SWACSM Abstract

The Effect of AICAR-Induced AMPK Activation on Gene Expression in Sarcopenic Muscle

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ABSTRACT

The loss of muscle mass and function (sarcopenia) afflicts 11-74% of all aging adults, with prevalence increasing with age. Exercise training is clearly effective in preventing or attenuating sarcopenia. The cellular mechanisms of exercise's protective effects are not entirely clear, but AMP-activated protein kinase (AMPK) is thought to play an important role, in part by regulating gene expression. **PURPOSE**: To determine the effect of chronic pharmacological AMPK activation on skeletal muscle gene expression in sarcopenic muscle. **METHODS**: 24-month-old C57Bl/6J mice received either one acute injection or chronic daily saline injections of the AMPK-activating drug AICAR for 31 days. 5-month-old saline-injected mice served as young controls for reference. Treadmill running capacity was measured before and after treatment. Expression of genes relating to mitochondria, muscle size regulation, and inflammation was measured by real-time polymerase chain reaction (RT-PCR). **RESULTS**: One hour after a single injection of AICAR, raptor phosphorylation was increased in both young and old mice, indicating AMPK activation. Phosphorylation of the mTORC1 targets 4EBP1, and S6k were both elevated in old muscle, consistent with previous reports of hyperactivated mTORC1 in aged muscle. Acute AICAR injection returned 4EBP1 and S6k phosphorylation to young levels. RNA sequencing demonstrated that chronic AICAR injections restored the expression of many genes in old muscle to the levels observed in young muscle. Among these, mitochondrial splicing suppressor 51 (*Mss51*) expression, which is associated with impaired mitochondrial function and muscle loss, was elevated in sarcopenic muscle but attenuated by AICAR treatment, and this was confirmed by RT-PCR analysis. **CONCLUSION**: AICAR treatment reverses several critical age-related changes in gene expression and mTORC1 activity. Our findings support further investigation of AMPK activation and Mss51 repression as targets for therapeutic interventions in sarcopenia.