Identification of an Actin-Based Antidiabetic Action of Chromium in Skeletal Muscle

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Abstract

We recently demonstrated that cortical filamentous actin (F-actin) loss contributes to cellular insulin resistance induced by hyperinsulinemia. New animal and human analyses suggest a similar loss of F-actin is present in insulin-resistant skeletal muscle and results from cellular cholesterol accrual. Interestingly, we found that chromium picolinate (CrPic), a dietary supplement recognized to improve insulin action, lowers plasma membrane cholesterol in cultured adipocytes. Understanding whether CrPic can improve F-actin structure in insulin-resistant skeletal muscle via lowering membrane cholesterol is not known, yet significant, as skeletal muscle is responsible for a large majority of insulin-stimulated glucose transport. In L6 myotubes stably expressing the insulin-responsive glucose transporter GLUT4 carrying an exofacial myc-epitope tag, acute insulin stimulation (20 min, 100 nM) increased myc-epitope labeling at the surface of intact cells by ~2-fold ($P<0.05$). In contrast, the ability of insulin to stimulate this process was inhibited 25% ($P<0.05$) by sustained exposure of L6 myotubes to insulin (12 h, 5 nM). Defects in insulin signaling did not readily account for the observed disruption. However, we found that insulin-induced insulin-resistant myotubes displayed a 28% elevation ($P<0.05$) in membrane cholesterol with a reciprocal 14% loss ($P<0.05$) in F-actin. This cholesterol/actin imbalance and insulin/GLUT4 dysfunction was corrected by the cholesterol-lowering action of CrPic. Mechanistically, CrPic increased the activity of the AMP-activated protein kinase (AMPK). Tests also revealed that other well-recognized activators of AMPK (e.g., AICAR, DNP) lowered membrane cholesterol and that, in a fashion similar to that witnessed for CrPic, improved regulation of GLUT4 in insulin-induced insulin-resistant myotubes. These data, as well as findings from ongoing siRNA-mediated AMPK knockdown experiments, are consistent with AMPK mediating its antidiabetic action by lowering cellular cholesterol. We predict that chromium, via AMPK activation, protects against cholesterol accrual that induces skeletal muscle F-actin loss and insulin resistance.