The Impact of a 48-Hour Fast on Mitochondrial Biogenesis in Young Healthy Men

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PURPOSE: Sirturins are proposed to be important regulators of skeletal muscle mitochondrial function; however, their exact role in human skeletal muscle remains controversial. Short term fasting up-regulates sirtuins in association with increased fatty acid oxidation in animal models. Therefore, the present study utilized short term fasting as a model to investigate the effects of fasting induced up-regulation of sirturin 1 (SIRT1) and sirtuin 3 (SIRT3) on mitochondrial function. **METHODS:** Ten healthy men (age, 22.0 ± 1.5 yrs; VO_2peak, 47.2 ± 6.7 mL/min/kg) underwent a 48-hour fast. Muscle biopsies were obtained in the fed and fasted state to examine changes in whole muscle signalling events via western blotting. Resting gas exchange was measured for 10 minutes before and following the fast using a metabolic cart. **RESULTS:** Resting respiratory exchange ratio (0.8 ± 0.11 vs. 0.91 ± 0.08), oxygen consumption (4.68 ± 0.55 L vs. 5.31 ± 0.39 L), and energy expenditure (23.4 ± 2.8 total kcal vs. 26.6 ± 2.0 total kcal) were significantly lower in the fasted vs. fed state, while the rate of fat oxidation (1.3 ± 0.37 kcal/min vs. 0.86 ± 0.51 kcal/min) and total fat oxidation (19.4 ± 5.6 total kcal vs. 13.0 ± 7.6 total kcal) were significantly higher ($p < 0.05$). No change was observed in the mitochondrial proteins cytochrome c oxidase subunits I (COX I) or IV (COX IV) following the 48-hour fast. Similarly, there was no change in whole muscle protein content of PGC-1α, SIRT1, SIRT3, the acetyltransferase general control non-repressible 5 (GCN5), AMP-activated protein kinase subunit alpha (AMPKα), acetyl-CoA carboxylase (ACC), or p38 mitogen-activated protein kinase (p38 MAPK). Phosphorylation of SIRT1 (Ser47), AMPKα (Thr172), p38 MAPK (Thr180/Tyr182), and downstream targets of protein kinase A (PKA) were also unaltered by fasting for 48 hours. Interestingly, there was a significant decrease ($p<0.05$, -16%) in acetylated p53, a downstream target of SIRT1. **CONCLUSION:** Fasting for 48-hours did not promote changes in skeletal muscle mitochondrial content or intracellular signalling events proposed to be involved in mitochondrial biogenesis; however, there was a decrease in acetylation of the SIRT1 target p53, suggesting an increase in SIRT1 activity.

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