ACTN3 R577X variant influences mitochondrial-related gene expression following a bout of exercise

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Background: Mice with α-actinin-3–deficient muscle fibres respond more effectively to endurance exercise training (Seto *et al.*, 2013). This may be related to higher calcineurin activity, which has been reported to induce skeletal muscle mitochondrial biogenesis (Jiang *et al.*, 2010). To date, however, no study has investigated how α-actinin-3 deficiency in humans (ACTN3 XX genotype) regulates mitochondrial-related gene expression in response to a bout of exercise. Potential pathways could involve the downstream targets of calcineurin, such as PGC-1α (Little *et al.*, 2011).

Aim: The purpose of this study was to determine whether the ACTN3 R577X variant influences *exercise-induced* changes in gene expression.

Methods: Fifteen Caucasian males between 18 and 40 years old, with moderate physical activity levels and a Body Mass Index between 20 and 30, were recruited. Genomic DNA was then extracted from leucocytes, and *ACTN3* genotype screening was conducted. Participants were either XX (α-actinin-3 deficient, n=9) or RR (n=6) and, following baseline testing to determine their lactate threshold, performed high-intensity interval exercise bout consisting of 8 × 2-min intervals at 120% of their lactate threshold (interspersed with 1-min rest periods). Muscle samples were collected at rest, immediately after, and 3 h post-exercise for the analysis of mRNA content.

Results: There was an increase in PGC-1α (5.2±2.1 fold for RR and 7.8±3.12 fold for XX), PDK4 (6.6±0.4 fold for RR and 13.0±3.7 fold for XX), and VEGF (1.7±0.37 fold for RR and 2.2±0.6 fold for XX) mRNA content 3 h post exercise. This, however was not statistically significant ($P>0.05$). There was neither a main effect nor an interaction effect for the mRNA content of COX-1, cytochrome-c or TFAM.

Discussion: There was an increase in PGC-1α, PDK4 and VEGF mRNA content in XX *vs* RR participants 3 h post exercise. Although not significant, possibly due to the small sample size, this increase was at least 3-fold greater in XX *vs* RR participants. We are currently recruiting more participants, but these data suggest *ACTN3* variant may influence exercise-induced changes in gene expression associated with endurance training.

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