954) and the cross-bridge theory of muscle contraction (Huxley 1957). This realization led to a body of work covering the last decade that was aimed at unraveling the mechanisms responsible for force depression and force enhancement, and in parallel, a re-evaluation of the sliding filament and cross-bridge theories of contraction.

For the purpose of the Borelli lecture, I will focus on the research on force enhancement and the implications of this work for the cross-bridge theory. Force enhancement is defined here as the extra force of an isometric, steady-state contraction that is preceded by stretching of the activated muscle, compared to the corresponding isometric, steady-state force of a purely isometric contraction (i.e., one that is not preceded by stretch – Figure 1).

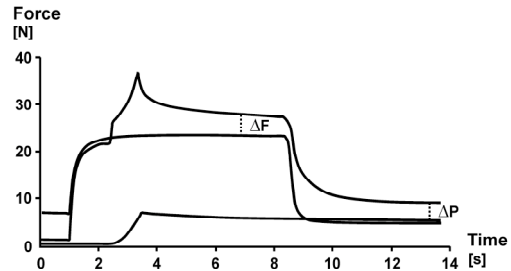


Figure 1: Definition of force enhancement (ΔF) and passive force enhancement (ΔP).

METHODS

Force enhancement was induced in all preparations by stretching an activated muscle by various amounts and at various speeds. The preparations tested included in vivo human muscles (Lee and Herzog 2002), an in situ preparation of the cat soleus (Herzog and Leonard 2002), single fibres of the tibialis anterior and lumbrical muscles of the frogs (Rassier et al. 2003), single myofibrils from the rabbit psoas (Leonard et al. 2006), and single cross-bridge interactions with isolated actin molecules (Mehta et al. 2006). For details of the preparations, please be referred to the original papers.

RESULTS AND DISCUSSION

Steady-state force enhancement was present in all preparations ranging from in vivo voluntary contractions to single myofibrils. Force enhancement was increased with increasing magnitudes of stretch (Figure 2), was independent of stretch speed, and was associated with an increase in muscle stiffness and a decrease in force relaxation time. Most importantly, at long muscle length, force enhancement was also

accompanied by an increase in passive force (after muscle relaxation – Figure 1) that could account in extreme cases for up to 85% of the total force enhancement measured in the activated muscle.

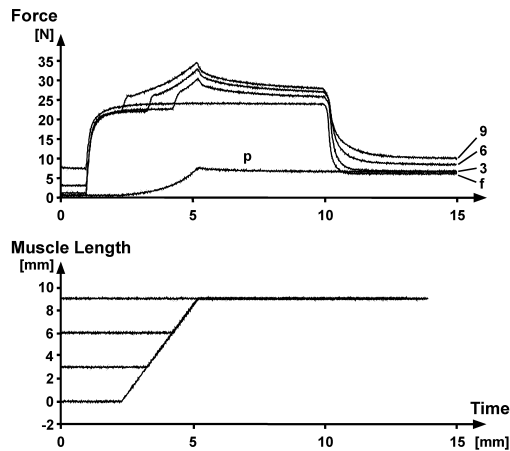


Figure 2: Force enhancement increases with increasing magnitudes of stretch

From the results of these studies, we concluded that force enhancement consists of an active and passive component. The active component was tentatively associated with a decrease in the rate of detachment of cross-bridges from actin; the passive component was hypothesized to originate from a calcium-dependent increase in stiffness of the molecular spring titin.

In order to test these two hypotheses, we first performed experiments on single cross-bridge interactions with actin and measured the duty ratio of cross-bridges subjected to stretching and shortening, and second, performed tests on single myofibrils which were activated with solutions of increasing calcium concentrations and measured the passive forces by inhibiting active forces through deletion of troponin C on actin.

The results indicated that stretched cross-bridges have a smaller duty ratio than shortened cross-bridges, therefore rejecting our first hypothesis that the active force

enhancement might be caused by an increase in the duty ratio.

The second experiment demonstrated that myofibril stiffness increased with increasing calcium concentration (in the troponin C deleted preparation), thereby supporting the hypothesis that at least part of the passive force enhancement was caused by a calcium-dependent increase in titin stiffness.

SUMMARY/CONCLUSIONS

Force enhancement has an active and a passive component. The active component is likely associated with an as of yet unknown stretch-dependent change in the cross-bridge kinetics, while the passive force enhancement is caused in part by a calcium-dependent increase in the stiffness of the molecular spring titin.

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