Ammonium chloride ingestion increases resting mRNA content, but blunts exercise-induced mRNA levels in human skeletal muscle

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We have previously observed that minimising the decrease in muscle pH that occurs during high-intensity exercise promotes greater aerobic adaptations (Edge *et al.*, 2006). We subsequently reported that rats ingesting sodium bicarbonate ($NaHCO_3$) before training sessions (which reduced the activity-induced decrease in muscle pH) had significantly greater adaptations to exercise training (Thomas *et al.*, 2007). This included greater mitochondrial respiration (Bishop *et al.*, 2010) compared to both a control group (no training) and a placebo group (identical training, but ingesting NaCl before each session). The aim of the present study was to test the hypothesis that intracellular pH may affect some of the cellular signalling pathways and genes that regulate mitochondrial biogenesis - which have previously been demonstrated to be up-regulated by physical activity (Little *et al.*, 2011). Eight active males (Mean±SD, age, 25±6, Body mass 84±9, $\dot{V}O_{2peak}$ 48±8) performed 10×2 min cycle intervals at 80% $\dot{V}O_{2peak}$ intensity on two occasions separated by ~2 weeks. Participants ingested either ammonium chloride (ACID) or calcium carbonate (PLA) the day before and on the day of the exercise trial in a randomised, counterbalanced order, using a crossover design. Biopsies were taken from the *vastus lateralis* muscle before and immediately after exercise as well as after 2 h of recovery. The mRNA levels of peroxisome proliferator-activated receptor coactivator 1α (PGC-1α), citrate synthase, cytochome c and FOXO1 were elevated at rest following ACID ($p < 0.05$). During the PLA condition, the mRNA content of mitochondrial- and glucose-regulating proteins was elevated following exercise ($p < 0.05$). In the early phase (0 – 2 h) of post-exercise recovery during ACID, PGC-1α, citrate synthase, cytochome C, FOXO1, GLUT4, and HKII mRNA levels were not different from resting levels (all $p > 0.05$), but the difference in PGC-1α mRNA 2 h post-exercise between ACID and PLA approached significance ($p = 0.08$). The present data show that in resting conditions, short-term metabolic acidosis increases the PGC-1α mRNA level and some of its downstream targets, to levels similar to that found in PLA post-exercise. However, metabolic acidosis abolished the early post-exercise increase of PGC-1α mRNA and the mRNA of downstream mitochondrial and glucose regulating proteins. These findings indicate that metabolic acidosis may affect mitochondrial biogenesis, with divergent effects in resting and exercised muscle.

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