Modulation of Pi flux by short term exercise

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Purpose/Introduction

Exercise training increases whole body insulin sensitivity due to increased muscle glucose transport in healthy and insulin resistant humans. Glucose intolerant 1st degree offspring (OFF) of type 2 diabetic patients (T2D) feature reduced insulin stimulated glucose transport which has been linked to impaired flux through ATP synthase in skeletal muscle [1]. Likewise lipid-induced insulin resistance is associated with decreased flux through ATP synthase under insulin stimulated conditions [2]. These studies suggest that mitochondrial dysfunction is involved in the development of insulin resistance. Exercise is known to ameliorate insulin sensitivity also in nondiabetic OFF [3]. Recent studies suggest that chronic exercise training stimulates AMP-activated protein kinase (AMPK) and augments mitochondrial biogenesis through peroxisome proliferators-activated receptor γ coactivator-1α (PGC-1α) and nuclear respiratory factors (NRFs) [4].

These studies raised the questions (i) whether mitochondrial dysfunction occurs also in glucose tolerant insulin sensitive OFF and (ii) if short-time exercise training is able to overcome this alteration.

Subjects and Methods

We recruited healthy glucose tolerant volunteers with (OFF: 4f/6m; Age:39+/-14; BMI:24+/-4) or without (CON:4f/6m; Age:38+/-11; BMI:24+/-3, P<0.05) family history of T2D. None of the participants was trained or performed intense exercise on regular basis and during experiment were on an isocaloric diet, refrained from any physical exercise for three days and fasted for 12 h before the start of the studies.

Experimental protocol (Fig.1):

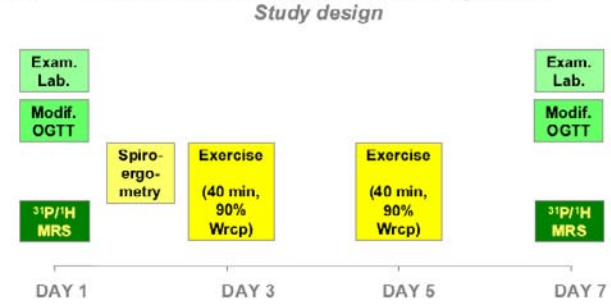
Day 1: baseline blood sampling, a 75-g oral glucose tolerance test (OGTT) and magnetic resonance spectroscopy (MRS) measurements.

Day 2: incremental exercise testing (+10-20 W/min until exhaustion) on a cycle ergometer and respiratory gas exchange was measured using an open-air spirometry system.

Day 3 and 5: exercise on a cycle ergometer (90% of power output determined at the respiratory compensation point, rcp). Each bout of exercise consisted of 40 min (two units of 20 minutes interrupted by 10 min of regeneration).

Day 7: Measurements of day 1 where repeated in identical fashion.

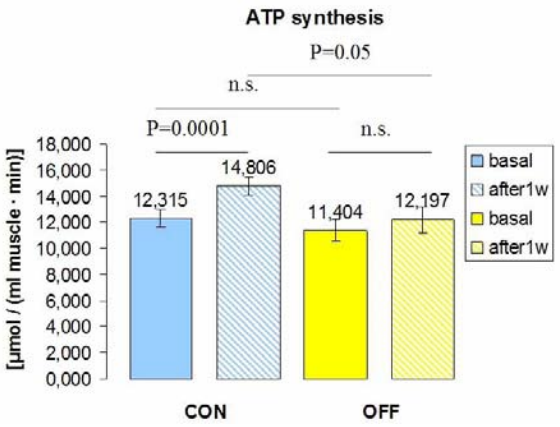
Fig.1 **Effect of short-term exercise on ATP synthesis**



MRS

All measurements were done on a 3 -T spectrometer (Bruker, Germany). Intramyocellular (IMCL) and hepatocellular (HCL) lipid contents were measured with single voxel ^{1}H MRS (Muscle ^{1}H MRS: volume resonator, STEAM,TE=20ms,1.2x1.2x1.2 cm^{3}, TR=4s, AVG=32-soleus,64-tibialis anterior)

For measurement of muscle ATP synthesis a 10-cm circular double resonant ^{1}H and ^{31}P surface coil was positioned above the medial head of the right gastrocnemius muscle as described previously. Rates of flux through ATP synthesis were assessed from the saturation magnetisation transfer experiment applied to the exchange between inorganic phosphate (Pi) and ATP using ^{31}P MRS (2).



Results

IMCL content tended to be higher in soleus muscle after training (CON: 0.97+/-0.5% vs. 1.21+/- 0.47%, P=0.07) and significantly decreased in tibialis anterior muscle after training (OFF: 0.25+/- 0.13% vs. 0.2+/- 0.1%, P=0.05). Before training, flux through ATP synthesis did not differ between the groups (CON: 12.3+/-2.2 µmol.ml^{-1}.muscle^{-1}.min^{-1}; OFF: 11.4+/-2.7 µmol.ml^{-1}.muscle^{-1}.min^{-1}). Exercise training increased ATP synthesis by ~20% in CON (14.8+/-2.2 µmol.ml^{-1}.muscle^{-1}.min^{-1}, P=0.0001 vs. basal) but did not change in OFF (12.2+/-3.2 µmol.ml^{-1}.muscle^{-1}.min^{-1})

Conclusion

Short term exercise training

(i) increases muscular ATP synthesis despite no changes in insulin sensitivity in healthy humans without a family history of T2D suggesting that improvement of mitochondrial function preceeds training effects on insulin sensitivity.

(ii) fails to stimulate ATP synthesis in glucose tolerant 1st degree relatives of T2D supporting the concept of inherited abnormalities in mitochondrial function.

References

[1] Petersen et al, PLoS Med 2005,2:e233.

[2]Brehm et al, Diabetes 2006,55:136-140

[3] Perseghin et al, N Engl J Med 1996, 335:1357-1362

[4] Roden, Int J Obes (Lond), 2005. 29 Suppl 2:S111-115.