REDD1 Knockout Reduces Whole Body Glucose And Insulin Tolerance, And Impairs Skeletal Muscle Insulin Signaling
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A lack of the REDD1 promotes dysregulated growth signaling, though little has been established with respect to the metabolic role of REDD1. **PURPOSE:** The goal of this study was to determine the role of REDD1 on glucose and insulin tolerance, as well as insulin stimulated growth signaling pathway activation in skeletal muscle. **METHODS:** First, intraperitoneal (IP) injection of glucose or insulin were administered to REDD1 wildtype (WT) versus knockout (KO) mice to examine changes in blood glucose over time. Next, alterations in skeletal muscle insulin (IRS-1, Akt, ERK 1/2) and growth (4E-BP1, S6K1, REDD1) signaling intermediates were determined before and after IP insulin treatment (10 min) using Western blot analysis. **RESULTS:** REDD1 KO mice were both glucose and insulin intolerant when compared to WT mice, following IP injections of glucose or insulin, respectively. REDD1 KO mice exhibited higher (p<0.05) circulating blood glucose concentrations and a greater (p<0.05) area under the curve. The REDD1 KO exhibited significant though blunted insulin-stimulated increases (p<0.05) in Akt S473 and T308 phosphorylation versus the WT mice. Additionally, acute insulin treatment had no effect on 4E-BP1 T37/46, S6K1 T389, IRS-1 Y1222, and ERK 1/2 T202/Y204 phosphorylation in skeletal muscle from REDD1 KO versus the WT mice. **CONCLUSION:** The results provide a deeper understanding of REDD1 as it relates to insulin-stimulated mTORC1 signaling, encompassing metabolism and insulin action. A lack of REDD1 contributes to glucose and insulin intolerance that is associated with dysregulated insulin stimulation of both mTORC1 and ERK1/2 pathways. Collectively, these novel data suggest that REDD1 has a more distinct role in whole body and skeletal muscle metabolism and insulin action than previously thought.
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