ACTN3 R577X genotype affects training-induced changes in mitochondrial respiration in humans

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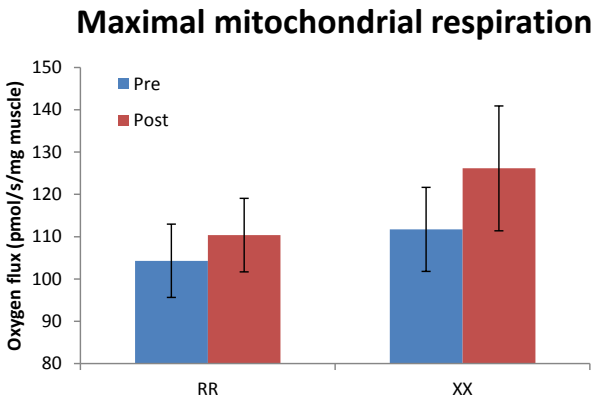
Individual differences in the response to similar exercise training are a well-known occurrence, and are influenced by both environmental and genetic factors. The common null polymorphism (R577X) in the *ACTN3* gene, which results in absence of α-actinin-3 in more than one billion humans worldwide (MacArthur & North, 2007), is a strong candidate to influence muscle performance and mitochondrial adaptations to training. The *ACTN3* R577X variant has previously been associated with athletic performance and the response to exercise training in both humans (Eynon *et al.*, 2013) and mice (Seto *et al.*, 2013). It has also been shown that the activity of mitochondrial (citrate synthase, succinate dehydrogenase, cytochrome C oxidase) enzymes are higher in α-actinin-3 deficient mice (*ACTN3* 577XX genotype) (MacArthur *et al.*, 2007,2008). However, little is known about how the *ACTN3* R577X variant influences training-induced changes in mitochondrial function in humans.

Aim. To investigate the influence of *ACTN3* genotype on performance outcomes and mitochondrial respiration following 4 weeks of High-Intensity Interval Training (HIIT).

Methods. We have recruited ten moderately-trained Caucasian males (age=32.6±1.2), who were either homozygous for α-actinin-3 deficiency (*ACTN3* XX genotype, n=5), or homozygous for the R allele (*ACTN3* RR genotype n=5). Participants in each group were matched for physical activity levels and body mass index (BMI). Subsequently, participants underwent 4 weeks of HIIT, 3 times per week. A 20 km time-trial (20km TT), and a graded exercise test (GXT), to assess peak oxygen uptake (VO_{2Peak}) and the Lactate threshold (LT), were performed pre and post training. Pre and post training, a resting muscle biopsy was taken from the *vastus lateralis* muscle and analysed for *in situ* mitochondrial respiration (Bishop *et al.*, 2010).

Results. Following 4 weeks of HIIT, the *ACTN3* 577XX participants showed a greater increase in maximal mitochondrial respiration (Vmax) (XX = 14.43 pmol s^{-1} mg^{-1} ww, RR = 6.11 pmol s^{-1} mg^{-1} ww, see Figure). Furthermore, the 577XX participants showed a higher increase (improved) in LT, following HIIT compared with their RR counterparts (LT XX = 18.7 W, LT RR=17.0 W). In contrast, the *ACTN3* 577RR participants recorded greater increases in 20km TT performance (3 min and 20s) than their *ACTN3* 577XX counterparts (48 s).



Maximal mitochondrial respiration (Vmax) across ACTN3 genotypes pre and post exercise training.

Conclusion. These preliminary results indicate at *ACTN3* 577XX individuals had a greater increase in both maximal mitochondrial respiration and the LT than their 577RR counterparts. Due to the small sample size tested to date, none of the differences reached statistical significance. However, our data raise the possibility that the *ACTN3* R577X variant influences training-induced improvement in both mitochondrial function and LT. These results also support recent data from our lab suggesting a disassociation between changes in mitochondrial respiration and endurance performance.

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