

Session 1: Integrated Cardiovascular and Mitochondrial Physiology.

I. Skeletal Muscle, Exercise, and Endurance

1-01. Repeated static contractions to fatigue increases mitochondrial vulnerability towards oxidative stress.

Kent Sahlin^{1,2,3}, M Mogensen², JS Nielsen², M Tonkonogi^{1,3,4}

¹Stockholm Univ. College Physical Education and Sports, Stockholm, Sweden; ²Inst. Sport Sciences Clinical Biomec., Univ. Southern Denmark, Odense; ³Dept. Physiology Pharmacology, Karolinska Institutet, Stockholm, Sweden; ⁴Dept. Health Social Sciences, Dalarna Univ., Falun, Sweden. - kent.sahlin@ihs.se

The effect of repeated static exercise (RSC) on mitochondrial function and SR Ca²⁺ kinetics was investigated in human muscle. Ten male subjects performed 5 sustained static contractions at 66 % of maximal voluntary contraction force (MVC) to fatigue with 10 min rest in between. Muscle contractility was measured pre- and post-exercise with MVC and transcutaneous electrical stimulation. Mitochondria isolated from muscle biopsies (pre-, 0 and 24 h post-exercise) were analyzed for respiratory function [with and without prior exposure to H₂O₂ (ROS)], mitochondrial resistance to Ca²⁺ induced pore opening (M_{CaR}) and in vitro sarcoplasmic reticulum (SR) Ca²⁺ uptake and release.

RSC had no effect on mitochondrial function. However, mitochondria isolated from muscle samples taken after RSC were more vulnerable to ROS as demonstrated by reduced respiratory control index (RCI=state 3/state 4), reduced P/O ratio and reduced maximal rate of oxidative phosphorylation (oxphos) ($P < 0.05$). After 24 h recovery P/O ratio and oxphos were restored, whereas RCI remained depressed and uncoupled respiration was elevated. M_{CaR} was related to % type II fibres (myosine heavy chain II) but was not affected by RSC. RSC resulted in altered muscle contractility (reduced MVC, twitch force, 20/50 Hz force ratio and faster force relaxation) which remained 3 h post-exercise. SR Ca²⁺ uptake rate was lower 0 h post-exercise ($P < 0.01$ vs. 24 h post-exercise) and could not explain the faster force relaxation.

It is concluded that RSC does not affect mitochondrial function but increases the vulnerability of mitochondria towards ROS. It is suggested that this is a consequence of augmented ROS formation and associated depression of scavenger substances during RSC, which is an ischemia-reperfusion type of exercise. The depressed 20/50 Hz force ratio and the slow recovery of muscle contractile function suggest that fatigue is related to non-metabolic factors e.g. failure of excitation-contraction coupling.

1-02. Mitochondrial regular arrangement in muscle cells: a "crystal-like" pattern.

Nathalie Béraud¹, M Vendelin^{1,2}, K Guerrero¹, VA Saks^{1,3}

¹Group Quantitative Structural Bioenergetics, Lab. Fundamental Applied Bioenergetics, INSERM E0221, Joseph Fourier Univ., Grenoble, France; ²Inst. Cybernetics, Tallinn Technical Univ., Akadeemia 21, 12618 Tallinn, Estonia; ³Lab. Bioenergetics, National Inst. Chemical Physics Biophysics, Akadeemia 21, Tallinn, Estonia. - nathalie.beraud@ujf-grenoble.fr

The aim of this work is to characterize quantitatively the arrangement of mitochondria in heart and skeletal muscles. For this, we studied confocal images of mitochondria in non-fixed cardiomyocytes and fibers from soleus and white gastrocnemius muscles of

adult rats. The arrangement of intermyofibrillar mitochondria was analyzed by estimating the densities of distribution of mitochondrial centers relative to each other (the probability density function).

In cardiomyocytes (1820 mitochondrial centers marked), neighboring mitochondria are aligned along rectangle, with distance between the centers equal to $1.97 \pm 0.43 \mu\text{m}$ and $1.43 \pm 0.43 \mu\text{m}$ in longitudinal and transversal directions, respectively.

In soleus (1659 mitochondrial centers marked) and in white gastrocnemius (621 pairs of mitochondria marked), mitochondria are mainly organized in pairs at the level of I-band. Due to such organization, there are two distances characterizing mitochondrial distribution in longitudinal direction in these muscles. The distance between mitochondrial centers in longitudinal direction within the same I-band is $0.91 \pm 0.11 \mu\text{m}$ and $0.61 \pm 0.07 \mu\text{m}$ in soleus and white gastrocnemius, respectively. The distance between mitochondrial centers in different I-bands is est $\approx 3.7 \mu\text{m}$ and $\approx 3.3 \mu\text{m}$ in soleus and in gastrocnemius, respectively. In the transversal direction, the mitochondria are packed considerably closer to each other in soleus than in white gastrocnemius | the distance is equal $0.75 \pm 0.22 \mu\text{m}$ (soleus) and $1.09 \pm 0.41 \mu\text{m}$ (gastrocnemius).

Our results show that intermyofibrillar mitochondria are arranged in highly ordered crystal-like pattern in a muscle-specific manner with relatively small deviation in the distances between neighboring mitochondria. This is consistent with the concept of the unitary nature of the organization of the muscle energy metabolism ^b.

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1-03. High-resolution respirometry in small biopsies of human muscle: correlations with body mass index and age.

Erich Gnaiger¹, C Wright-Paradis², H Sondergaard³, C Lundby³, JA Calbet⁴, B Saltin³, J Helge³, R Boushel²

¹D. Swarovski Research Lab., Dept. Transplant Surgery, Innsbruck Medical Univ., Austria; ²Dept. Exercise Science, Concordia Univ., Montreal, Canada; ³Copenhagen Muscle Research Centre, Denmark; ⁴Dept. Physical Education, Univ. Las Palmas, Gran Canaria, Spain. - erich.gnaiger@uibk.ac.at

Aerobic exercise and several aspects of life style influence mitochondrial respiratory function in human muscle, in addition to effects of age, gender and genetic background. In the present study, a significant part of the variability in respiration of human mitochondria [1] was explained by analysis of readily accessible background information on 25 healthy human subjects (19 males and 6 females; 22 to 46 years). Based on a novel multi-substrate/inhibitor protocol, this approach advances the functional analysis in mitochondrial physiology and pathology.

A protocol for high-resolution respirometry (with two or three OROBOROS Oxygraph-2k operated in parallel) was designed for quantification of mitochondrial respiratory capacities in permeabilized muscle fibers obtained from small needle biopsies (2 to 6 mg per run; 2 or 4 runs per subject). Cell membranes were selectively permeabilized [2], and lack of respiratory stimulation by cytochrome c indicated an intact outer mitochondrial membrane (Fig. 1). Measurements were performed at 30 °C in the range of 20 to 50 kPa oxygen pressure (210 to 530 μM), to avoid oxygen limitation [3]. In this range, autoxidation of ascorbate and TMPD was a linear function of oxygen, which was applied for correction of chemical background oxygen flux.

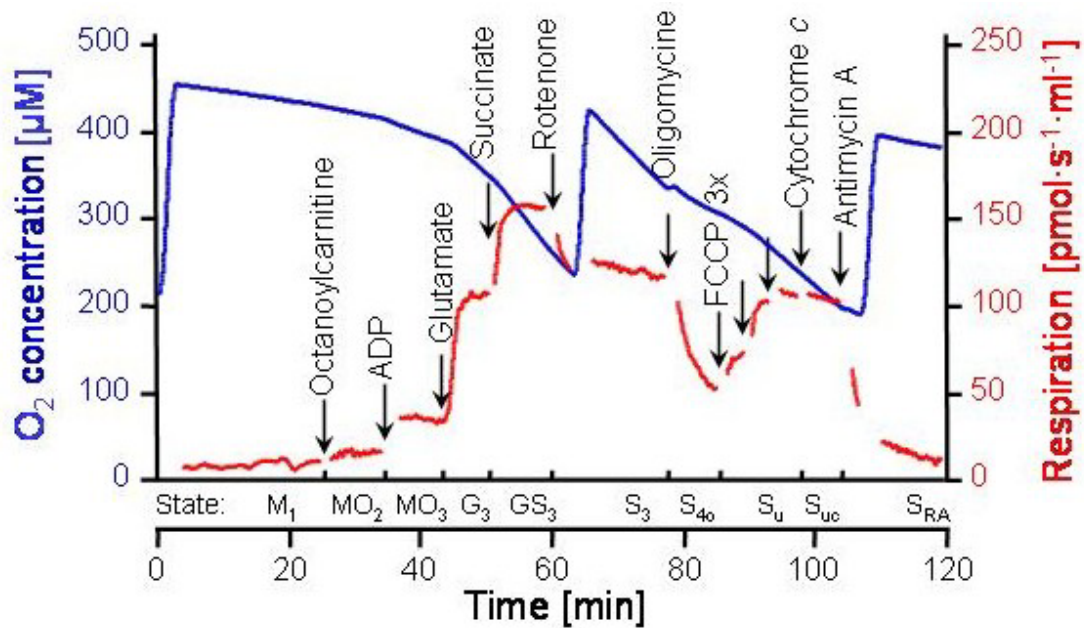


Fig. 1. Oxygen concentration and oxygen flux per volume of permeabilized fibers (vastus lateralis, 5.0 mg wet weight) in medium MiR05 containing malate. The titration steps are shown by arrows (continued with titrations of ascorbate and TMPD; not shown), and the corresponding states are defined on the time axis. Oxygenations were performed with pure oxygen purged into the gas phase of the intermittently opened chamber.

ADP-stimulated respiration with malate+octanoylcarnitine (state OM_3) was 46 % compared to further addition of glutamate (state GM_3). An additive effect was exerted by parallel complex I+II electron input (the GS_3/GM_3 ratio was 1.6), since respiration with succinate/rotenone (S_3) was only 1.1 times the state GM_3 (Fig. 1). In a variation of this protocol, FCCP was titrated upon state GS_3 , yielding a further 44 % increase (and a corresponding GS_u/GM_3 ratio of 2.4). State GS_3 , therefore, reflects the capacity of the phosphorylation system, in agreement with results on isolated mitochondria [4]. The coupled state GS_3 represents the physiologically relevant upper limit of respiration, providing parallel complex I and II input in accordance with an operational TCA cycle. The physiological excess capacity of COX, expressed as the COX/GM_3 ratio was 2.7, whereas the COX/GS_3 ratio was 1.4. Respiratory adenylate control ratios were identical with octanoylcarnitine (OM_3/OM_2) and succinate (S_3/S_0).

State GS_3 declined significantly as a function of body mass index (BMI; body weight/high²) in the 19 males, which explained ~60 % of total variability. BMI was independent of age, as was the GS_3 respiratory capacity. Fatty acid oxidation capacity (state OM_3), however, declined significantly with age (males and females combined), thus extending a study on isolated mitochondria [1] to a surprisingly narrow range of ages. Consideration of BMI and age, therefore, improves the diagnostic resolution of functional mitochondrial respiratory analyses.

Supported by the Copenhagen Muscle Research Centre and Fonds de la Recherche en Sante Quebec (FRSQ), Concordia Univ., The Natural Science and Engineering Research Council of Canada (NSERC).

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1-04. Local adaptations in mitochondrial substrate-specific O₂ flux capacity with prolonged, low intensity, whole-body endurance training.

Robert Boushel¹, C Wright-Paradis¹, H Sondergaard²,
JA Calbet³, B Saltin², J Helge², E Gnaiger⁴

¹Dept. Exercise Science, Concordia Univ., Montreal, Canada; ²Copenhagen Muscle Research Centre, Denmark; ³Dept. Physical Education, Univ. Las Palmas, Gran Canaria, Spain; ⁴D. Swarovski Research Lab., Dept. Transplant Surgery, Innsbruck Medical Univ., Austria. - boushel@alcor.concordia.ca

Endurance training elevates peak muscle oxygen uptake by means of hemodynamic increases in oxygen delivery and local increases in muscle capillary and mitochondrial density. In addition, training enhances the rate of muscle fat oxidation for energy supply during submaximal exercise [1]. The purpose of this study was to investigate the temporal adaptations in whole body and local arm and leg muscle oxidative capacity and substrate utilization at several stages of low intensity endurance training. Seven healthy Danes skied for 6 hours daily at 65 % of maximum heart rate over 42 days in the polar region of northern Greenland. High-resolution respirometry (OROBOROS Oxygraph-2k) allowed quantification of mitochondrial respiratory capacities from saponin-permeabilized skeletal fibers (2-6 mg) of the deltoid and vastus muscles [2].

At baseline, state 3 O₂ flux (in the presence of ADP) with parallel electron input into complexes I+II (glutamate, malate and succinate) was higher in the vastus compared to the deltoid (54 ±7 vs. 37±2 pmol·s⁻¹·mg⁻¹, respectively; *P*<.05). At training day 7, state 3 phosphorylation capacity was unchanged in the deltoid but reduced to 31±5 pmol·s⁻¹·mg⁻¹ in the vastus (*P*<.05). After 42 days of skiing, flux capacity was the same in both muscles (38±3 pmol·s⁻¹·mg⁻¹). State 3 O₂ flux with octanoylcarnitine+malate was also higher in the vastus compared to deltoid at baseline (13±0.5 vs 10±0.5 pmol·s⁻¹·mg⁻¹, respectively; *P*<.05), but after 42 days of skiing both muscles had equal flux capacity with fat substrate (12.3±0.8 vs. 12.7±1 pmol·s⁻¹·mg⁻¹). Despite a daily energy expenditure of ~25,000 kJ (~6,000 kcal) over the 42 day ski sojourn, there were no changes in muscle mass, whole body $V_{O_{2max}}$ or substrate utilization measured by whole body respiratory quotient, nor whole-leg and arm $V_{O_{2max}}$.

These data reflect that (1) prolonged low intensity endurance exercise induces local adaptations to equalize substrate-specific muscle phosphorylation capacity preferentially towards energy sustainability rather than for peak respiratory power, and (2) high-resolution respirometry provides insight into local, muscle-specific adaptations not detectable with whole body or limb measures of oxidative capacity or substrate utilization. Considering previous findings indicating that mitochondrial function is not a limiting factor for $V_{O_{2max}}$, these local muscle adaptations support the novel concept of exercise-specific muscle 'metabolic fitness'. In addition to the importance of cardiovascular fitness, these findings may have important implications for health.

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1-05. Mitochondrial studies *in situ* reveal a novel mechanism of dysfunction: uncoupling in aged muscle.

CE Amara, DJ Marcinek, KE Conley, SA Jubrias, EG Shankland,
Martin J Kushmerick

Dept. Radiol., Univ. Washington, Seattle, WA 98195, USA. -
kushmeri@u.washington.edu

Studies of mitochondria in biochemically purified organelles or permeabilized fibers *in vitro* are not always made under conditions mimicking their normal *in situ* environment of intact muscle. We developed NMR and optical spectroscopic methods to quantify mitochondrial function directly in intact muscle of humans and mice to establish a "gold standard" by which to identify and quantify abnormal function. We focused on aging because muscles in the elderly have reduced aerobic ATP synthetic capacity. We showed a substantial decline in aerobic phosphorylation capacity due to both reduced mitochondrial volume and reduced ATP synthesis capacity per mitochondrial unit. The latter is an example of dysfunction, not merely reduced function. Most work on mitochondria in aged muscle focuses on respiration. However, our recent *in vivo* experiments revealed significant uncoupling of ATP synthesis and respiration with age in both mouse and human muscle as we now describe.

In order to evaluate the effect of mitochondrial dysfunction on energetics in intact muscle, the following characteristics need to be quantified: ATP energy store generated, oxygenation, capacity for ATP synthesis by mitochondria, and coupling of phosphorylation to respiration (P/O ratio). In aged human and mouse muscle there is little change in total creatine and a tendency for ATP to be reduced with the consequence that the energy stores are maintained with minimal decrement in chemical potential. In young and aged muscle myoglobin is normally not fully saturated indicating that mitochondria function *in vivo* at very low p_{O_2} (<8 torr, 1.1 kPa). The rate of PCr resynthesis following a metabolic perturbation is reduced in aged muscle and phosphorylation is decreased in elderly muscle per unit mitochondrial volume.

In addition our results also revealed the novel finding that phosphorylation is uncoupled to respiration in aged muscle. Mouse young adult leg muscle has a P/O = 2.2 whereas it is reduced to 1.1 in 30 month old mice. In elderly human muscle our recent data reveal the tibialis anterior muscle is normally well-coupled (P/O ~ 2.5) whereas the first dorsal interosseous of the hand can be substantially uncoupled in the same individual with P/O~1.9 for subjects >65 years. There is also a reduction in resting energy demand because oxygen consumption is not increased with uncoupling. The differences found in human individuals can be exploited to characterize the underlying mechanisms and their functional consequences.

To summarize, our work identified uncoupling of oxidative phosphorylation in elderly muscle (a mitochondrial dysfunction) as a new mechanism accounting for the reduced capacity of ATP synthesis characteristic of muscle in elderly subjects. This mechanism is in addition to the known loss of mitochondrial mass (sarcopenia, reduced mitochondrial volume) and respiratory chain capacity. Our ability to measure coupling *in vivo* in different human muscles allows us to design new experiments to identify variation in the effects of aging on mitochondrial function. We are actively exploring the mechanisms involved in this novel observation of uncoupling in both mouse and human muscle and their functional consequences.

1-06. Role of gender and caloric restriction in mitochondrial respiration-phosphorylation capacities and biogenesis in rat skeletal muscle.

Bartomeu Colom, MP Alcolea, A Valle, J Oliver, P Roca, FJ Garcia-Palmer

Grup Metabolisme Energètic i Nutrició, Dept. Biologia Fonamental Ciències Salut, Inst. Univ. Investigació Ciències Salut (IUNICS), Univ. Illes Balears, Ctra Valldemossa s/n (07122), Palma de Mallorca, Spain. - vdbsbcp4@uib.es

Previous work has shown the existence of a sexual dimorphism in the mechanisms in charge of the adaptation to food deprivation periods in rodents. Accordingly, females may have evolved adaptations to better withstand caloric restriction, a frequent condition in nature, probably because they are subjected to more severe selection pressures during time of food supply than males [1]. One of these mechanisms is the great ability of females to conserve energy in periods of food restriction, with their consequent higher energy efficiency [2,3]. Changes in this efficiency can be linked to changes in the necessary mechanisms to obtain sufficient energy, which are the mitochondrial oxidative-phosphorylation (OXPHOS) complexes.

In this work, we studied the role of gender and caloric restriction in the modification of mitochondrial respiration-phosphorylation capacities and mitochondrial biogenesis in rat skeletal muscle. For this purpose, Wistar rats of both genders were subjected to a three months of 40 % caloric restriction diet and compared to control rats fed ad libitum. Skeletal muscle gastrocnemius were removed, and we measured the nuclear and mitochondrial DNA (mtDNA) contents, the enzymatic activities of mitochondrial respiratory chain complexes I, III, IV, and ATPase (OXPHOS system), as well as the expression and protein content of several genes involved in mtDNA replication, transcription, and mitochondrial function, such as peroxisome proliferator-activated receptor γ coactivator-1 α (PGC-1 α), nuclear respiratory factors 1 and 2 (NRF-1, NRF-2), mitochondrial transcription factor A (TFAM), mitochondrial single DNA binding protein (mtSSB) and cytochrome c oxidase subunits I and IV (COX I, COX IV). The results indicated that mitochondrial muscle biogenesis was not altered either by gender or by three months of caloric restriction diet. Besides, skeletal muscle of female rats had a higher mitochondrial respiratory chain machinery and phosphorylation capacity than males, which is not due to differences in mitochondrial mass, but due to a higher cellularity index.

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1-07. Cycling efficiency is positively correlated to type I fibre content and negatively correlated to UCP3 protein but not to mitochondrial efficiency determined *in vitro*.

Martin Mogensen¹, M Bagger¹, PK Pedersen¹, M Fernström², K Sahlin^{1,2}

¹*Inst. Sports Science Clinical Biomechanics, Univ. Southern Denmark, Odense, Denmark;*

²*Stockholm Univ. Coll. Physical Education Sports, Stockholm, Sweden. - mmogensen@health.sdu.dk*

The biochemical efficiency of the mitochondrion (P/O ratio) is an important determinant for the overall efficiency of the cell. Numerous factors have an influence on the mitochondrial efficiency such as the choice of substrate and the structural and biochemical composition of the inner mitochondrial membrane. There are some data from animal and cell culture studies, which indicate that the P/O ratio is influenced by muscle fibre type composition and content of UCP3 proteins [1,2]. Previous studies have shown

a negative correlation between the efficiency during cycling and UCP3 expression and a positive correlation between cycling efficiency and % type I fibres [3,4]. These studies indicate, that individual differences in cycling efficiency could be related to the mitochondrial efficiency. Training is known to decrease the UCP3 protein content and may also to some extent alter the fibre type distribution (increased oxidative fibres). These training induced changes should in theory increase the cycling efficiency of trained subjects. However, previous studies have shown contradicting results. The purpose of this study was to investigate the hypothesis that individual variations in cycling efficiency is related to mitochondrial efficiency. Furthermore we wanted to test the hypothesis that trained subjects have a higher cycling efficiency compared with untrained subjects.

On minimum two occasions trained ($n = 9$) and untrained ($n = 9$) subjects completed a submaximal cycle test at 40, 80 and 120 W. Based on the oxygen consumption the energy expenditure (EE) was calculated for assessment of individual cycling efficiency (gross-efficiency, GE; work-efficiency, WE; and delta-efficiency, DE). GE and WE were determined at all intensities. DE was calculated as the slope of the linear relationship between the EE and the work loads accomplished by the subject. GE, WE and DE were determined as the percentage conservation of energy in external work. Biopsies were taken on a separate day and used for determination of the mitochondrial respiratory efficiency, UCP3 protein content and fibre type distribution. Mitochondrial efficiency was determined during state 3 and submaximal respiration (constant rate of ADP infusion) with pyruvate+malate (Pyr) or palmitoyl-L-carnitine+malate (PC) as substrates. The relationship between the submaximal mitochondrial respiration and the resulting P/O ratio was fitted to a logarithmic function. Significance was considered at $P < 0.05$.

Trained subjects had a higher maximal mitochondrial respiration when the respiration was expressed per kg wet weight. The relationship between the mitochondrial P/O ratio and the absolute respiration showed that the P/O ratio increased with increasing respiration. There was no significant difference between trained and untrained subjects in their mitochondrial efficiency. Untrained subjects had a significantly higher amount of UCP3 protein compared to trained individuals, but there was no difference in the fibre type distribution. UCP3 protein was negatively correlated with DE ($r = -0.48$), WE at 80 W ($r = -0.49$) and WE at 120 W ($r = -0.56$). Furthermore, WE was positively correlated to the % type I fibres at 80 W ($r = 0.57$) and at 120 W ($r = 0.53$). However, GE, WE and DE were not correlated to the mitochondrial efficiency determined during submaximal or maximal respiratory rates. Furthermore, there were no differences in GE, WE or DE between trained and untrained subjects.

It is concluded that cycling efficiency is correlated to the mitochondrial UCP3 protein and fibre type distribution. However, these correlations could be caused by fibre type differences in the content of UCP3 protein [5]. It is also concluded that mitochondrial efficiency is lower at low rates of respiration. This may be explained by an increased membrane potential, which triggers an increased proton leak. Individual cycling efficiency was not correlated to mitochondrial efficiency determined *in vitro* and there was no difference between trained and untrained subjects in their cycling efficiency. The results indicate that cycling efficiency *in vivo* is not influenced by the mitochondrial efficiency as determined *in vitro*.

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1-08. Polymorphisms in the mtDNA hypervariable region related to individual difference in endurance performance.Yun Chang¹, CL Yu², XL Gao¹, AJ Liu³¹China Inst. Sports Science, Beijing 100061, P.R. China; ²Sports Medicine Inst. Peking Univ., ³China Canoe Team. - changyun2518@vip.sina.com

It is well known that trainability of exercise widely differs from one person to another. The individual difference is evidently determined not only by environmental factors such as life-style and habitual meals, but also by genetic factors [1-2]. It is hypothesized that there are genes affecting endurance capacity and their responses to regular exercise. Searching the factors causing the individual difference is considered meaningful in terms of a more accurate prescription for how to forecast and evaluate the exercise capacity. The purpose of this study was to investigate whether the polymorphisms in the hypervariable region I of mitochondrial DNA (mtDNA HVR-I) related to individual difference in the aerobic capacity. 94 elite endurance athletes and 92 healthy controls participated in this study. The single nucleotide polymorphisms (SNPs) of mtDNA HVR-I and the $\dot{V}O_{2\max}$ were determined. The relation between $\dot{V}O_{2\max}$ and SNPs in the endurance athletes and their controls was analyzed. The polymorphism in the mtDNA HVR-I was decided based on the 'Cambridge sequence'. The total numbers of SNPs of mtDNA HVR-I were 19 variable sites. The subjects were classified into two groups at each variable site, the Cambridge sequence group and the non-Cambridge sequence group. The results indicated that $\dot{V}O_{2\max}/\text{kg}$ were significant difference between Cambridge and non-Cambridge sequence groups at nucleotide positions 16362, 16085, and 16297 ($P < 0.05$). The male athletes with non-Cam sequence at nucleotide position 16297 has a significant lower $\dot{V}O_{2\max}/\text{kg}$, while the female athletes with non-Cam sequence at nucleotide positions 16362 and 16085 have significant lower $\dot{V}O_{2\max}/\text{kg}$. In contrast of endurance athletes, $\dot{V}O_{2\max}$ of the healthy controls were difference between Cam and non-Cam sequence groups at nucleotide position 16298 ($P < 0.05$), but after body weight revising, the difference of $\dot{V}O_{2\max}/\text{kg}$ was not significant at this position. The controls with non-Cam sequence at nucleotide position 16219 has a significant lower $\dot{V}O_{2\max}/\text{kg}$ ($P < 0.05$). In conclusion, we suggest that several polymorphisms in mtDNA HVR may relate to individual differences in endurance capacity and trainability, as SNPs markers, nucleotide positions of 16298, 16129, 16362, 16085 and 16297 related to individual difference of human aerobic endurance and their trainability [3]. As a rare unique heteroplasmic SNPs site in the endurance athletes, nucleotide position 16085 obviously is an important gene marker. Those mtDNA markers are significant for forecasting and assessing the athletic capability.

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1-09. A feedback molecular regulation of uncoupling on ROS generation in muscle mitochondria during the prolonged exercise.

Yong Zhang¹, GZ Zhang¹, N Jiang¹, GD Ma¹, L Wen¹, H Bo¹, DN Cao¹,
F Zhao¹, L Shusen²

¹Tianjin Research Inst. Sports Medicine; Dept. Health Exercise Science, Tianjin Inst. Physical Education, Tianjin 300381, China; ²National Key Lab. Biomembrane Membrane Biotechnology, Inst. Zoology, Chinese Acad. Sci., Beijing 100080, China. - yzhang@tjipe.edu.cn

The mitochondrial electron leak is an important source of endogenous ROS in exercise. The recent researches show that effect of 'mild uncoupling' of respiratory chain is involved in mitochondrial anti-oxidation event [1]. The purpose of present research is to investigate whether mitochondrial mild uncoupling is induced and/or activated during strenuous exercise and to explore its possible molecular regulation.

SD rats were divided into 5 groups to rest or run for 45, 90, 120 and 150 min respectively on the treadmill according to the incremental protocol and sacrificed at rest or immediately after every exercise time course. The following parameters were determined: 1) Separated mitochondrial State 4 respiration rate in the presence of malate and glutamate by using Clark Oxygen Electrode; 2) ROS generation of separated mitochondria by fluorometric probe; 3) Expression of UCP-3 mRNA in muscle homogenate and its protein in mitochondria using RT-PCR and Western-Blotting respectively.

(1) Mitochondrial ROS generation were significant higher at 45, 90, 120 min than at rest ($P<0.05$, $P<0.001$, and $P<0.01$, respectively) with the peak at the point of 120 min, then obviously declined at 150 min subsequently ($P<0.001$). (2) In a parallel change, state 4 rate increased significantly when exercising for 90 and 120 min ($P<0.01$ and $P<0.001$ respectively) and lowered in exercising to 150 min ($P<0.001$). (3) There were remarkably higher levels of UCP-3 mRNA at 90, 120 and 150 min ($P<0.001$, $P<0.01$ and $P<0.01$ respectively), and following UCP-3 protein contents increased at 120 and 150 min (both $P<0.001$).

According to the observed changes, we hypothesize that ROS may contribute to activated and/or induced expression of UCPs. A functioning of the UCPs may cause mild uncoupling in response to matrix superoxide and other oxidants during exercise, leading to increased proton leak and feedback decreased superoxide production. This complicated and precise feedback loop would constitute a self-limiting cycle to protect against excessive superoxide production [2], leading to early protection against oxidation and regulation of cellular and mitochondrial redox.

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1-10. Effect of coenzyme Q₁₀ supplementation on heart and liver mitochondrial function during exercise.

Li Wen¹, JL Nie^{1,3}, Y Zhang¹, L Shusen²

¹Tianjin Research Inst. Sports Medicine; Dept. Health Exercise Science, Tianjin Inst. Physical Education, Tianjin 300381, China; ²National Key Lab. Biomembrane Membrane Biotechnology, Inst. Zoology, Chinese Acad. Sci., Beijing 100080, China; ³Coll. Physical Education, Liaoning Normal Univ., China. - wenli@tjipe.edu.cn

Several studies have showed the effect of supplement of coenzyme Q (CoQ) on ability of exercise, but the effect of supplement of coenzyme on mitochondria function in exercise is unclear [1,2]. This investigation will research the effect of Coenzyme Q₁₀ on mitochondrial function during exercise from the point of view of biochemistry and bioenergetics.

SD rats were divided into four groups: normal control group (NC); supplement Q control group (QC); normal exercise group (NE); supplement Q and exercise group (QE). Exercise group rats were forced to run on the treadmill and were sacrificed at 120 min after exercise. The parameters were following: (1) Mitochondria CoQ concentrations in heart and liver were analyzed by HPLC [3]. (2) The activities of syntheses were measured with luciferase-luciferin. (3) The initial rates of proton ejection and electron transferring were measured with potassium ferricyanide as an electron acceptor. (4) ROS generation rate were determined by fluorometric probe. (5) MDA concentrations were measured in myocardium, livers and serum.

(1) In coenzyme Q₁₀-treated rats, the coenzyme Q₁₀ level of mitochondria increased significantly in myocardium and liver; the coenzyme Q₉ level of mitochondria increased significantly in myocardium also. (2) Comparing with normal control group, QC and QE group H⁺/2e and H⁺-ATPase synthesis activity increased significantly in myocardium and liver. Comparing with NE group, QE group H⁺/2e increased significantly in myocardium. The results indicated that supplement of exogenous coenzyme Q improves the coupling of oxidative phosphorylation and increases the rate of mitochondria ATP synthesis activity. (3) Supplementing CoQ increased significantly ROS generation in rats in stage of exercise. The level of MDA of mitochondria increased significantly after treat with coenzyme Q₁₀ in myocardium and livers. There are no differences in the level of MDA in serum in each group.

Supplement of exogenous coenzyme Q₁₀ can increase the level of CoQ in mitochondria and the efficiency of energy transduction and the rate of ATP synthesis in mitochondria. At the same time, it increases production of free radicals and level of LPO.

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