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The role of calsequestrin in muscle function

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INTRODUCTION

Meat quality depends on muscle quality which is related to the regulation of muscle function by the contraction-inducing ion, calcium. If the process of Ca^{2+} uptake, sequestration or release at the level of the muscle cell is interrupted or altered, there is a loss of muscle quality. Two well-characterized conditions that result directly from altered Ca^{2+} regulation are porcine malignant hyperthermia and chicken crook neck syndrome. The protein calsequestrin (CSQ) is essential to calcium storage and release in muscle cells. Although CSQ can bind 40 to 50 molecules of calcium per molecule of CSQ, the mechanisms involved are poorly understood. Our laboratory has discovered a direct interaction between two intramolecular sites in CSQ which are responsible for converting it from a low to a high-capacity calcium binding protein.

MATERIALS AND METHODS

CSQ was purified from rabbit skeletal muscle (Mitchell *et al.*, 1988) and shown to undergo a conformational change in the presence of Ca^{2+} (He *et al.*, 1993). The canine cardiac CSQ gene was used to produce recombinant wild type CSQ and mutations of the CSQ protein. Ca^{2+} (mM) induced a protein conformational change and 0.5mM trifluoperazine (TFP) was used to block this change. Protein folding effects were evaluated by changes in trypsin digestion patterns, (He *et al.*, 1993). The hydrophobic character of the protein was assessed with the fluorescent hydrophobic probe, 1-anilino-naphthalene-8-sulfonate (ANS).

RESULTS

1mM Ca^{2+} induced a conformational change in CSQ that occurred simultaneously with a change from low to high-capacity Ca^{2+} binding. TFP was observed to block the intramolecular interaction and inhibit both the conformational change and high-capacity Ca^{2+} binding. Moreover, we demonstrated that conditions that prevent the Ca^{2+} induced conformational change also prevent the formation of a hydrophobic domain on CSQ that is created or exposed when the protein is folded. ANS binds to folded CSQ but binding to unfolded CSQ is approximately 5-fold less (Figure 1). Recombinant CSQ has been expressed in yeast and *E. coli* and show to have properties similar to muscle-derived CSQ (Figure 2).

These data allowed us to develop a model of CSQ function in the regulation of muscle Ca^{2+} (Figure 3).

FIGURE 1: ANS binding to exposed hydrophobic domain.

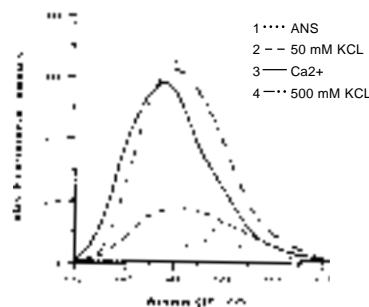


FIGURE 2: Calcium-induced CSQ conformational changes were monitored by resistance to trypsin digestion.

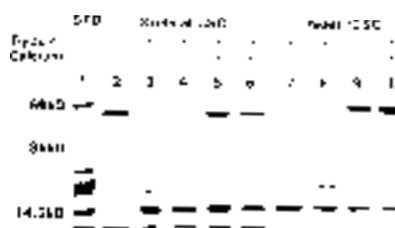
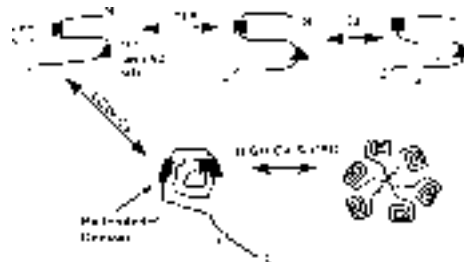


FIGURE 3: Model for calcium regulation by CSQ.



CONCLUSIONS

The protein CSQ acts to control muscle function by regulating cellular Ca^{2+} levels. We have elucidated some of the molecular events involved and proposed a mechanistic model. The model suggests points where deliberate intervention may allow alteration of muscle function and quality.

REFERENCES

- Mitchell *et al.* (1988) *Journal of Biological Chemistry* **263**: 1376.
He *et al.* (1993) *Journal of Biological Chemistry* **268**: 24635.