

The effect of acute exercise on skeletal muscle SIRT1

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Introduction. Previous studies have shown acute exercise increases peroxisome proliferator-activated receptor γ coactivator-1 α (PGC-1 α) transcriptional activity, regulating contraction-induced mitochondrial biogenesis in skeletal muscle. Fasting in rodents and *in vitro* studies suggest SIRT1, a protein deacetylase allosterically activated by NAD⁺, may stimulate this pathway in skeletal muscle through its deacetylation and activation of PGC-1 α . Fasting, which elevates the cellular metabolic NAD⁺:NADH ratio, increases SIRT1 expression and reduces PGC-1 α acetylation in rodent skeletal muscle implying SIRT1 to be active in this metabolic profile. Whilst it has been assumed acute exercise stimulates this pathway through increases in the NAD⁺:NADH ratio, no study has examined whether this SIRT1/PGC-1 α interaction is activated by acute exercise. This experimental study examined the effect of acute exercise on SIRT1 activity, interaction of SIRT1 with PGC-1 α , and mRNA and protein expression of SIRT1 and PGC-1 α within rat skeletal muscle. As previous findings implicate SIRT1 to regulate skeletal muscle PGC-1 α pathways during fasting, the fed state of the rats was controlled for.

Methods. Six-week old male Sprague-Dawley rats were randomly allocated to one of six groups (n=8 per group). Three groups were *ad libitum* fed, three groups were overnight fasted (16 hours). For each fed state one group of rats was killed at rest, one group was killed immediately following one hour of acute exercise on a motorized treadmill (25m/min at a 5% incline), and one group was killed three hours post acute exercise. Gastrocnemius muscle was rapidly excised, frozen in liquid nitrogen and used for all analyses.

Results. No change in SIRT1 activity was detected following fasting or exercise, implying that fasting and exercise did not cause covalent modification of SIRT1 and that allosteric binding of NAD⁺ (which is lost during the extraction) may be the primary regulator of SIRT1 activity under these circumstances. Attempts to immunoprecipitate PGC-1 α were unsuccessful, therefore we were unable to examine PGC-1 α acetylation (as an indicator of SIRT1 activity *in vivo*). Immunoprecipitation for SIRT1 revealed PGC-1 α to directly associate with SIRT1 in skeletal muscle, although exercise and fasting did not appear to alter the extent of this association. Three hours following acute exercise PGC-1 α mRNA was significantly higher ($p < 0.05$). Fasting further increased PGC-1 α mRNA expression three hours post acute exercise ($p < 0.05$), in parallel with a tendency for increased SIRT1mRNA expression ($p = 0.07$). However, exercise and fasting had no effect on PGC-1 α or SIRT1 α protein levels.

Conclusions. This study has demonstrated that SIRT1 and PGC-1 α interact in skeletal muscle *in vivo*, and that SIRT1 mRNA has a tendency to increase following acute exercise in a fasted, but not fed state. Fasting increases PGC-1 α mRNA expression following acute exercise to a greater extent than exercise in fed condition. Further investigation is required to investigate whether the SIRT1/PGC-1 α interaction facilitates deacetylation during exercise *in vivo*.