The differential effect of Ca^{2+} and Mg^{2+} on the ATPase activity of cardiac myofibrils

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Cardiac myofibrils respond to an increasing concentration of free Ca in an increased rate of ATP splitting due to an increased number of "switched on" troponin molecules. Of great interest is the sensitivity of the contractile system with respect to Ca and the steepness of the Ca-induced response. Both determine the degree of activation and the velocity of the development of mechano-chemical activity at a given intracellular Ca-transient. One of the most important factors (1) in determining the dose-response behaviour under physiological conditions is Mg. Since the exchange with extracellular Mg is low, any increase in Ca, e.g. due to catecholamines, will perturb the ratio of Ca and Mg bound to sites on troponin and myosin. Thus, Ca might act not only by increasing the degree of activation via binding to the triggering site(s) of troponin.
In an attempt to elucidate the action of Mg, myofibrillar ATPase was activated by a range of free Ca concentrations in the presence of different concentrations of free Mg. The concentration of the substrate for myosin, MgATP, and ionic strength were kept constant. The experimental data (ATPase vs. Ca) were fit to the model-independent Hill equation (2) and to the state function of Tawada's model (3) of inter-tropomyosin co-operation. It was found that by lowering free Mg from 5 mM to 1 mM, the Ca-sensitivity of the contractile system is increased, whereas neither the positive co-operativity (n=2.4) nor maximum ATPase at saturating Ca concentrations were changed. This is attributed to a competition of Mg with Ca for the triggering (low-affinity) site(s) of troponin. This conclusion is corroborated by the change in the apparent dissociation constant of Ca bound to troponin. An increase in the Ca-sensitivity as derived from the Hill equation corresponds to a decrease in the dissociation constant in Tawada's model. At low Mg (0.3 to 0.056 mM) Ca-sensitivity is changed not greatly. By contrast, at 0.032 mM Mg, Ca-sensitivity is increased. The positive co-operation is lost at low Mg concentrations as reflected by the Hill n value of 1.3 at 0.032 mM Mg. This would indicate a smaller interaction between tropomyosin molecules. Furthermore, at 0.032 mM Mg, maximum ATPase is decreased by 32%. At low Mg concentrations, Ca is bound in an increasing amount to the light chain-2 of myosin and could, therefore, influence the kinetics of the cross-bridge mechanism. This approach should prove helpful in elucidating the possible differential effect of Ca and Mg bound to myosin light chain-2 on the unloaded velocity of shortening of skinned muscle fibres.

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