REGULATION OF GLUT4 IN SKELETAL MUSCLE INVOLVES Ca^{2+}/CALMODULIN-DEPENDENT PROTEIN KINASE AND HISTONE DEACETYLASE-5.

Smith J A H, Noakes T D and Ojuka E O

University of Cape Town, Department of Human Biology, UCT/MRC Research Unit for Exercise Science and Sports Medicine, Cape Town, South Africa.

Regular exercise increases glucose transporter 4 (GLUT4) expression in skeletal muscle (1). GLUT4 expression is mediated by the transcription factor myocyte enhancer factor-2 (MEF2) (2) and Ca^{2+}/calmodulin-dependent protein kinase (CaMK) (3). CaMK signaling increases the expression of certain other MEF2-dependent genes by dissociating MEF2 from the repression of histone deacetylase (HDAC) 5 (4).

To further characterize the role of CaMK in GLUT4 regulation, we expressed a constitutively active (CA) or a dominant negative (DN) CaMK IV gene in C2C12 cells using recombinant adenoviruses. We used chromatin immunoprecipitation (ChIP) assays with PCR primers specific to the MEF2 binding site on the GLUT4 promoter to detect DNA that had been co-immunoprecipitated with either a MEF2A or HDAC5 specific antibody. We detected an association between both MEF2A and HDAC5, with the GLUT4 promoter in CA CaMK but not in DN CaMK treated cells.

To determine if these results mimicked the effects of exercise, we subjected Wister rats to 5 X 17 minutes of intermittent swimming bouts and performed ChIP assays on triceps muscles. MEF2A that was associated with the GLUT4 promoter was detectable at 6h post-exercise but not at 0h and 24h post-exercise or in un-exercised controls. HDAC5 that was associated with the GLUT4 promoter was detectable at 0h, 6h and 24h post exercise but was undetectable in control rats.

Because CaMK is activated by a bout of exercise (5), these results support the hypothesis that CaMK signaling and HDAC5 are involved in the regulation of exercise-induced GLUT4 expression, via MEF2.

References

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