CONCLUSION: Aging causes a decrease in mitochondrial respiratory function but appears to stimulate compensatory biogenic pathway in rat type 1 skeletal muscle. Endurance training enhances both bioenergetic and biogenic capacity but the effect is compromised at old age.

1054 June 5 9:30 AM - 9:45 AM
Mitochondrial Fusion/fission And Bioenergetics In Aged Muscle: Influences Of Exercise Training And Calorie Restriction

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(No disclosure reported)

Mitochondrial fission and fusion have recently been shown to play an important role in regulating mitochondrial function during aging. Both endurance training and caloric restriction can stimulate skeletal muscle structural and functional remodeling but their impact on aging muscle is little known.

PURPOSE: To investigate the individual and combined effects of exercise training and calorie restriction on the gene expression of fusion protein Mfn1 and fission protein Fis1, and their potential influence on mitochondrial function.

METHODS: Male Sprague-Dawley rats (final age 19 mo) were randomly divided into 4 groups: control (C, ad lib feeding), caloric restriction (CR, 60% of C caloric intake), exercise training (E, treadmill running at 15 m/min, 5% grade for 60 min/day, 5 days/wk for 12 wk), and CR+E. Mitochondria were isolated from mixed hindlimb muscles 48 h after last training bout.

RESULTS: Mfn1 mRNA level measured with RT-PCR was elevated with both E and CR ($P<0.01$), whereas Mfn1 protein content (Western blot) was lower in CR and CR+E ($P<0.05$) vs. their free feeding counterparts. Fis1 mRNA and protein were increased with E ($P<0.05$), but decreased in CR+E vs. E ($P<0.01$). State 4 respiration measured with Clark oxygen electrode was unaltered with E or CR; state 3 respiration and respiratory control index (RCI) were both decreased with CR ($P<0.01$). E increased ATP synthesis activity ($P<0.05$) and ATP/O ratio ($P<0.01$). Both E and CR decreased H_2O_2 production in mitochondria ($P<0.01$) and increased glutathione peroxidase activity ($P<0.05$), whereas E-induced Mn superoxide dismutase was abolished with CR ($P<0.05$).

CONCLUSION: CR appears to reduce fusion and fission protein expression in aged muscle, whereas training promotes mitochondrial fission. Relationship of these dynamic changes with training-induced mitochondrial bioenergetic and antioxidant function during aging remains to be investigated.

1055 June 5 9:45 AM - 10:00 AM
AMPK Phosporylation, Sirt1 And PGC-1a Protein Expression After Sprint Exercise In Fed And Fasted Conditions

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AMPK is activated by exercise, particularly when it elicits a concomitant rise in AMP/ATP ratio. Activated AMPK decreases ATP-consuming processes and stimulates ATP-producing processes. Sprint exercise induces Thr^{172}-AMP-activated protein kinase (AMPK) phosphorylation and increased PGC-1a mRNA, by an unknown mechanism. SIRT1 plays an important role in mitochondrial biogenesis, fatty acid oxidation and glucose homeostasis through deacetylation of PGC-1a. However, it remains unknown if AMPK phosphorylation through sprint exercise may affect SIRT1 protein expression in human skeletal muscle and how this may influence PGC-1a protein levels.

PURPOSE: To determine if SIRT1 and PGC-1a protein expression is increased by AMPK phosphorylation in response to a single bout of sprint exercise and the effect of glucose ingestion prior to the sprint exercise may have on this response.

METHODS: Muscle biopsies were obtained in fifteen young healthy men in response to a 30 s sprint exercise (Wingate test) randomly distributed into two groups: the fasting (n=7, C), and the glucose group (n=8, G), who ingested 75g of glucose one hour before exercising to downregulate AMPKa phosphorylation.

RESULTS: Thirty min after the control sprint, compared to pre-exercise values, Thr^{172}-AMPKa phosphorylation was enhanced 5-fold (from 100 ± 4% to 531 ± 215%, $P < 0.05$). Moreover, under control conditions, SIRT1 protein expression was increased by 72% (from 100 ± 6.5% to 172.8 ± 21.8%, $P < 0.05$) and PGC-1a protein expression was decreased by 38% (from 100 ± 12% to 61.6 ± 8.7%, $P < 0.05$), 120 min into the recovery period. These effects were prevented by the ingestion of glucose prior to exercise.

CONCLUSIONS: SIRT1 and PGC-1a protein expression was increased and reduced, respectively, in response to a single bout of sprint exercise performed in fasting conditions, and this effect appears to be mediated by AMPKa phosphorylation. Glucose ingestion prior to a sprint exercise profoundly affects Thr^{172}-AMPKa phosphorylation and its downstream signaling during the recovery period.
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1056 June 5 10:00 AM - 10:15 AM
Blockade Of Prostaglandins And Nitric Oxide In-vivo Reduces State 3 Mitochondrial Respiration In Human Skeletal Muscle

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(No disclosure reported)

Combined inhibition of nitric oxide (NO) and prostaglandins (PG) reduces skeletal muscle blood flow and oxygen delivery at rest and during exercise. It has recently been found that combined inhibition of NO and PG blockade reduces muscle oxygen uptake during exercise (Mortensen et al. 2007) suggesting a partial inhibition of aerobic metabolism or improved muscle efficiency of oxidative phosphorylation or actin-myosin cycling.

PURPOSE: The purpose of this study was to examine in humans the independent and combined effect of NO and PG blockade with L-NMMA and Indomethacin (Indo) on mitochondrial respiration in muscle from biopsies of the vastus lateralis (VL) following knee extension (KE) exercise.

METHODS: Mitochondrial respiration was measured ex-vivo by high resolution respirometry in saponin-permeabilized fibers following 6 min KE in control (CON, n=8), arterial infusion of LNMMA (n=4) and Indo (n=4) randomized in order, followed by combined inhibition of NO and PG (L-NMMA + Indo, n=8). RESULTS. ADP-stimulated state 3 respiration with substrates for complex I (glutamate, malate) was reduced 50% by Indo compared to CON. State 3 O2 flux with convergent electron input through both complex I and II with addition of succinate was equally reduced with Indo (20%) and L-NMMA + Indo (15%) compared to CON and LNMMA alone. Uncoupled O2 flux determined by titration of the ionophore FCCP was not increased above state 3 respiration with Indo suggesting tight coupling to oxidative phosphorylation. Graded titrations of L-NMMA into the respirometer in CON muscle reduced state 3 respiration by 12% only at a supra-physiological dose, while titration of Indo caused a linear reduction at all doses within and above the physiological range.

CONCLUSION: The results indicate that inhibition of PG by indomethacin inhibits state 3 mitochondrial respiration primarily at complex I of the respiratory chain. This effect may in part explain the in-vivo reduction in muscle O2 uptake during exercise with double blockade of NO and PG, since blockade of NO by L-NMMA counteracts the inhibitory effect of Indo.