

The repressors of mTORC1 signaling, REDD1 and REDD2, are induced in immobilized rat skeletal muscle

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Purpose: Limb immobilization, limb suspension, and bed rest cause substantial loss of skeletal muscle mass, a phenomenon termed disuse atrophy. In order to acquire new knowledge that will assist in the development of therapeutic strategies for minimizing or preventing disuse atrophy, the present study was undertaken with the aim of defining molecular mechanisms that mediate control of protein synthesis and mTORC1 signaling. **Methods:** Male Sprague-Dawley rats were subjected to unilateral hindlimb immobilization for 1, 2, 3, or 7 days or served as non-immobilized controls. Following an overnight fast, rats received either saline or L-leucine by oral gavage as a nutrient stimulus. While under isoflurane anesthesia, hindlimb skeletal muscles were extracted 30 min post-gavage, and analyzed for the rate of protein synthesis, mRNA expression, phosphorylation state of key proteins in the mTORC1 signaling pathway, and mTORC1 signaling repressors. **Results:** Protein synthesis and mTORC1 signaling were attenuated 50% as early as 1 day following hindlimb immobilization and the response of the latter to a nutrient-stimulus was attenuated. Potential repressors of mTORC1 signaling and/or protein synthesis including p53, Sestrins 1 and 2, ATF4, and HIF1- expression, or AMPK and eIF2 phosphorylation were not altered following hindlimb immobilization. In contrast, expression of REDD1 and REDD2 mRNA was induced 50-200% and 400-600%, respectively, in parallel with the changes in mTORC1 signaling and protein synthesis. **Conclusion:** Hindlimb immobilization-induced disuse atrophy results from attenuated protein synthesis and mTORC1 signaling that are in part mediated by induction of REDD1 and REDD2 expression.

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