Cardiovascular exercise physiology

Presentation Number: 73

Board #1

An Alternative Model for a Meta-Analysis on Exercise and Blood Pressure in Older Adults

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PURPOSE: Using a traditional random-effects model, a recent meta-analysis by Herrod et al. (2018) reported statistically significant reductions in both resting systolic blood pressure (SBP) and diastolic blood pressure (DBP) as a result of aerobic, resistance, and combined aerobic and resistance exercise in adults with a mean age of 65 years and older. However, a recently proposed and alternative method, the inverse heterogeneity model (IVhet), has been shown to provide more robust findings. The purpose of this study was to apply the IVhet model to these previous meta-analytic findings. **METHODS:** Data from 44 randomized controlled trials representing 92 groups (48 exercise, 44 control) were pooled using the IVhet model. In addition, absolute and relative differences between the IVhet and random-effects model were calculated. Data were reported using the mean difference (exercise minus control) with non-overlapping 95% confidence intervals considered statistically significant. **RESULTS:** Using the IVhet model, statistically significant reductions in resting blood pressure were found as a result of aerobic exercise (SBP, -4.7 mmHg, 95% CI, -7.7 to -1.8; DBP, -2.0 mmHg, 95% CI -3.13 to -0.89), SBP but not DBP for resistance training (SBP, -7.0 mmHg, 95% CI, -10.5 to -3.4; DBP, -1.2 mmHg, 95% CI -2.7 to 0.31), and both SBP and DBP for combined aerobic and resistance training (SBP, -5.5 mmHg, 95% CI, -8.3 to -2.7; DBP, -3.7 mmHg, 95% CI -4.8 to -2.7). When compared to the random-effects model, findings from four of the six mean differences in blood pressure were smaller, ranging from -0.82 to -0.19 mmHg (6.1% to 41.0%) while all six 95% CI were wider, ranging from 0.24 to 1.56 mmHg (11.5% to 36.8%). **CONCLUSIONS:** These findings suggest that with the exception of changes in DBP as a result of resistance training, exercise (aerobic, resistance, combined aerobic and resistance) reduces resting SBP and DBP in older adults. Importantly, these findings are generally smaller than those previously reported, a factor that could have practical implications. Future studies should consider using the IVhet model when conducting an aggregate data meta-analysis.

Cardiovascular exercise physiology

Presentation Number: 74

Board #2

Calf Oxygen Saturation and Vascular Biomarkers are Associated with Exercise Pressor Response in Claudication Patients

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Purpose: To determine whether markers of lower extremity ischemia and vascular inflammation were associated with an exercise pressor response during treadmill walking in patients with symptomatic peripheral artery disease (PAD). **Methods:** A total of 179 claudication patients were characterized on demographic variables, comorbid conditions, cardiovascular risk factors, ankle/brachial index (ABI), peak walking time (PWT), claudication onset time (COT), and calf muscle oxygen saturation during a graded maximal treadmill test, and on objective and patient-based measures of physical function. The exercise pressor response was measured as the change in blood pressure from rest to the end of the first 2-minute treadmill exercise work stage (2 mph, 0% grade). Patients were further characterized on endothelial effects of circulating factors present in the sera using a cell culture-based bioassay on primary human arterial endothelial cells, and on circulating inflammatory and vascular biomarkers. **Results:** During the maximal treadmill test, patients experienced COT at 197±164 seconds (mean±SD) and PWT at 395±254 seconds. After only walking for two minutes at low intensity exercise, there was a wide range in the change in systolic blood pressure (-46 to 50 mm Hg; mean change = 4.3±17.6 mm Hg), and in diastolic blood pressure (-23 to 38 mm Hg; mean change = 1.4±10.1 mm Hg). In multiple regression analyses, changes in diastolic blood pressure were positively associated with the percentage decrease in calf muscle oxygen saturation during exercise (p=0.010), cultured endothelial cell apoptosis (p=0.014), and plasma glucose (p=0.026). In multiple regression analyses, changes in systolic blood pressure was positively associated with plasma glucose (p<0.001) and was negatively associated with plasma insulin (p=0.036). **Conclusion:** In patients with symptomatic PAD, a greater exercise pressor response in diastolic blood pressure after only two minutes of walking at no incline was independently associated with impaired microcirculation of the ischemic calf musculature during exercise, greater cultured endothelial cell apoptosis and impaired glucose metabolism. Changes in systolic blood pressure were primarily associated with impaired glucose metabolism. The clinical implication is that the exercise pressor response in patients with symptomatic PAD may be ameliorated with behavioral interventions such as exercise and nutritional programs designed to improve microcirculation, endothelial cell apoptosis, and glucose metabolism. Supported by grants from the National Institute on Aging (R01-AG-24296) and General Clinical Research Center (M01-RR-14467).

Cardiovascular exercise physiology

Presentation Number: 75

Board #3

Delayed VO_2 Recovery Kinetics Reflect Differential VO_2 Responses to Exercise in the Framingham Heart Study

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Purpose: Patterns of oxygen uptake (VO_2) upon initiation of exercise, in relation to workload, and during recovery all predict outcomes in referral populations of patients with established heart failure. These three VO_2 patterns, and their relationship to each other, remain under investigated in large community-based populations. We hypothesized that in a community-based sample of middle aged individuals, delayed VO_2 kinetics upon initiation of exercise and lower VO_2/workload slopes are associated with prolonged VO_2 recovery kinetics.

Methods: Maximal upright cycle ergometry cardiopulmonary exercise testing (CPET) was performed on 1865 Framingham Heart Study participants (age 55±9 yrs, 54% women, BMI 28±5, peak VO_2 23±7 ml/kg/min, peak RER 1.22±0.10). Breath-by-breath gas exchange measures were obtained during 3-min unloaded exercise, incremental ramp exercise, and 4-min recovery. Mean response time (MRT; 63% of duration to achieve steady state VO_2) and VO_2/work slope starting 1-min into incremental work were derived. VO_2 recovery delay (VO_2RD; time until post-exercise VO_2 falls permanently below peak VO_2) and $T^1/_2$ (time for VO_2 to decline by 50%) were measured to assess VO_2 recovery kinetics. Because normative values for each of these variables in population studies are not well established, we compared VO_2 recovery kinetics among groups stratified by median MRT and VO_2/W slope values. Below median MRT and above median VO_2/W slope (↓MRT/↑VO_2/W) and above median MRT and below median VO_2/W slope (↑MRT/↓VO_2/W) groups were compared.

Results: Mean (±SD) values were 30±15s for MRT, 9.0±1.0ml/W for VO2/W, 80±33s for $T_{1/2}$ and 10.4±10.7s for VO_2RD. Overall, 30% (n=550) were categorized in the ↑MRT/↓VO_2/W group and 30% (n=550) in the ↓MRT/↑VO_2/W group. Mean (±SD) MRT and VO_2/W values were 41±11s and 8.2±0.7ml/W, in the ↑MRT/↓VO_2/W group, respectively, and 17±7s and 9.8±0.5ml/W in the ↓MRT/↑VO_2/W group. Prolonged recovery kinetics were observed in the ↑MRT/↓VO_2/W group when compared with the ↓MRT/↑VO_2/W group (VO_2RD 14±13s vs 7±7s, p<0.001 and $T^1/_2$ 99±40s

vs 65±16s, p<0.001). The differences in VO_2 recovery kinetics persisted after adjustment for peak VO_2, age, and sex (p<0.001 for both measures).

Conclusions: These cross-sectional data indicate that longer VO_2 mean response time and more shallow increment in VO_2 relative to work during exercise are associated with delayed VO_2 recovery kinetics among community-based adults. This relationship persisted after adjustment for peak VO_2, suggesting that VO_2 patterns beyond peak VO_2 may help identify maladaptive responses to exercise in non-referral populations.

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Board #4

Effects of High-Intensity Training in Moderate and Mild Hypoxia in Horses

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PURPOSE: We tested the hypothesis that horses trained in moderate and mild hypoxia would experience greater improvements in performance and aerobic capacity compared with horses trained in normoxia.

METHODS: Seven untrained Thoroughbred horses completed 4-weeks (3 sessions/week) of three training protocols, consisting of 2-min at 95% of maximal oxygen consumption ($\dot{V}O_2$max) under two different hypoxic conditions (*H16*, F_IO_2=16%; *H18*, F_IO_2=18%) and in normoxia (*N*, F_IO_2=21%), followed by 2 weeks of post-hypoxic training in normoxia using a randomized crossover study design with a 3-month washout period. Normoxic incremental treadmill tests were conducted at week 0, 4 and 6. Effects of training protocols were analyzed using mixed models.

RESULTS: Run distance (*H16*, +30.6%; *H18*, +19.6%; *N*, +6.6%) and speed at $\dot{V}O_2$max ($V_{\dot{V}O_2max}$: *H16*, +7.7%; *H18*, +5.4%; *N*, -0.9%) increased in *H16* and *H18* after 4-weeks of training and were different between *H16* and *N*, but not between *H18* and the other two groups. $\dot{V}O_2$max (*H16*, +9.8%; *H18*, +12.8%; *N*, +8.8%) and maximal cardiac output ($\dot{Q}_{max}$: *H16*, +7.8%; *H18*, +8.9%; *N*, +6.7%) increased in all groups after 4-weeks of training and were not different between groups. Run distance, $\dot{V}O_2$max, $V_{\dot{V}O_2max}$, $\dot{Q}_{max}$ and lactate threshold did not change after 2-weeks of post-hypoxic training in all groups compared with those at week 4, and they were not different between groups.

CONCLUSIONS: These results suggest that 4-weeks of training in moderate (H16), but not mild hypoxia (H18), was sufficient to elicit greater improvements in performance and aerobic capacity than normoxic training and that 2-weeks of post-hypoxic training could maintain the effects of hypoxic training. Supported by the Japan Racing Association.

Cardiovascular exercise physiology

Presentation Number:77

Board #5

Exercise Training and Autonomic Nervous System Function in Cancer Patients and Survivors: A Systematic Review

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PURPOSE: In cancer survivors, cardiovascular disease (CVD) is the leading cause of non-malignant late disability and death. Cancer treatments have toxic effects on the autonomic nervous system (ANS), which precede overt CVD. Exercise training improves ANS function in non-oncological populations, however less is known regarding its effect in patients undergoing and following cancer treatment. This systematic review aimed to determine the effect of exercise training on ANS function in people with cancer (cancer patients; i.e. those currently undertaking treatment or who concluded treatment <1 month prior), and in those who had completed treatment (cancer survivors).

METHODS: Seven electronic databases were searched; PubMed, Scopus, Web of Science, Embase, CINAHL, MEDLINE and PEDro. This search was limited to randomized controlled trials, controlled, non-controlled, comparative, and cohort studies. Included studies implemented an exercise intervention and assessed ANS function in individuals with a histologically-confirmed diagnosis of cancer.

RESULTS: Five independent interventions met the inclusion criteria, including 305 participants of mixed cancer diagnoses and treatments. Assessments of ANS function included heart rate variability (HRV), heart rate recovery (HRR) post-cardiopulmonary exercise test, and respiratory sinus arrhythmia (RSA). Significant improvements in various HRV parameters, HRR and RSA were observed following exercise training in studies involving cancer survivors, as well as those studies that did not report time since treatment (n=2). However, studies involving cancer patients found exercise did not improve HRV parameters. When analyzed according to baseline cardiorespiratory fitness, one study observed significant improvements in HRR favoring the below median cardiorespiratory fitness group, regardless of cancer patient or survivor status.

CONCLUSIONS: Exercise training appears to improve ANS function in cancer survivors but not in cancer patients currently undergoing, or who have recently completed, treatment. This may be attributable to the direct inhibition of cancer treatment on exercise-induced improvements in ANS function. However, exercise appeared to improve ANS function in those with lower baseline cardiorespiratory fitness, regardless of time since treatment cessation. Exercise is recommended to prevent the deterioration of, and even potentially improve, ANS function in cancer survivors. Further research is required early in the cancer-treatment continuum to identify whether exercise training can improve ANS function in cancer patients and thus reduce this early marker of CVD risk.

Cardiovascular exercise physiology

Presentation Number: 78

Board #6

Impact Of Dietary Nitrate Supplementation On Dynamic Cerebarl Authoregulation In Hypoxia

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PURPOSE: In healthy humans, cerebral blood flow (CBF) is maintained at relatively constant levels over a wide range of perfusion pressures via cerebral autoregulation (CA). However, dynamic CA is impaired at high-altitude in healthy lowlanders. Dietary inorganic nitrate has been linked to improvements in the oxygen supply of peripheral tissue, and reductions in blood pressure, causing greater vascular conductance. It has also been suggested that greater vascular conductance in cerebrovasculature may impair dynamic CA. Thus, dietary nitrate supplementation may have both advantages and disadvantages (i.e., increased CBF and impaired CA). Therefore, the current study hypothesized that dietary nitrate supplementation increases resting CBF, but it may not effective for improvement of dynamic CA in hypoxia.

METHODS: Resting CBF and dynamic CA were compared in eight healthy young males after four days of supplementation with (A) placebo drink (PL) in normoxia (room air), (B) PL in hypoxia (after 60 min exposure to 13.95% O_2), (C) beetroot juice (BR) in normoxia, and (D) BR in hypoxia. To measure volumetric changes, duplex ultrasonography was used to assess the resting CBF and dynamic CA in the internal carotid artery (ICA). Dynamic CA, which represents the rate of regulation (RoR) of vascular conductance, was evaluated using the thigh-cuff method.

RESULTS: In normoxia, after four days of BR supplementation, the resting ICA diameter and blood flow were slightly greater than the BR trial, but the difference was not significant (diameter: 0.49 ± 0.03 cm in PL vs. 0.51 ±0.02 cm in BR; blood flow: 305 ± 23 ml min^{-1} in PL vs. 324 ± 24 ml min^{-1} in BR, $P > 0.05$). The RoR as indices of dynamic CA was also unaffected with BR supplementation (0.253 ± 0.060 s^{-1} in PL vs. 0.221 ± 0.055 s^{-1} in BR, $P > 0.05$). PL and BR significantly increased the participants' resting ICA diameter and blood flow in hypoxia over those of the participants in

normoxia (diameter: 0.53 ± 0.04 cm in PL vs. 0.57 ±0.03 cm in BR; blood flow: 342 ± 31 ml min^{-1} in PL vs. 374 ± 38 ml min^{-1} in BR, $P < 0.05$). The RoR was significantly lower in hypoxia (0.142 ± 0.072 s^{-1} in PL vs. 0.153 ± 0.055 s^{-1} in BR, $P < 0.05$) than in normoxia, while no differences in the RoR were found between PL and BR in hypoxia ($P > 0.05$).

CONCLUSIONS: These results demonstrated that short-term dietary nitrate supplementation did not affect ICA responses in either normoxia or hypoxia. The findings indicate that the effects of hypoxic exposure may have counteracted the beneficial effects of dietary nitrate supplementation on the cerebrovasculature responses of the subjects in the present study.

Cardiovascular exercise physiology

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Board #7

Respiratory Muscle Unloading by Normoxic Helium-O2 Breathing during Cycling Exercise Delays Volitional Exhaustion in Obese Adolescents

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Purpose: In obesity increased work and O_2 cost of breathing contribute to a higher O_2 cost of exercise and negatively affect exercise tolerance. The purpose of this study was to determine whether, in obese adolescents (OB), acute respiratory muscle unloading during cycling exercise, obtained by switching the inspired gas from ambient air (AIR) to normoxic helium-O_2 (HeO_2) at exhaustion (AIR+HeO_2) can prolong exercise duration than in normal-weight controls (CTRL). Patients were blinded with respect to AIR or HeO_2. **Methods:** Ten OB (age: 16 ± 2.0 years; body mass: 117.5 ± 21.3 kg; BMI: 38.9 ± 6.1 kg m^{-2}) and 10 CTRL (age: 17 ± 0.9 years; body mass: 68.4 ± 10 kg; BMI: 21.4 ± 2.7 kg m^{-2}) performed five separate exercise tests on a cycle ergometer: - an incremental test to determine peak V'O_2 and gas exchange threshold (GET) in AIR; two moderate-intensity constant work rate (CWR) exercises at 80% of GET (<GET), carried out for 40min or to voluntary exhaustion; two heavy-intensity CWR exercises at 50% of the difference between GET and peak V'O2 (>GET) to voluntary exhaustion. In one of the two CWR exercises patients switched from AIR to HeO_2 when they were facing exhaustion. **Results:** During CWR<GET CTRL completed the 40 min exercise duration, whereas OB reached exhaustion before the 40-min mark; in OB time to exhaustion was longer ($p<0.05$) in AIR+HeO_2 (1524 ± 480) vs. AIR (1308 ± 408 s), whereas end exercise heart rate (HR) was not different (148 ± 16 vs. 147 ± 13 b min^{-1}) in the two conditions, despite the longer exercise duration in AIR+HeO_2. During CWR>GET in OB time to exhaustion was longer ($p<0.05$) in AIR+HeO_2 (570 ± 306) vs. AIR (408 ± 150 s), whereas in CTRL no significant difference was observed (582 ± 348 vs. 588 ± 252 s); also, during CWR>GET in OB HR was not significantly different in AIR+HeO_2 (165 ± 12) vs. in AIR (160 ± 11 b min^{-1}), despite the longer exercise duration. **Conclusions:** Acute respiratory muscle unloading obtained via switching the inspired gas from ambient air to HeO_2, when the patients were reaching exhaustion, prolonged cycling exercise duration in OB both during moderate- and heavy-intensity exercise. In OB respiratory constraints can limit exercise tolerance also during moderate intensity daily-living activities.
Funding: "Progetti di Ricerca Corrente" from the Istituto Auxologico Italiano

Cardiovascular exercise physiology

Presentation Number: 80

Board #8

Similar Improvements of Cardiopulmonary Exercise Parameters between Linear and Nonlinear Periodization Training in CHD Patients

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PURPOSE: High intensity interval training (HIIT) can be used complementary as compared to guidelines-based moderate intensity continuous training (MICT) in patients with coronary heart disease (CHD). Training periodization, a mix of HIIT and MICT is commonly used in athletes to increase training load and to improve cardiorespiratory fitness (measured as peak VO_2). Training periodization has never been studied in CHD patients. The aim of this study was to compare the different training periodization protocols (linear periodization [linear] vs. non-linear periodization [nonlinear]) on cardiopulmonary exercise test (CPET) and hemodynamic parameters. **METHODS:** We randomized 39 CHD patients from the Montreal Heart Institute to either linear or non-linear groups (n=20, 65 ± 10 years and n=19, 66 ± 5 years, respectively). All patients completed a CPET including gas exchange analysis and hemodynamic measurements with impedance cardiography. Patients trained for 12 weeks, 3 times a week. Training load (training duration and intensity) was constantly increased in the linear group. In the linear group, training load increased during the first 3 weeks, and decreased the fourth week. This training cycle was repeated until the end of the intervention. CPET parameters such as peak VO_2, oxygen uptake efficiency slope (OUES), and ventilatory efficiency slope (VE/VCO_2), VO_2 at the first (VT_1) and second (VT_2) ventilatory thresholds were assessed and calculated based on recent recommendations. Data were compared using ANOVA with repeated measures. **RESULTS:** There was a similar improvement with regard to peak VO_2 in both groups (22.0 ± 5.6 to 23.7 ± 5.9 in the linear group, and from 22.5 ± 5.2 ml/min/kg to 23.7 ± 5.7 ml/min/kg in the nonlinear group, p=0.0004). OUES, VT_1 and VT_2 were the only ventilatory parameters that improved in both groups ($p<0.0001$). There was no significant improvement with regard to hemodynamic variables ($p>0.05$). For any variables, there were no interaction effect. **CONCLUSIONS:** This is the first study to show similar improvements regarding peak VO_2 to both training periodization protocols in CHD patients. Both periodized aerobic training protocols improved similarly ventilatory efficiency (OUES) and aerobic endurance parameters (VT_1, VT_2). *This study was funded by Fonds de Recherche du Québec - Santé, the EPIC foundation, and the Montreal Heart Institute foundation.*

Cardiovascular exercise physiology

Presentation Number: 81

Board #9

The Dose Difference in Isl1 Expression Affected the Function of the Heart after Aerobic Eexercise Stimulation

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Purpose: The LIM-homeodomain transcription factor Islet-1 (Isl1) as a marker of cardiovascular progenitors during embryogenesis, plays essential roles in cell proliferation, differentiation, and survival. Recent studies showed that Isl1-expressing cells also exist in adult heart tissues in several species, including mice, rats, and humans. However, the role of Isl1+ cells in the adult heart remains unknown. The aim of this study is to dissect the function of Isl1 in adult mammals under aerobic exercise.

Methods: We used the genome editing system CRISPR-Cas9 to insert CreERT2 into the mouse Isl1 endogenous gene promoter. In combination with the Cre/loxP system, Isl1-CreERT/Rosa26-LacZ double hybrid mice were obtained. We divided 2-month old adult male Isl1-CreERT/Rosa26-LacZ double hybrid mice and C57BL/6J mice into 4 groups(9 mice/group): wild type control (CW), hybrid control (CH), wild type aerobic exercise group (WA) and hybrid aerobic exercise group(HA). Mice in WA and HA were underwent 4-week's training program using small animal treadmill. Heart function was evaluated by small animal echocardiography. Marker of Cardiac Progenitor Cells (Isl1) and Proliferating cell nuclear antigen (PCNA) were observed and analyzed by Real Time PCR. Myocardium was observed hematoxylin-eosin staining. Myocardial enzymes were measured by blood biochemical tests.

Results: Regular moderate aerobic exercise resulted in the up-regulation of gene expression both for Marker of Cardiac Progenitor Cells (Isl1) and cell proliferation factor (PCNA) in wild type aerobic exercise group (WA), but there is no statistical difference in hybrid aerobic exercise group(HA). The results of echocardiography show that wild type aerobic exercise group (WA) can significantly improve cardiac function and heart coefficient, shorten the left ventricular short axis, and improve heart function. But there is no statistical difference in hybrid aerobic exercise group(HA).

Conclusions: We found that the responses of Isl1-CreERT/Rosa26-LacZ hybrid mice and wild type to aerobic exercise stimulation were different; the dose difference in Isl1 expression affected the shape and function of the heart after exercise stimulation. The specific mechanism underlying these effects will be studied in subsequent experiments.
Keywords: Cardiac progenitor cell, Isl1, Aerobic exercise, Heart Function, Dose Difference
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Cardiovascular exercise physiology

Presentation Number: 82

Board #10

Validity in Ekblom-bak Test and its Ability to Track Changes in an Elderly Population

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Background: Maximal oxygen uptake (VO2max) has a high prognostic value for CVD and all cause mortality, however the test is hard to administer and requires a maximal effort, which can be arduous for an elderly population. The submaximal Ekblom-Bak cycle ergometer test (EB test) has shown to be valid in adults, but its applicability in an elderly population is unknown.

Aim: The purpose of this study was to validate the submaximal EB test and to examine its ability to detect changes in VO2max in an elderly population.

Methods: The sample consisted of 108 elderly participants; aged 65-75 years (54 women, 54 men) with a measured VO2max of 1.42-3.69 L/min. 34 women and 40 men performed a retest (VO2max 1.45-3.59 L/min) after an intervention period. During the intervention, participants performed 30 training sessions over 12 weeks where they cycled for 30 min at 65-75 % of maximal heart rate. On pre- and retests participants completed a submaximal Ekblom-Bak test. Directly after participants completed an individually adjusted VO2max test on a treadmill where VO2 max was measured using indirect calorimetry.

Results: For the validation of the EB-test on an elderly population there was a correlation (R) between measured and estimated VO2max of 0.64 for women and 0.47 for men, mean (95% CI) difference was 0.01 (-0.45 - 0.07) for women and -0.05 (-0.11 - 0.07) for men. Standard error of the estimate was 0.17 for women and 0.31 for men. Coefficient of variation was 10 % for women and 11 % for men. When analyzing the ability of the EB test to track change in VO2max after a 12 week training intervention there was a significant (P<0.001) average increase in estimated VO2max of 0.11 L/min for both genders (CI for women 0.06 - 0.16 and for men 0.08 - 0.15), with no change in the measured values. Changes in the estimated values were linked to a decrease of the submaximal HR on both work rates (3.0 bpm and 3.2 bpm on the standard work rate and 5.4 bpm and 6.4 bpm on the higher work rate, for women and men, respectively)

Conclusion: Validity of the EB-test in a population between 65-75 years was fairly good but we found larger standard error of the estimate for the men. The higher error for men in contrast to women could be derived from a difference in change of physiological variables that affect VO2max with increasing age. Since there was no change in measured VO2max while there was an improvement in estimated VO2max after the intervention, the EB-test appears to respond to changes in fitness that are not reflected in a VO2max.
Grant funding: European Research Council.

Hot topics in exercise physiology

Presentation Number: 83

Board #11

A Class of Steroids That Are Structural Analogues of (+)-Epicatechin As Possible Molecular Mediators of Exercise Effects

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Purpose: Mitochondrial depletion is a shared feature of many diseases. The flavanol epicatechin has demonstrated to induce mitochondrial biogenesis (MB) and enhance exercise performance. Given the structural similarity between flavanols and steroids, we tested the hypothesis that (+)-epicatechin (+Epi) may act as a structural mimic of a class of "novel" steroid(s) capable of stimulating MB in mammalian systems and possibly act to mediate exercise effects. We developed a new synthetic process for obtaining enantiomerically pure preparations of +Epi. Applying spatial analytics and molecular modeling, we determined that +Epi structurally resembles 11β-OH-pregnenolone, a sterol with no previously described biological activity. On the basis of known tissue/organ metabolic pathways available for the physiological modification of steroids, it is also feasible that 11β-OH-pregnenolone may convert to 11β-OH-progesterone while conserving its similarity to +Epi. To test the capacity of both sterols to stimulate MB and cell growth, we evaluated their biological activity (in parallel to +Epi) using cell culture systems. **Methods:** Primary bovine coronary endothelial cells (EC) and the skeletal muscle (SkM) cells lines C2C12 (mouse) or L6 (rat) were used to test for the effects of both sterols and +Epi using 9 incremental doses. For MB, we utilized a commercial kit (Abcam) that evaluates changes in mitochondrial complex II and IV protein levels. For the assessment of markers of SkM differentiation and growth, biochemical assays and Westerns were used. **Results:** Treatment of EC for 48 h with 10-6 nM – 100 nM +Epi led to a progressive and significant increase of ~125% in complex II and IV protein levels that peaked at 0.1 nM and decreased at higher doses yielding an inverted V curve. EC treated with 11β-OH-pregnenolone at the same doses yielded a similar magnitude/pattern of effects that peaked at 0.01 nM. The effects of 11β-OH-progesterone on EC paralleled that of 11β-OH-pregnenolone. Using C2C12 cells effects largely resembled those noted for EC using any of the 3 compounds. Effects were linked to AMPK phosphorylation after 30 min of treatment using "optimal" doses. Using L6 cells at optimal doses, 48+ h treatment with 11β-OH-progesterone yielded an induction of MB related regulatory proteins including Tfam, Nrf1, Nrf2, PGC1α, porin, citrate synthase activity and the differentiation factors myogenin and Mef2. **Conclusions:** 11β-OH-pregnenolone and 11β-OH-progesterone stimulate MB, cell growth/differentiation and may represent candidate sterols that act as molecular transducers of exercise effects. In vivo experiments are being pursued to address this possibility.

Hot topics in exercise physiology

Presentation Number: 84

Board #12

Exercise Induces Transient Macrophage Activation, Inflammation, and Pro-Fibrotic Remodeling of Intra-Articular Knee Fat

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PURPOSE: Inflammatory cytokines and adipokines are critical mediators of synovial joint remodeling and osteoarthritis risk. Recent studies indicate that the infrapatellar fat pad (IFP), which is located between the synovial lining and patellar tendon, is an important site of knee pain and inflammation. Exercise can significantly improve osteoarthritis pain and joint function, but the mechanisms are not well understood. The goal of this study was to investigate the effect of exercise on IFP inflammation and remodeling in a healthy knee. We hypothesized that increased exercise would reduce IFP adipocyte size and the expression of pro-inflammatory cytokines and adipokines.

METHODS: Following IACUC approval, 14-wk old male C57BL/6J mice were housed with running wheels for 0, 1, 3, and 14 days. IFP remodeling was evaluated by histomorphology and Sirius red staining under epipolarized light to quantify fibrotic collagen deposition (n=5). IFP inflammation was evaluated by custom qPCR array, including pro- and anti-inflammatory cytokines, adipokines, and inflammatory cell surface markers (n=6). Inflammatory cellular mediators were evaluated by flow cytometry.

RESULTS: Running induced a transient (day 3) increase in IFP collagen deposition and the population of CD11c+, F4/80+ cells that resolved by 14 days of running. Running did not alter T-cells (CD3+) and slightly reduced B-cells (CD19+) at 3 and 14 days (p=0.04 and 0.08, respectively). Pro-inflammatory gene expression peaked after one night of running; whereas, anti-inflammatory gene expression peaked at 3 days, consistent with an acute activation and resolution of inflammation. Lipid hydrolysis and synthesis genes were also differentially expressed with exercise. After 14 days of running, the expression of adiponectin, leptin, and *Pparg* were reduced.

CONCLUSIONS: Running induced acute IFP inflammation accompanied by increased activated macrophages and collagen deposition. These changes resolved by 14 days of running and were associated with reduced IFP adipokine expression. These findings suggest a physiologic role for inflammation in load-induced IFP remodeling in young, healthy knees. Consequently, osteoarthritis treatments that block inflammation may interfere with exercise-induced IFP remodeling. Supported by NIH R03AR066828 to TMG.

Hot topics in exercise physiology

Presentation Number: 85

Board #13

Mediator Effect of Physical Fitness on the Relationship Between Arterial Stiffness and Cognitive Function

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Evidence shows that physical fitness is associated with arterial stiffness and cognitive function, but the mediation of physical fitness between arterial stiffness and cognition has not been yet observed. **PURPOSE:** To investigate physical fitness as a mediator of the relationship between arterial stiffness and cognitive function in apparently healthy seniors. **METHODS:** This is a cross-sectional study comprising 155 individuals free from chronic diseases (75.5 ± 6.5 years; 69.7% female). The arterial stiffness index was carotid-femoral pulse wave velocity, and it was assessed through applanation tonometry. Cognitive function was evaluated using the Portuguese validated version of the Montreal Cognitive Assessment (MoCA). Physical fitness was assessed through handgrip strength and Senior Fitness Test [cardiorespiratory fitness (6-Min Walk), agility (8-foot Up and Go), upper (30-second Arm Curl) and lower body strength (30-second Chair Stand) and flexibility tests (Chair Sit & Reach and Back Scratch)]. A Z-score including all physical fitness components was computed as a global index of physical fitness. Hayes's PROCESS macro for SPSS was used for the simple mediation analysis, using bootstrapped procedures. **RESULTS:** After adjustments for sex and age, physical fitness Z-score mediated the relationship between arterial stiffness and cognitive function (Indirect effect = – 0.382; 95% CI, – 0.670 to –0.138). **CONCLUSIONS:** The present findings suggest that physical fitness, independently of sex and age, is a mediator on the relationship between arterial stiffness and cognitive function in apparently healthy seniors. Results highlight exercise programs as a tool to develop physical fitness to maintain cardiovascular and cognition functions. CIAFEL is a Research Unit granted by FCT (UID/DTP/00617/2013).

Hot topics in exercise physiology

Presentation Number: 86

Board #14

Recruitment and Retention Strategies for the Molecular Transducers of Physical Activity Consortium (MoTrPAC)

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Purpose Our objective is to examine the multi-faceted recruitment strategies for MoTrPAC, a national multi-center exercise trial. We also highlight the importance of addressing recruitment and retention challenges in the early stages of project development to minimize participant, investigator, and financial burden.

Methods MoTrPAC aims to randomize ~2,400 adults across 11 clinical sites to control, aerobic, or resistance exercise training groups for 12-weeks. Participants will undergo multiple fat and muscle biopsies and provide blood samples for cutting-edge multi-omics analyses to study the molecular changes occurring during and after exercise training. As one of the clinical sites, we have been heavily involved in recruitment and retention preparation by employing multiple strategies to address the challenges of the extensive participant involvement. The Recruitment and Retention Committee engages in monthly planning meetings to address key topics such as written recruitment materials, study remuneration, newsletters, local outreach plans, and protocol concerns. To further address these key topics, we employed a Community Engagement Studio (CES), a novel tool for researchers to gain insight from local community members to consider potential barriers and enhance study implementation efforts.

RESULTS The CES participants, a diverse group aged 18-40, reflected the general characteristics of the MoTrPAC inclusion/exclusion criteria. From the CES, we received detailed input concerning study protocol, potential barriers to participation, and written recruitment materials (e.g., flyers and logos). A central theme from the CES encompassed participant burden, including the extensive time commitment, perceived invasiveness of multiple biopsies, and study remuneration. To simplify the clinical protocols, this valuable input helped create recruitment, messaging, and implementation recommendations for the entire MoTrPAC scientific committee to consider. Examples included reducing the number of biopsies, time commitments and study burden (e.g., number of study visits, number of training sessions/week), as well as addressing remuneration amounts and potential scientific contribution.

CONCLUSIONS The CES highlighted input crucial for the early stages of project development, especially for a national clinical trial of this magnitude. Dedicating resources specifically to recruitment prior to study initiation allows for vital study design modifications. Utilizing these approaches will enhance participant enrollment, retention, and experience, without compromising the overall ability to answer the scientific question.

Hot topics in exercise physiology

Presentation Number: 87

Board #15

Regulation Of Telomeric Transcription And Cellular Senescence By Endurance Exercise And Age In Skeletal Muscle

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Purpose : Telomeres are nucleoprotein structures that preserve the end of chromosomes from being recognized as DNA double-strand breaks by inhibiting the DNA damage response. For a long time, telomeres have been considered transcriptionally silent. Yet it turns out that telomeres are transcribed into Telomeric Repeat Containing RNAs (TERRA). Once transcribed, TERRA remains partly associated with telomeres to play crucial protective functions. Telomere length and TERRA expression are negatively correlated: high levels of TERRA are associated with shorter telomeres. Damaged telomeres trigger cellular senescence and impair tissue turnover. While endurance training is associated with numerous health benefits, there is currently no evidence that it regulates the cellular aging process in skeletal muscle. The aim of this work is to investigate whether and how endurance training can regulate telomeric transcription and impact cellular senescence in skeletal muscle of young and old adults. **Methods :** Thirty-four men [18 young (18-24 years) and 16 old (61-72 years)] were studied in this retrospective study. Half of the subjects were trained cyclists (6 ± 1h/w), while the others were sedentary. VO_{2max} was measured directly on a cycloergometer. One week later, a muscle biopsy sample was obtained from the vastus lateralis at rest. TERRA and the mRNA expression of *p16, p21, CXCL8, TNF-*α and *IL-6* were measured using qRT-PCR. After the isolation and culture of satellite cells, senescence was measured by SA-β-Gal staining. **Results :** Sedentary subjects had higher TERRA levels (16p, +38%, p=0.002; 1q-2q-4q-10q-13q-22q, +25%, p = 0.02) compared to trained subjects, independently of age. Endurance training reduced the mRNA expression of *CXCL8* (-69%, p = 0.01) and tended to decrease *TNF-*α mRNA level (-38%, p = 0.1). SA-β-Gal staining in satellite cells revealed a higher senescence rate with aging (+31% positive cells, p = 0.002), independently of the training status. Similarly, the senescence markers, *p16* and *p21* mRNA levels, were higher in tissues from aged subjects (+471% and +135% respectively, p = 0.0001). **Conclusions :** In human skeletal muscle, *p16* and *p21* mRNA levels, as well as cellular senescence rate, are higher in old compared to young subjects. A sedentary behavior tends to increase markers of inflammation and telomeric transcription. As high TERRA expression is associated with shorter telomeres, we hypothesize that the sedentary subjects will have shorter/more damaged telomeres compared to the trained subjects. Supported by a FSR from Université catholique de Louvain.

Hot topics in exercise physiology

Presentation Number: 88

Board #16

The Effects of Blood-Flow Restriction Training on Muscle Hypertrophy, Strength, and Power in College-Age Adults

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PURPOSE: The purpose of this study is to compare changes in strength, power, and hypertrophy between high-load (HL) resistance training (70% 1RM) and low-load blood flow restriction (LL-BFR) training (30% 1RM). **METHODS:** Sixteen healthy individuals, ages 23-31 (8 male, 8 female) underwent protocols to find their 1-repetition maximum (1RM) for squats, split squats, step-ups, and lunges. Thigh circumference was measured as a hypertrophy baseline measure, and vertical jump height was measured as the baseline for power. Participants were then randomly assigned to either HL or LL-BFR groups and underwent training for 8 weeks. The HL group performed the four exercises at 70% 1RM for 3 sets of 8 repetitions with 2-3 minutes of rest between sets and exercises. LL-BFR group performed the same four exercises at 30% 1RM for repetitions of 30-15-15-15 with 30 seconds rest between sets and 2-3 minutes rest between exercises. HL group trained 3x/wk and LL-BFR trained 2x/wk. Session rating of perceived exertion (sRPE) was measured for each participant following each training session. **RESULTS:** Significant differences were found within groups for pre/post vertical jump height ($p = .001$), left thigh circumference ($p = .03$), and 1RM squat ($p < .001$). No significant difference was found between the LL-BFR and HL groups in measures of vertical jump height or 1RM squat. sRPE was significantly higher for LL-BFR than HL throughout the life of the study. **CONCLUSIONS:** LL-BFR training can achieve similar results in strength and power as HLR training without the strenuous effects of higher loads placed on the body. In addition, LL-BFR is perceived as more difficult than HL training.

Hot topics in exercise physiology

Presentation Number: 89

Board #17

The Muscle-Specific Permanency of Myonuclei Following Progressive Weighted Wheel Running (PoWeR): Insight Into "Skeletal Muscle Memory" of Hypertrophy

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PURPOSE: Myonuclear density increases during skeletal muscle hypertrophy, and it has been suggested that newly-acquired myonuclei are permanent; however, the available evidence supporting this is equivocal. Thus, our goal was to determine if the increase in myonuclear content in skeletal muscle during hypertrophy is maintained following a period of prolonged detraining utilizing a novel progressive weighted-wheel running (PoWeR) protocol.

METHODS: PoWeR involved the progressive addition of weight (2-6g) to an unbalanced running wheel over 8 weeks. Four month old female C57Bl/6J mice (n=8-10/group) underwent PoWeR, while another cohort underwent PoWeR followed by 12 weeks of detraining. Age-matched ambulatory controls were used for baseline comparisons. Following training and detraining, the soleus and plantaris muscles underwent immunohistochemical and single muscle fiber analyses.

RESULTS: Relative to controls, wet weight normalized to body weight of the soleus and plantaris muscles was 30% and 13% greater, respectively, following 8 weeks of PoWeR ($P<0.05$). Fiber cross-sectional area (CSA) was 20% greater in the soleus and 16% greater in the plantaris ($P<0.05$) concomitant with a fast-to-slow fiber type transition, and myonuclei quantified by both isolated single fiber and muscle cross-sectional analyses were significantly higher ($P<0.05$) in both the soleus and plantaris following PoWeR. After detraining, muscle fiber CSA and fiber-type distribution returned to baseline only in the plantaris. Similarly, only the plantaris exhibited a significant ($P<0.05$) reduction in myonuclear density following detraining.

CONCLUSIONS: PoWeR provides a significant methodological advantage over current hypertrophy models used in mice since it is non-surgical and elicits oxidative and hypertrophic adaptations in both slow-twitch and fast-twitch muscles. Moreover, we provide evidence that the permanency of myonuclei is muscle-specific and may be largely dependent upon the function and fiber-type composition of a given muscle (soleus - tonic activation, highly oxidative; plantaris - phasic activation, highly glycolytic), and/or its ability to detrain. Supported by AR060701 and AG049806 to JJM and CAP, and [AR071753] to KAM.

Integrative exercise physiology and metabolism

Presentation Number: 90

Board #18

A High Fat/High Sugar Diet Alters the Gastrointestinal Metabolome in a Sex Dependent Manner

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PURPOSE: We have observed chronic overfeeding via a high fat/high sugar diet in mice decreases wheel running. However, the exact mechanism(s) that connect increased caloric intake and decreased physical activity is unknown. The microbiome may be a potential mediator as it produces numerous metabolites that are vital physiological modulators of host health. In this study, we tested the hypothesis that consumption of a high fat, high sugar diet alters host and microbial metabolite production in the gastrointestinal tract.

METHODS: C57BL/6J female and male mice were weaned at 3 weeks of age, individually housed, and randomly assigned to either a standard "chow" diet (CHOW) or a high fat/high sugar diet (HFHS) for nine weeks. Total caloric and fluid intake, and body composition were measured weekly. Cecal metabolites were extracted and analyzed on QExactive mass spectrometer coupled to liquid chromatography. Data were analyzed using Progenesis QI, Mummichog, and Metaboanalyst.

RESULTS: The HFHS mice (female: n=6, male: n=6) consumed significantly more calories per day than CHOW mice (female: n=6, male: n=5; 22 and 26.3% kcal) and had significantly higher body fat (12.8 and 26.3%). Significant changes were found in the cecal metabolome of HFHS fed mice in a sex-dependent manner. Data analysis reveals 6,191 and 4,327 features to be significantly altered in the females and males respectively. In males, metabolites from seven pathways were significantly altered with HFHS diet including the androgen biosynthesis/metabolism pathway. Tryptophan metabolism was the main pathway that was altered with the HFHS diet in females. Indole 3 carboxaldehyde, an anti-inflammatory beneficial metabolite, was depleted with HFHS diet in both males and females.

CONCLUSIONS: A HFHS diet depletes many beneficial metabolites in the gut, alters the sex hormones, with some metabolomic changes being sex-dependent. The distinct metabolomic features from female and male mice show that sex plays an important role and should be considered while investigating the effects of diet.

Integrative exercise physiology and metabolism

Presentation Number: 91

Board #19

A Metabolic and Biomechanical Comparison of Two Land Based Surf Paddling Simulators

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PURPOSE: Interacting with the surf and competing for waves requires maintenance of paddling strength and stamina [1-3]. However, during periods of small surf many athletes remain out of the water, often leading to reductions in physical conditioning. In recent years, there has been interest in developing land-based training techniques that may help to address this problem [4], yet few data exist to characterize or verify the impact of these efforts. One approach involves the use of exercise simulators that approximate the resistance and metabolic demands of paddling in water. The purpose of this study was to compare the physiological and biomechanical demands of a newly developed, granular medium, surf-paddling simulator (S4) to those of an existing cable-pulley driven mechanical simulator (VASA).

METHODS: Six experienced surfers were fitted with reflective markers for motion capture and 5 wireless EMG/accelerometers over 5 muscles of the left arm and trunk. HR and VO2 were also acquired. Participants paddled continuously for 5 minutes on each device, at a pace that produced a target heart rate (60% age-predicted HRmax), followed by 15 minutes of recovery. Participants were provided real-time display of HR in order to maintain comparable workload between devices. The protocol was then repeated on the other device, with the order of devices randomized.

RESULTS: The HR, VO2, and cardiovascular-metabolic interaction value (HR/VO2/kg) were not significantly different between the S4 and VASA conditions. Stroke cadence was lower for the VASA, while the average stroke duration, length, and width was significantly less for the S4 ($p < 0.05$). Differences in hand-stroke trajectory were greater between the devices during the final 2 minutes of each trial, indicating that fatigue had a greater impact on the biomechanics of paddling with the VASA ($p < 0.01$). No statistically significant differences were noted in muscle activation between the S4 and VASA.

CONCLUSIONS: Simulated paddling at 60% age-predicted HRmax yielded VO2 results that were comparable to paddling at 1.1 m/s in water [5]. Differences in biomechanical performance suggest that use of paddling simulators for land-based training may have different performance outcomes, depending upon the design of each device.

Integrative exercise physiology and metabolism

Presentation Number: 92

Board #20

Acute Resistance Exercise Effect on FOS and BDNF mRNAs in Hippocampal Dentate Gyrus

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PURPOSE: BDNF is an important modulator of brain health. Due to its ability to increase neuroplasticity, increased BDNF is associated with amelioration of depression, cognitive impairment, and other neurodegenerative diseases. Numerous studies show aerobic exercise elevates BDNF levels in the hippocampus. Studies also suggest that acute aerobic exercise leads to the induction of immediate early gene FOS that can lead to downstream increases in BDNF, which eventually leads to increased phosphorylation of CREB producing the increased neuroplasticity and associated benefits. Aerobic exercise ability to elevate BDNF raises the question whether resistance exercise is also able to elevate BDNF levels in the same manner as aerobic exercise. Yet, the underlying mechanisms of resistance exercise effect on BDNF is still largely unknown.

METHODS: Therefore, to determine the effects of acute resistance exercise on BDNF, four-week-old Wistar rats underwent six bouts of progressive weighted ladder climbing (exercise group), with age and weight-matched control rats undergoing two bouts of climbing without weights attached (sham group). Both exercise and sham groups were immediately sacrificed (within five minutes of last bout), the brain was excised, and the hippocampus (including the dentate gyrus and Ammon's horn) of these rats was examined.

RESULTS: Resistance exercised rats did not show any significant differences in BDNF or CREB mRNA expression in their dentate gyrus. However, resistance exercised rats did have a significant increase in immediate early gene FOS mRNA expression compared to sham counterparts in the dentate gyrus. Immediate early genes ARC and Homer1 were not significantly different in the dentate gyrus.

CONCLUSIONS: These data suggest BDNF stimulation following resistance exercise by rat ladder climbing may be time dependent, in which induction of the immediately early gene FOS is increased prior to increases in BDNF expression in the dentate gyrus. These data also provide evidence that other immediate early genes ARC and Homer1 are not increased 5-min post exercise, suggesting that if BDNF is increased at a later time point, it may not be dependent on ARC and Homer1 induction. Based on the above results, I am now adding a second time point at 75 minutes post exercise to determine if there is a delayed increase in BDNF levels following acute resistance exercise.

Integrative exercise physiology and metabolism

Presentation Number: 93

Board #21

Cardiovascular and Skeletal Muscle Health with Lifelong Exercise

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Purpose: We examined the effects of lifelong aerobic exercise (LLE) on cardiorespiratory fitness (VO_2max) and skeletal muscle metabolic fitness in trained females (n=7, 72±2y) and males (n=21, 74±1y), and compared them to old healthy non-exercisers (OH; females: n=10, 75±1y; males: n=10, 75±1y), and young exercisers (YE; females: n=10, 25±1y; males: n=10, 25±1y). LLE males were further subdivided based on intensity of lifelong exercise and competitive status into performance (LLE-P, n=14) and fitness (LLE-F, n=7). On average, LLE exercised 5d/wk for 7h/wk over the past 52±1y. **Methods:** Each subject performed a maximal cycle test to assess VO_2max and had a vastus lateralis muscle biopsy to examine capillarization and metabolic enzymes (citrate synthase, β-HAD, and glycogen phosphorylase). **Results:** VO_2max had a hierarchical pattern (YE>LLE>OH, P<0.05) for females (44±2>26±2>18±1 ml•kg^{-1}•min^{-1}) and males (53±3>34±1>22±1 ml•kg^{-1}•min^{-1}), and was greater (P<0.05) in LLE-P (38±1 ml•kg^{-1}•min^{-1}) than LLE-F (27±2 ml•kg^{-1}•min^{-1}). LLE males, regardless of intensity, and females had similar capillarization and aerobic enzyme activity (citrate synthase and β-HAD) as YE, which were 20-90% greater (P<0.05) than OH. **Conclusion:** These data show a substantial cardiovascular benefit with LLE (performance > fitness > old healthy) that tracked similarly among the sexes. For skeletal muscle, 50+ years of lifelong aerobic exercise appeared to fully preserve skeletal muscle capillarization and aerobic enzymes, regardless of intensity. These data suggest that skeletal muscle metabolic fitness may be easier to maintain with aging than the cardiorespiratory system. Sponsored by NIH R01 AG038576

Integrative exercise physiology and metabolism

Presentation Number: 94

Board #22

Dropjumps: Effect Of An Acute Fatiguing Intervention On Indexes Of Exercise Tolerance And Efficiency

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PURPOSE: We tested the hypothesis that dropjumps (DJ)[1], an acute, non-metabolic fatiguing intervention, by reducing maximal power output and possibly increasing the recruitment of high-threshold motor units at a given exercise intensity, will reduce maximal and submaximal indexes of exercise tolerance, increase muscle activation and reduce efficiency as a function of workload during a cycling incremental exercise.

METHODS: Ten healthy males (25±4 years) performed two ramp incremental tests respectively after 100-dropjumps from a 40-cm box interspersed by 20-seconds rests (DJ) or 40' of control condition (CTRL), on different days, in random order. Pre and post DJ/CTRL maximal power output ($_{sprint}$PO) was determined during isokinetic-sprints on a cycle ergometer with pedal-force measurement. During the ramp incremental tests, we measured: *i*) oxygen consumption (VO_2) and power output (W) at peak, gas exchange threshold (GET) and respiratory compensation point (RCP); *ii*) Surface electromyography (Normalized Root Mean Square, nRMS) and *iii*) Submaximal VO_2 at a given absolute workload (corresponding to 10-100 % of CTRL W_{peak}). $_{sprint}$PO data were compared by RM ANOVA; Peak, GET and RCP data after CTRL/DJ intervention by paired t-test; data between interventions as a function of workload were compared using 2-way RM-ANOVA (intensity and intervention).

RESULTS: $_{sprint}$PO was significantly reduced after DJ (-35±19 W p=0.032) yet not after CTRL (8±29 W p=0.492). W_{peak} was significantly reduced after DJ (300±37 W p= 0.023) *vs* CTRL (314±41 W); on the contrary, VO_{2peak} was not different among interventions (DJ 3413±466, CTRL 3505±486 ml/min p=0.094). Furthermore, DJ was associated with an early occurrence of GET and RCP (GET 136±52 W, 1998±524 ml/min p= 0.049; RCP 205±45 W, 2585±451 ml/min p= 0.004) *vs* CTRL (GET 153±44 W, 2150±464 ml/min; RCP 236±44 W, 2883±488 ml/min). Finally, a significant main effect of DJ was detected for $_n$RMS (p= 0.003) and VO_2 (p=0.006), that were both increased at a given absolute workload *vs* CTRL.

CONCLUSION:

In agreement with our hypothesis, DJ significantly reduced maximal cycling power output in turn reducing maximal and submaximal indexes of exercise tolerance, increasing muscle activation and inefficiency during incremental cycling. Although further studies are warranted to identify a direct cause-effect relationship, this finding suggest a link between exercise intolerance/loss of efficiency and the observed decrease in the ability to produce force as a result of acute, non-metabolic fatigue.

[1]Marcora SM et al., *AJP Regul Integr Comp Physiol.* 2008;294(3):R874-R883

Integrative exercise physiology and metabolism

Presentation Number: 95

Board #23

Effect of Exercise on PGC-1α, PPAR-α, Irisin, and UCP1 Levels in Experimental Type 1 Diabetic Heart

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PURPOSE: Nowadays, exercise is evaluated as a treatment protocol for metabolic diseases such as metabolic syndrome, diabetes mellitus and obesity, which are increasing in sedentary living conditions. Molecular studies on exercise physiology give some answers to questions about how exercise affects metabolism by showing the functions of myokines released from various tissues, especially skeletal muscles, during exercise. Exercise-induced PGC-1α increases irisin secretion, whereas irisin raises the expression of mitochondrial UCP1 via PPAR-α receptors. The net effect of that is the conversion of white adipose tissue in the human body to brown adipose tissue, resulting in more calories being consumed.The aim of the study is to evaluate the effect of exercise on PGC-1α, PPAR-α, irisin, and UCP1 mRNA and protein levels in type 1 diabetic heart by applying two different exercise protocols. **METHODS:** Twelve weeks old male Wistar albino rats were divided into two main groups as non-diabetic, and diabetic group (i.p. 50 mg/kg streptozotocin). And each main group consisted of sedentary, moderate exercise and high intensity exercise subgroups (each subgroup n=10). Moderate (10 meters/minute, 0º slope, 60 minutes/day) or high intensity (20 meters/minute, 10º slope, 60 minutes/day) exercises were performed on a rat treadmill for 5 days a week for 6 weeks. After the experiments, the left ventricles of the rats were collected and mRNA levels of PGC-1α, PPAR-α, irisin, and UCP1 were measured by RT-PCR and the protein levels were evaluated by ELISA.

RESULTS: Irisin, PPAR-α, and UCP1 mRNA levels increased significantly in non-diabetic moderate exercise group compared to non-diabetic high intensity exercise, diabetic sedentary and diabetic moderate exercise groups (consecutively p<0.001, p<0.001, p<0.001). There was no change in PGC-1α and PPAR-α protein levels among the groups. Irisin, and UCP1 protein levels increased significantly in diabetic high intensity exercise group compared to non-diabetic sedentary group (consecutively p<0.001 and p<0.05).

CONCLUSIONS: Considering the studies showing that it contributes positively to diabetic cardiomyopathy, this study re-emphasizes the importance of exercise, as it causes increases of mRNA of irisin and related gene products. The missing part of the study is that heart function data is not given. And also time-course exercise protocols should be performed to better understand the mRNA and protein responses of the irisin and related genes.
Supported by Grants from Ankara University 15A0230006 and 17L0230010 (Ali Dogan Dursun)

Integrative exercise physiology and metabolism

Presentation Number: 96

Board #24

Hypoxic Training Improves Glucose Tolerance and Insulin Response during a Glucose Challenge in Obese Adolescents

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PURPOSE: Prevalence of obesity tripled during the last 40 years and is currently associated with insulin resistance, which can lead to type 2 diabetes (T2D) development. Therefore, improving insulin sensitivity in adolescents with obesity could prevent T2D development in the early adulthood. One evident and efficient non-drug based strategy to treat insulin resistance is physical activity. Interestingly, recent evidence also suggests that repeated sessions of oxygen restriction could improve insulin sensitivity and glucose tolerance. Several studies also show an immediate additional effect of an acute session of hypoxic exercise to normoxic exercise on insulin sensitivity and glucose tolerance in adult patients with T2D. However, no study has been realized in pre-diabetic adolescents with obesity while this population is particularly of interest in the optic to prevent insulin resistance-induced T2D development and it remains unknown what the effect of a whole hypoxic training period is on glucose metabolism and insulin resistance. **METHODS:** Fourteen obese adolescents (8 girls and 6 boys) were randomly assigned to 6 weeks of exercise training either in normoxic (NE) or in hypoxic conditions (HE; FiO2 15%). Adolescents trained 3x/w for 50-60min, including endurance and resistance exercises. Oral glucose tolerance test (OGTT), blood and morphological analyses as well as physical performance tests were performed before and after the training period. **RESULTS:** After the 6-week training, hypoxia, but not normoxia, decreased the area under the curve of plasma insulin (-49%; $p = 0.001$) and glucose levels (-14%; $p = 0.005$) during OGTT. These results were associated with decreased plasma triglycerides levels ($p = 0.03$) and increased maximal aerobic power ($p = 0.002$), work capacity at 160 beats/min (WC160; $p = 0.002$) and carbohydrate consumption during exercise ($p = 0.03$) in the hypoxic compared to the normoxic group. **CONCLUSIONS:** Hypoxia had an additive effect on exercise-induced glucose tolerance and insulin response to a glucose challenge in obese adolescents, potentially through enhancement of skeletal muscle glucose metabolism and reduction of adipose tissue fatty acid release. These results suggest that exercise training in hypoxia could be an interesting strategy against insulin resistance and type 2 diabetes development in obese adolescents. Supported by Fonds National de la Recherche Scientifique (FNRS).

Integrative exercise physiology and metabolism

Presentation Number: 97

Board #25

Lactate Shuttle Theory Applied To Clinical Practice

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PURPOSE: We seek to apply Lactate Shuttle (LS) theory to manage clinical conditions. Once thought to be the product of oxygen limited (anaerobic) metabolism, a metabolic waste and fatigue agent we now know that lactate is formed continuously under fully aerobic conditions. The shuttling of lactate between producer and consumer cells fulfills at least three purposes: lactate is a major energy source, the major gluconeogenic precursor; and a signaling molecule with autocrine-, paracrine- and endocrine-like effects. “Cell-Cell Lactate Shuttle” and “Intracellular Lactate Shuttle” concepts describe the roles of lactate in delivery of oxidative and gluconeogenic substrates as well as in cell signaling. Examples of the Cell-Cell Lactate Shuttles include lactate exchanges between white-glycolytic and red-oxidative fibers within a working muscle bed and between working skeletal muscle and heart, brain, liver and kidneys.

METHODS: Literature review reveals that with benefit of Lactate Shuttle theory, clinicians are coming to recognize that lactatemia is a “strain,” and not a “stress” biomarker.

RESULTS: In the ill and injured lactate containing resuscitation fluids such as Lactated Ringers and hypertonic sodium L-lactate are used to provide water, energy and electrolytes as well as to control acidosis. As the major gluconeogenic precursor lactate therapy controls glycemia without necessity of continual dextrose-insulin treatments to maintain blood [glucose] within Center for Medicare and Medicaid(CMS) guidelines. The literature on clinical experiments and registries of clinical trials indicate that lactate therapy is being used to manage inflammation and provide brain fuel following Traumatic Brain Injury (TBI) as well as other pro-inflammatory conditions such as acute pancreatitis, hepatitis and dengue. Lactate-containing cardioplegic solutions are being used to treat myocardial infarction, acute heart failure, and recovery from cardiac surgery. Perhaps most impressive is that some are recommending lactate solution resuscitation in severe sepsis in which a 4 mM blood [lactate] is a biomarker for major infection. Moreover, use of lactate containing solutions to deliver fuel to the brain working muscles has been established in sports medicine.

CONCLUSIONS: Lactate therapy is anti-inflammatory and can help control acidosis. As well lactate therapy can provide, water, energy and electrolytes and maintain euglycemia in a variety of clinical conditions. Supported by the Pac-12 Student-Athlete Health & Well-Being Grant Program

Integrative exercise physiology and metabolism

Presentation Number: 98

Board #26

Low-Load Blood Flow Restricted and High-Load Resistance Training Stimulate Muscle Mitochondrial Protein Synthesis and Respiration

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PURPOSE: It is well established that high-load resistance exercise (HLRE) can stimulate myofibrillar accretion. Interestingly, recent studies suggest that HLRE can also stimulate mitochondrial biogenesis and respiratory function. However, in several clinical situations, the use of resistance exercise with high loading may not constitute a viable approach. Low-load blood flow restricted resistance exercise (BFRRE) has emerged as a time-effective low-load alternative to stimulate myofibrillar accretion but it is unknown whether BFRRE can also stimulate mitochondrial biogenesis and respiratory function. **METHODS:** To study this, 34 healthy previously untrained individuals (24±3 yr.) participated in BFRRE, HLRE, or non-exercise control intervention (CON) 3 times per week for 6 weeks. Skeletal muscle biopsies were collected; (1) before and after the 6-week intervention period to assess mitochondrial biogenesis and respiratory function, and; (2) during recovery from single-bout exercise to assess myocellular signaling events involved in transcriptional regulation of mitochondrial biogenesis. During the 6-week intervention period, deuterium oxide (D_2O) was continuously administered to the participants to label newly synthesized skeletal muscle mitochondrial proteins. Mitochondrial respiratory function was assessed in permeabilized muscle fibers with high-resolution respirometry. Mitochondrial content was assessed with a citrate synthase activity assay. Myocellular signaling was assessed with immunoblotting. **RESULTS:** Mitochondrial protein synthesis rate was higher with BFRRE (1.19 %/day) and HLRE (1.15 %/day) compared to CON (0.92 %/day) ($P < 0.05$) but similar between exercise groups. Mitochondrial respiratory function increased to similar degree with both exercise regimens and did not change with CON. For instance, coupled respiration supported by convergent electron flow from complex I and II increased 38 % with BFRRE and 24 % with HLRE ($P < 0.01$). Training did not alter citrate synthase activity compared to CON.

BFRRE and HLRE elicited similar myocellular signaling responses. **CONCLUSIONS:** These results support recent findings that resistance exercise can stimulate mitochondrial biogenesis and respiratory function to support healthy skeletal muscle and whole-body metabolism. Noteworthy, BFRRE produces similar mitochondrial adaptations at a markedly lower load, which entail important implications for populations in whom exercise with high loading is untenable. Supported by Novo Nordisk Foundation (NNF15OC0016674), NIH (R01-AG042569), and Aarhus University Research Foundation (AUFF-E-2O15-FLS-7-32).

Integrative exercise physiology and metabolism

Presentation Number: 99

Board #27

Metabolic Flexibility: Effects of Exercise and Exercise plus Diet, Methodological Challenges and Unanswered Questions

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Purpose: To measure changes in metabolic flexibility (MetFlex) — changes in respiratory quotient (RQ) in response to glucose plus insulin infusions — after 6-month interventions.

Methods: Subjects enrolled in Studies Targeting Risk Reduction Interventions through Defined Exercise-Prediabetes trial were randomized to one of four 6-month interventions: 1) Low Amount/Moderate Intensity (LM): ~8.6 miles/wk at 50% $VO_{2reserve}$; 2) High Amount/Moderate (HM): ~13.8 miles/wk at 50% $VO_{2reserve}$; 3) High Amount/Vigorous (HV): ~13.8 miles/wk at 75% $VO_{2reserve}$; 4) Clinical Lifestyle (CL): same as LM plus diet and 7% weight loss. Indirect calorimetry was used to estimate the relative contribution of fat and carbohydrate oxidation (RQ) at rest/fasting, after glucose infusion and after insulin infusion during an insulin-modified intravenous glucose tolerance test (IVGTT). MetFlex, which reflects the ability to switch between fat and glucose oxidation, was defined as the greatest RQ obtained after insulin infusion minus the fasting RQ. However, several non-fuel oxidation factors can affect changes in RQ, such as hyperventilation, weight change, low fat vs high fat diet, and de novo lipogenesis (DNL; indicated by a fasting RQ > 1.0). Thus, these potential confounders present methodological challenges and, in some cases, unanswered questions surrounding the interpretation of RQ and MetFlex.

Results: At baseline (N=133), fasting RQs ranged from 0.70-0.91 with RQs after glucose + insulin infusions of 0.81-1.06. At baseline, subjects displayed a wide MetFlex range (-0.01 to +0.23). Sixty-nine subjects completed pre and post intervention IVGTTs with RQ measures. Compared to baseline, there were no significant changes in either fasting RQ or MetFlex following intervention. However, when we looked at only glucose intolerant subjects (2-hr glucose > 139 mg/dL; N=31) we observed a significant increase in MetFlex in the CL group (+0.02 ± 0.06) and a significant decrease in MetFlex for the HV group (-0.01 ± 0.05). ANCOVA revealed significant group differences between CL and HV and between CL and HM.

Conclusions: The CL group experienced a significant increase in MetFlex, in part due to the expected lowering effect of a low-fat diet on fasting RQ (mirroring the lower food index), but also due to a greater max RQ after infusions. Interestingly, the HV group experienced a reduction in MetFlex, possibly suggesting a reduced ability to switch to glucose oxidation. This MetFlex reduction may also reflect an increased partitioning of glucose uptake to glycogen instead of oxidation, perhaps to prepare the muscle for the next vigorous exercise bout.
Supported by NIH-NIDDK R01DK081559

Integrative exercise physiology and metabolism

Presentation Number: 100

Board #28

Palmitoyl-CoA Induces Mitochondrial Uncoupling in Rat Myofibres Exposed to Heat Stress

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PURPOSE: Several physiological or pathological conditions alter substrate utilization by skeletal muscle. While glucose dependence has already been assumed during exercise in the heat, the effect of heat on fatty acid oxidation remains largely unknown. Our hypothesis is that heat exposure could specifically decrease fatty acids oxidation by skeletal muscles.

METHODS: Oxygen consumption was monitored using increasing concentrations of physiological substrates, pyruvate (Pyr) or palmitoyl-Coenzyme A (PCoA), by in situ mitochondria respiration measurements in permeabilized fibres of rats' soleus (n=8) exposed either to 35°C or to 40°C. Km for each substrate was calculated from Michaelis-Menten's model. Maximal oxygen consumption was determined for pyruvate (Pyr-Vmax) and palmitoyl-CoA (PCoA-Vmax). At the end of each protocol atractyloside was added to assess oxygen consumption in non-phosphorylating conditions for pyruvate ($Pyr\text{-}V_0$) and PCoA (PCoA-V0). Respiration measurements were realized with or without Guanosin TriPhosphate (GTP), an antagonist of uncoupling proteins (UCP). Reactive oxygen species (ROS) production was studied measuring Hydrogen Peroxide (H_2O_2) production by fluorimetry in non-phosphorylating conditions in permeabilized fibres for each condition. Results were normalized by the weight of dry fibres. Means were compared by non-paired T-test.

RESULTS: At 35 °C and 40 °C, **Pyr-Vmax (6.95 ± 0.51 vs 7.13 ± 0.43 µmol.min^{-1}.g^{-1}** respectively) and **Pyr-V0 (1.61 ± 0.33 vs 2.16 ± 0.44 µmol.min^{-1}.g^{-1}**) remained similar. **Thus heat did not alter** Pyr acceptor control ratio (**Pyr-ACR**), corresponding to the **Vmax-V_0** ratio ***(4.99 ± 0.55 vs 4.51 ± 1.06 µmol.min^{-1}.g^{-1} , 35 vs 40 °C***). **PCoA-V_0** was higher at 40°C than at 35°C (**1.77 ± 0.33 vs 2.21 ± 0.37 µmol.min^{-1}.g^{-1}**, p=0.029), while **PCoA-Vmax** was unchanged. **PCoA-ACR** significantly decreased at heat (**3.05 ± 0.35 to 2.06 ± 0.46 µmol.min^{-1}.g^{-1}**, p=0.007). Km for each substrate was not modified by heat exposure. With GTP, when compared 35 to 40 °C, **PCoA-V_0** (1.25 ± 0.24 vs 1.70 ± 0.18 µmol.min^{-1}.g^{-1}) was unchanged. Only **PCoA-ACR** still decreased (**3.48 ± 0.49 at 35°C vs 2.22 ± 0.17 µmol.min^{-1}.g^{-1}** at 40°C, p= 0.023). **H_2O_2** production was not altered by heat whatever the substrate.

CONCLUSIONS: The decrease of ACR observed at 40°C for PCoA suggests a heat-induced mitochondrial uncoupling specifically for LCFA oxidation. This heat-induced uncoupling could involve UCP independently from ROS production. Mechanisms underlying this uncoupling effect of LCFA and consequences on muscle efficiency contraction and potential additional heat strain on thermoregulation capacities remain to be explored.

Integrative exercise physiology and metabolism

Presentation Number: 101

Board #29

Passive stretching: Effect of an Acute Fatiguing Intervention on Indexes of Exercise Tolerance and Efficiency

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PURPOSE: We tested the hypothesis that passive stretching (STRC)[1], an acute, non-metabolic fatiguing intervention, by reducing maximal power output and possibly increasing the recruitment of high-threshold motor units at a given exercise intensity, will reduce maximal and submaximal

indexes of exercise tolerance, increase muscle activation and reduce efficiency as a function of workload during a cycling incremental exercise.

METHODS: Ten healthy males (25±4 years) performed two ramp incremental tests respectively after 40' of passive stretching intervention (STRC) or 40' of control condition (CTRL), on different days, in random order. Pre and post STRC/CTRL maximal power output ($_{sprint}$PO) was determined during isokinetic-sprints on a cycle ergometer with a pedal-force measurement. During the ramp incremental tests, we measured: *i*) oxygen consumption (VO_2) and power output (W) at peak, gas exchange threshold (GET) and respiratory compensation point (RCP); *ii*) Surface electromyography (Normalized Root Mean Square, $_n$RMS) and *iii*) Submaximal VO_2 at a given absolute workload (corresponding to 10-100 % of CTRL W_{peak}). $_{sprint}$PO data were compared by RM ANOVA; Peak, GET and RCP data by paired t-test; Data between interventions as a function of workload were compared using 2-way RM-ANOVA (intensity and intervention).

RESULTS: $_{sprint}$PO was significantly reduced after STRC (-33±29 W p=0.049) yet not after CTRL (8±29 W p=0.492). W_{peak}, and VO_{2peak} were significantly different after STRC (302±39 W p= 0.033, 3365±465 ml/min p= 0.015) vs CTRL (314±41 W, 3505±486 ml/min). Furthermore, STRC was associated with an early occurrence of GET and RCP (GET 136±48 W, 1955±484 ml/min p= 0.018; RCP 209±34 W, 2615±402 ml/min p= 0.006) vs CTRL (GET 153±44 W, 2150±464 ml/min; RCP 236±44 W, 2883±488 ml/min). Finally, a significant main effect of STRC was detected for $_n$RMS (p=0.026) and VO_2 (p<0.001), that were both increased at a given absolute workload vs CTRL.

CONCLUSION:

In agreement with our hypothesis, STRC significantly reduced maximal cycling power output in turn reducing maximal and submaximal indexes of exercise tolerance, increasing muscle activation and inefficiency during incremental cycling. Although further studies are warranted to identify a direct cause-effect relationship, this finding suggest a link between exercise intolerance/loss of efficiency and the observed decrease in the ability to produce force as a result of acute, non-metabolic fatigue.

1.

Behm DG et al. *Appl Physiol Nutr Metab.* 2016;41(1):1-11. doi:10.1139/apnm-2015-0235.

Integrative exercise physiology and metabolism

Presentation Number: 102

Board #30

Post-Exercise Protein and Polyphenol Supplementation Improves Recovery Following 300 Maximal Eccentric Quadriceps Contractions: Preliminary Findings

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PURPOSE

Unaccustomed eccentric exercise presents a metabolic and mechanical stress to the contracting muscle resulting in loss of muscle function, increased soreness and appearance of muscle proteins in plasma. Recovery rate is likely to be dependent on muscle remodeling, which may be influenced by dietary protein and polyphenol availability. The present study aimed to determine if a commercially available post-exercise protein and polyphenol supplement could accelerate recovery from eccentric exercise.

METHODS

Eighteen young, recreationally active participants (age: 22 ± 1 y; BMI: 24.3 ± 0.8 $kg \cdot m^{-2}$) consumed a beverage containing 20 g protein from a blend of whey, casein, and pea, and 650 mg pomegranate extract (Beachbody LLC, USA; PRO; n = 9; 3 females) or an isocaloric carbohydrate placebo (CHO; n = 9; 4 females) daily for 1 week prior to and during 1 week of recovery from 300 maximal unilateral quadriceps contractions. Participants underwent 14 days of full isocaloric dietary control (1.2 $g \cdot kg^{-1}$ protein) during this time. Total work over 30 isokinetic knee extensions (W30), muscle soreness, and pain pressure threshold (PPT) of *vastus lateralis, rectus femoris* and *vastus medialis* were measured on day 1 and every 24 h for 7 d post eccentric exercise, with data analysed relative to the contralateral limb. Blood samples were collected prior to assessing muscle function and the supplement was consumed immediately after. All data were analysed by 2-way ANOVA.

RESULTS

Eccentric exercise significantly reduced W30 ($P < 0.001$) to 67.6 ± 5.9% at 48 hour from 104.9 ± 3.3% at baseline in CHO ($P < 0.001$). This remained suppressed until 144 h (96.0 ± 4.3%; $P > 0.05$). There was a differential response of PRO during recovery ($P < 0.05$), whereby W30 dropped to 78.3 ± 7.2% at 24 h (versus 97.4 ± 3.6% at baseline; $P < 0.01$) and had recovered by 48 h (82.3 ± 6.8%; $P > 0.05$). Muscle soreness rose significantly in CHO between 24 - 96 h ($P < 0.05$), peaking at 48 h ($P < 0.001$). In PRO, soreness was elevated only at 48 h and was 54.7% lower than CHO ($P < 0.001$). The PPT of all muscle groups was lowered by eccentric exercise ($P < 0.001$), but there were no group differences ($P > 0.05$). Plasma creatine kinase activity increased > 25-fold between 96 - 144 h ($P < 0.01$) in CHO, before returning to baseline at 168 h, and PRO did not affect this response ($P > 0.05$).

CONCLUSION

Consumption of a post-exercise protein supplement accelerates recovery of muscle function and attenuates muscle soreness after eccentric exercise. Whether this is due to a protein- and/or polyphenol-mediated greater rate of muscle remodeling immediately post-exercise requires further investigation.

This work was supported by a grant from Beachbody LLC, USA.

Integrative exercise physiology and metabolism

Presentation Number: 103

Board #31

Reversing Palmitate-induced Inhibition Of Pyruvate Dehydrogenase Complex Activity And Mitochondrial Atp Production In C2c12 Muscle Cells By Electric Pulse Stimulation

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Purpose: Increased fatty acid acid availability following high dietary fat intake leads to reduced mitochondrial pyruvate dehydrogenase complex (PDC) controlled carbohydrate (CHO) oxidation, which is a hallmark of insulin resistance. Electric pulse stimulation (EPS) is widely employed as an *in vitro* model of contracting skeletal muscle and evidence suggests that EPS improves muscle glucose metabolism and insulin sensitivity. Besides, contraction activates PDC by increasing the amount of PDC in dephosphorylated (active) form (PDCa). But, the role of EPS in palmitate-induced CHO inhibition has not been elucidated. **Methods:** In this study, we tested the efficacy of EPS at recovering PDC activity and the mitochondrial ATP production in a mouse SKM C2C12 cell line co-treated with palmitate (300 μM) to reduce carbohydrate use. **Results:** Our results showed that EPS rescued palmitate induced inhibition of cell glucose uptake (~30% increased of control). EPS per se increased PDC activity, and also restored it after palmitate-induced PDC inhibition (3.7±0.2 vs 4.6±0.2; P<0.01, and 3.1±0.2 vs 3.7±0.1 pmol acetyl-CoA/min/mg, P<0.01, respectively). Mitochondrial ATP production (real-time bioluminescence using pyruvate +malate as substrates) and acetylcarnitine concentration, a marker of PDC flux, were increased by EPS (10.0±0.3 vs 11.1±0.3 nmol ATP/min mg protein, P<0.05 and 82.3±11.0 vs 141.3±19.3 pmol/mg protein, P<0.01; respectively). EPS also reduced palmitate induced expression of FOXO1 mRNA. **Conclusions:** Collectively, our data show that palmitate reduced PDC activity and flux and pyruvate +malate derived mitochondrial ATP production, which was rescued by EPS.

Integrative exercise physiology and metabolism

Presentation Number: 104

Board #32

Sodium-glucose cotransporter-2 Inhibition Combined with Exercise Alters Metabolism in a Model of Type 2 Diabetes

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Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are a class of type 2 diabetes (T2D) medication whose primary mechanism of action is increased urinary glucose excretion. Exercise (EX) is also recommended for the management of T2D. Both SGLT2i and EX independently affect glucose metabolism. **PURPOSE:** To determine if combining SGLT2i and EX induces additional metabolic adaptations that may lead to improved T2D-status. **METHODS:** Procedures were performed following established guidelines and were approved by the Pfizer IACUC. A low-dose of streptozotocin (30mg/kg) and high-fat feeding were used to induce T2D in male Sprague-Dawley rats. Animals were randomized to the following conditions (n=7-10/group): vehicle (0.5% methylcellulose) sedentary (VEH SED), VEH EX, canagliflozin (3mg/kg/d) SED (SGLT2i SED), or SGLT2i EX for 12 weeks. EX ran for 60 min/d, 5d/wk, on a 10% incline at ~50% of maximal running speed during a graded exercise test. **RESULTS:** Following the intervention, EX had lower body weight (BW; $p<0.05$) compared to SED, with SGLT2i EX tending to have lower BW than VEH EX (~10%, $p=0.07$). SGLT2i had ~15% greater relative (kcal/kg BW) food intake than VEH ($p<0.0001$), while EX had no effect on relative food consumption. During 24h calorimetry, SGLT2i and EX independently increased VO_2 and energy expenditure (EE) in dark and light cycles. Compared to SGLT2i SED, SGLT2i EX had further enhanced VO_2 during dark ($p<0.01$) and light ($p<0.01$) cycles and EE during dark ($p<0.01$) and light cycles ($p<0.0001$). SGLT2i EX had higher VO_2 during the light cycle than VEH EX ($p<0.05$). These increases occurred despite lower ambient activity in EX ($p<0.05$ vs. SED). SGLT2i relied more on fat for energy in dark ($p<0.01$) and light cycles ($p<0.05$) vs VEH, while EX relied more on fat in the light cycle vs SED ($p<0.05$). SGLT2i had higher hepatic pAMPK/AMPK ($p<0.05$) and lower liver glycogen content ($p<0.0001$) vs VEH. Conversely, pAMPK/AMPK was lower with SGLT2i in the gastrocnemius-plantaris ($p<0.05$ vs VEH). Finally, SGLT2i had higher circulating β-hydroxybutyrate ($p<0.0001$ vs VEH) despite no differences in hepatic protein content of HMG-CoA synthase-1 or -2. The ketolysis protein OXCT1 was higher in the gastrocnemius-plantaris with SGLT2i ($p<0.05$ vs VEH) while EX had lower OXCT1 ($p<0.001$ vs SED). **CONCLUSION:** SGLT2i treatment and EX have independent metabolic effects; however, the combination of SGLT2i EX further enhanced VO_2 and EE which could have significant health implications if these findings translate to people with T2D.

Funding: TTR, DAB, and WPE are employees and shareholders of Pfizer. MAL is a former Pfizer employee. MAL, KLH, BFM, and BB have received research funding from Pfizer.

Integrative exercise physiology and metabolism

Presentation Number: 105

Board #33

Supervised, Clinical Aerobic and Resistance Exercise Improves Physical Fitness in Overweight and Obese Breast Cancer Survivors

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Purpose: Due in part to the nature of cancer-related treatments, breast cancer survivors (BCS) are less physically active than age-matched counterparts rendering them less physically fit. Physical inactivity and reduced fitness can result in muscle atrophy, weight gain, and an increased risk of diabetes and hypertension, known predisposing risk factors to the development of cardiovascular disease, among other diseases. Exercise is an effective method to improve physical fitness in BCS. Few studies have focused on the early survivorship period, minority populations, sedentary and obese women, or tested a combined exercise program. Here, we report the effects of a 16-week supervised, clinical aerobic and resistance exercise intervention on physical fitness in ethnically diverse, sedentary, and overweight or obese BCS.

Methods: One hundred overweight or obese, sedentary women diagnosed with stage I-III breast cancer were randomized to either the Exercise (EX, n=50) or Control (CON, n=50) groups. The exercise intervention consisted of 3 weekly sessions including moderate-vigorous (65%-85% heart rate maximum) aerobic exercise and resistance exercise (65-85% one-repetition maximum). Physical fitness was assessed at baseline, post-intervention, and a three-month follow-up (exercise group only) using a submaximal treadmill walk test to estimate VO_2max. Maximal voluntary muscle strength was evaluated by a 10-repetition maximum (10-RM) method for the following exercises: chest press, latissimus pulldown, knee extension, and knee flexion. The CON group was offered the exercise program after the 16-week study period. Differences in mean change for outcomes were evaluated using mixed-model repeated measure analysis.

Results: Participants were 53 ± 10.4 years old, primarily overweight (BMI>25.0 kg/m^2; 54%) and Hispanic (63.1%), had undergone a mastectomy (90%) and chemotherapy + radiation therapy (76%). At baseline, there were no differences in physical fitness between the 2 groups ($p>0.05$). Post-intervention, all physical fitness measures significantly improved (mean percent increase: 43%) in EX when compared to baseline and CON ($p<0.001$). At the three-month follow-up, all physical fitness variables in the EX group remained significantly improved in comparison to the baseline ($p<0.01$).

Conclusion: This 16-week supervised aerobic and resistance exercise intervention significantly improved the physical fitness in ethnically-diverse and overweight or obese BCS. These findings support the integration of supervised clinical exercise programs into breast cancer treatment and care.

Funding: This project was supported by NIH/NCI K07CA160718

Integrative exercise physiology and metabolism

Presentation Number: 106

Board #34

The Effects of Aerobic, Resistance, and Combination Training on Markers of Insulin Resistance

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PURPOSE To determine the effects of aerobic training (AT), resistance training (RT), and combination training (AT/RT) on traditional measures of insulin action and a nuclear magnetic resonance (NMR)-derived multimarker of insulin resistance [Lipoprotein Insulin Resistance Index (LP-IR)].

METHODS Participants (n=142 from the STRRIDE AT/RT randomized trial) completed one of three 8-month exercise programs: 1) AT: ~12 miles/wk at 75% peak O_2 consumption; 2) RT: 3 days/wk, 8 exercises, 3 sets/exercise, 8-12 repetitions/set; 3) AT/RT: full combination of the AT and RT programs. Insulin action was determined via a 3-hr frequently sampled intravenous glucose tolerance test performed after an overnight fast at both baseline and 16-24 hr after the final exercise bout. Measures included fasting insulin, insulin sensitivity (Si), acute insulin response to intravenous glucose (AIRg), disposition index, and homeostasis model assessment of insulin resistance (HOMA). LP-IR was calculated from six lipoprotein subclass and size parameters, which were measured via NMR at LipoScience/LabCorp. LP-IR score ranges from 0 (most insulin sensitive) to 100 (most insulin resistant). Paired t-tests were used to determine whether the post- minus pre-intervention change score within each group

was significant (p<0.05). Analysis of covariance, with baseline values used as covariates, was used to determine difference between groups.

RESULTS After 8-months of exercise training, the AT group significantly decreased their fasting insulin (-1.7 ± 3.0 µU/mL), AIRg (-130.0 ± 216.5 mU/L/min), HOMA (-0.5 ± 0.9), and LP-IR (-5.0 ± 17.2). The AT/RT group also experienced significant decreases in fasting insulin (-1.7 ± 4.5 µU/mL), AIRg (-85.2 ± 250.4 mU/L/min), HOMA (-0.4 ± 0.9), and LP-IR (-10.2 ± 16.6).

Only the AT/RT group experienced significant improvement in Si (2.2 ± 5.3 mU/L/min). There were no significant changes observed for these variables in the RT only group. For the AT/RT group, change in LP-IR was significantly greater than the RT group (p=0.02). The AT/RT group's improvement in Si was significantly different from both the AT (p=0.01) and RT (p=0.001) groups.

CONCLUSIONS Performing the combination of AT/RT resulted in more robust improvements in markers of insulin action compared to AT or RT alone. Whether these greater improvements in measures of insulin resistance were due to qualitative synergistic effects of the different exercise modes or the fact that twice the volume of exercise was performed in the AT/RT group remains unclear.
Study funded by NHLBI grant 2R01-HL-057354. LMR supported by NHLBI T32 fellowship T32HL007101.

Integrative exercise physiology and metabolism

Presentation Number: 107

Board #35

The Effects of Exercise Training on Body Composition in Adults with Prediabetes

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PURPOSE To determine the effects of different amounts and intensities of exercise on body composition in previously sedentary adults with prediabetes.

METHODS Participants (n=155) were enrolled in the Studies Targeting Risk Reduction Interventions through Defined Exercise-Prediabetes (STRRIDE-PD) randomized trial. Participants completed one of four 6-month interventions: 1) Low Amount/Moderate Intensity (LM): ~8.6 miles/wk at 50% $VO_{2reserve}$; 2) High Amount/Moderate Intensity (HM): ~13.8 miles/wk at 50% $VO_{2reserve}$; 3) High Amount/Vigorous Intensity (HV): ~13.8 miles/wk at 75% $VO_{2reserve}$; 4) Clinical Lifestyle (CL): same as LM plus diet and 7% weight loss. Body weight, fat mass and lean body mass were determined using BOD POD™ air displacement plethysmography (Life Measurement, Inc., Concord, CA). Visceral (VAT) and subcutaneous adipose tissue (SAT) were measured by computed tomography. Paired t-tests were used to determine whether the post- minus pre-intervention change score within each group was significant (p<0.05). Analysis of variance (ANOVA) was used to determine any differences among groups.

RESULTS At baseline, there were no significant differences between groups in any of the body composition measures. Following 6-months of exercise training, the total sample significantly decreased their body weight by 2.7 ± 4.0 kg (p< 0.0001). The total sample also experienced significant improvements in fat mass (p<0.0001), while maintaining lean mass. When assessing changes within each group, the LM group experienced significant improvements in fat mass (-1.3 ± 3.0 kg), VAT (-11.1 ± 24.5 cm^2), and SAT (-13.4 ± 37.4 cm^2), while the HM group significantly improved body weight (-1.9 ± 2.7 kg), fat mass (-2.1 ± 2.9 kg) and SAT (-13.8 ± 39.0 cm^2). The HV group experienced significant improvements body weight (-1.7 ± 2.6 kg), fat mass (-2.2 ± 3.6 kg) and SAT (-16.8 ± 27.8 cm^2). The CL group experienced significant improvements in body weight (-6.3 ± 5.0 kg), fat mass (-5.9 ± 5.8 kg), VAT (-39.6 ± 39.6 cm^2) and SAT (-48.4 ± 44.7 cm^2). ANOVA revealed that the changes in body weight, total fat mass and both abdominal adipose tissue measures were significantly better for the CL group than any of the three exercise only groups.

CONCLUSIONS While the combination of diet and lifestyle changes was the most effective for eliciting beneficial body composition changes, participation in any of the 6-month exercise training interventions significantly improved body weight, fat mass and subcutaneous adipose tissue in previously sedentary adults with prediabetes.
Study funded by NIDDK grant R01DK081559.

Integrative exercise physiology and metabolism

Presentation Number: 108

Board #36

The Effects of Exercise Training on Self-rated Sleep Quality in Adults with Prediabetes

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PURPOSE To determine the effects of different amounts and intensities of exercise on subjective sleep quality in previously sedentary adults with prediabetes.

METHODS Participants (n=158) were enrolled in the Studies Targeting Risk Reduction Interventions through Defined Exercise–Prediabetes (STRRIDE-PD) randomized trial. Participants completed one of four 6-month interventions: 1) Low Amount/Moderate Intensity (LM): ~8.6 miles/wk at 50% $VO_{2reserve}$; 2) High Amount/Moderate Intensity (HM): ~13.8 miles/wk at 50% $VO_{2reserve}$; 3) High Amount/Vigorous Intensity (HV): ~13.8 miles/wk at 75% $VO_{2reserve}$; 4) Clinical Lifestyle (CL): same as LM plus diet and 7% weight loss. Self-rated sleep quality and patterns were assessed via the Pittsburgh Sleep Quality Index (PSQI) at both baseline and post-training. The seven sleep domains assessed included: subjective quality, latency, duration, efficiency, disturbances, use of sleep medication, and daytime dysfunction over the past month. Global PSQI score is calculated from these domains (each scored from 0 to 3), and a global score ≥5 indicates "poor" sleep. Paired t-tests were used to determine whether the post- minus pre-intervention change score within each group was significant (p<0.05). Analysis of variance (ANOVA) was used to determine difference among groups.

RESULTS At baseline, the total sample had a global PSQI score of 5.4 ± 3.1. After 6-months of exercise training, the total sample significantly decreased their global score by 0.7 ± 2.5 (p=0.0005). The total sample also reported significant improvements in the subscale scores for sleep duration, sleep efficiency, and subjective sleep quality (all p<0.02). When assessing changes within each group, the LM group experienced significant improvements in global (-1.3 ± 2.8), duration (-0.3 ± 0.7), and subjective sleep quality (-0.3 ± 0.6) scores, while the HM group reported a significant improvement in sleep latency score (-0.2 ± 0.6). The HV group experienced significant score improvements for sleep duration (-0.2 ± 0.6) and subjective sleep quality (-0.3 ± 0.8). There were no significant changes observed for these sleep parameters in the CL group. ANOVA did not reveal any significant difference among groups.

CONCLUSIONS Overall, participation in a 6-month exercise training intervention significantly improved self-reported measures of sleep quality and patterns in previously sedentary adults with prediabetes. However, more research is needed in order to determine the differential effects of varying amounts and intensities of exercise on these sleep parameters.
Funded by NIDDK grant R01DK081559.

Integrative exercise physiology and metabolism

Presentation Number: 109

Board #37

Tissue Oxygenation and Microvascular Hemodynamics in Recovery from Incremental Handgrip Exercise

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Total-[heme] and deoxy-[heme] estimate microvascular hematocrit and myocyte myoglobin, and skeletal muscle fractional oxygen extraction, respectively. Following heavy-intensity cycling exercise, it was observed that total-[heme] off-kinetics were dramatically slowed compared to exercise onset, and deoxy-[heme] fell substantially below resting baseline values. The former suggests differing proportional reliance on perfusive and diffusive oxygen delivery between exercise onset and recovery while the latter suggests a hyperperfusive microvascular blood flow response. **PURPOSE:** The purpose of this study was to compare the responses of total-[heme], deoxy-[heme], and microvascular blood flow index (BFI) during recovery from exercise. We hypothesized that 1) total-[heme] would decrease significantly less than deoxy-[heme] and BFI relative to the overall exercise response, 2) deoxy-[heme] would fall below resting baseline values, and 3) BFI would remain elevated above resting baseline values during the first 2 minutes of recovery. **METHODS:** Thirteen subjects (23.5 ± 4.0 yr, 170.0 ± 8.1 cm, 71.5 ± 14.7 kg) completed an incremental handgrip exercise test to task failure. Total-[heme], deoxy-[heme], and BFI of the flexor digitorum superficialis were measured continuously via near-infrared spectroscopy (NIRS) and diffuse correlation spectroscopy (DCS) during the first 2 minutes of recovery. **RESULTS:** During recovery, total-[heme] decreased by 35.3 ± 16.3 % of the overall response to exercise while deoxy-[heme] and BFI decreased by a significantly greater 109 ± 18.6% and 59.1 ± 22.0%, respectively ($p < 0.01$). Deoxy-[heme] decreased from 153 ± 50.0 μM at end-exercise to 81.7 ± 20.8 μM following 2 minutes of recovery which was not different from resting baseline (86.3 ± 23.3 μM; $p > 0.05$). BFI following 2 minutes of recovery (1.03 ± 0.36 $cm^2/s \times 10^{-8}$) was significantly elevated above resting baseline values (0.40 ± 0.15 $cm^2/s \times 10^{-8}$; $p < 0.01$). The mean response time for BFI (6.6 ± 4.0 s) was significantly shorter than for deoxy-[heme] (23.3 ± 12.9 s; $p < 0.001$). **CONCLUSIONS:** The relatively small decline in total-[heme] during recovery suggests that diffusive oxygen conductance, via increased microvascular hematocrit, remained elevated. The magnitude of decrease in deoxy-[heme] to resting levels coupled with an elevated BFI suggests a microvascular hyperemic response relative to the overall muscle oxygen consumption during recovery from maximal exercise.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 110

Board #38

(+)-Epicatechin Improves Biomarkers Of Muscle Growth, Oxidative Stress, Injury, NO Reserve And Exercise Response In DMD Patients

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Purpose: (+)-Epicatechin is a flavanol that activates the AMPK/PGC1-alpha signaling pathway leading to mitochondrial biogenesis and stimulation of skeletal muscle growth and regeneration. In vivo, epicatechin stimulates mitochondrial biogenesis related endpoints and improves muscle structure and function in MDX mice, sarcopenic animals and Becker muscular dystrophy (MD) patients. We conducted an open-label escalating dose cohort study of (+)-epicatechin in non-ambulatory Duchenne's MD patients with preclinical cardiomyopathy in support of a planned Phase II study. **Methods:** 15 patients were recruited and received (+)-epicatechin 25 mg PO BID, 25 mg PO TID, and 75 mg PO TID for a total of 8 weeks. Pre- and post-assessments included serial biomarker evaluation of plasma follistatin, myostatin, nitrate/nitrite ratio, troponin I and protein carbonylation (2, 4 and 8 week sampling), and assisted 6-minute cycle test. Additional measures included baseline and 8 week tagged cardiac strain imaging by cMRI and speckle-tracking echocardiography, as well as a safety laboratory panel. **Results:** After 8 weeks of treatment, serum follistatin levels increased to 200% of baseline ($p<0.0001$) with a corresponding increase in the follistatin:myostatin ratio to 194% of baseline ($p<0.0001$). Nitrite/nitrates (reflecting nitric oxide levels) increased to 150% of baseline ($p<0.0001$). Troponin I decreased to 70% of baseline ($p<0.0001$). Protein carbonylation (oxidative stress) decreased to 69% of baseline ($p<0.0001$). Assisted 6-minute cycle test performance increased to 112% of baseline ($p<0.0001$). The highest selected dose (150 mg/day) was well tolerated with no indication of adverse effects or intolerance as per multiple parameters measured. Evaluation of cardiac imaging data is underway. **Conclusions:** (+)-Epicatechin improves circulating biomarkers of muscle growth, nitric oxide levels and decreases oxidative stress and markers of injury. It is the only oral compound ever demonstrated to increase plasma follistatin and improve follistatin:myostatin ratio, which may comprise a future plasma pharmacodynamic biomarker for effects over muscle growth. The small but significant increase in exercise performance is consistent with a short-duration exercise training effect. Results support the implementation or larger and longer duration clinical trials in Becker and Duchenne's MD patients.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 111

Board #39

(+)-Epicatechin Stimulates Mitochondria Biogenesis Related Pathways Leading To Improved Exercise Performance In Rats

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Purpose: (+)-Epicatechin (+Epi) is a flavanol that although rare, can be found in natural products such as cacao and guarana. We previously conducted a study in mice demonstrating the capacity of +Epi to beneficially impact the metabolic profile of obese/insulin resistant mice. In this study, we demonstrated the dose dependent capacity of +Epi to beneficially impact metabolic status related endpoints including body weight, blood glucose, triglycerides, cholesterol and lipid content in adipose tissue. Peak effects were noted at oral doses ranging from 0.1-0.3 mg/kg/day. Central to these actions are the effects that the flavanol may exert on mitochondria. However, the mechanisms underlying such actions are not fully understood, as is the impact on exercise performance. Thus, a study was implemented in mice to address these issues.

Methods: Ten month old male C57/B6 mice (n=6/group) were used. Studies were implemented to assess the effects of +Epi on exercise capacity (treadmill testing) and SkM (gastrocnemius) markers of mitochondrial biogenesis (MB). Animals were treated by gavage with vehicle (water for the control group), -Epi (for comparison purposes @ 1 mg/kg) or +Epi (0.1, 0.3 or 1 mg/kg) for 2 weeks. The effects of treatment were compared vs. those recorded at baseline (before treatment) values.

Results: Replicating our published studies, the use of -Epi lead to a statistically significant increase in total distance traveled by treadmill vs. controls. +Epi led to a progressive (staircase) increase in exercise capacity. The increase in exercise capacity with +Epi at 0.3 mg/kg was comparable to -Epi at 1 mg/kg. Animals treated with +Epi at 1 mg/kg demonstrated a further increased in exercise capacity by ~30%. The assessment of total SkM AMPK and PGC1α protein levels by Westerns, also demonstrated similar stimulatory effects with 0.1-0.3 mg/kg of +Epi as with 1 mg/kg of –Epi. However, +Epi at 1 mg/kg demonstrated greater efficacy (40% increase in AMPK and 75% for PGC1α) vs. 1 mg/kg -Epi.

Conclusions: Results indicate that +Epi can activate in a dose dependent fashion, signaling pathways associated with the upstream activation

of MB. +Epi appears to exert a more effective stimulation of such pathways at lower doses vs. its (-)-epimer form. Such effects translate into greater exercise capacity as demonstrated by treadmill testing. Thus, +Epi appears to be a particularly effective agent for activating MB and translating into improved exercise performance.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 112

Board #40

A Novel Amino Acid Composition (AXA2678) Prevents Muscle Disuse Atrophy in Young Healthy Men

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Even short periods of skeletal muscle disuse, which are often unavoidable and due to illness or injury, have profound effects on skeletal muscle. The negative health consequences include a reduction in muscle cross-sectional area (CSA), volume (Mvol), and strength, and recovery is oftentimes slow or potentially incomplete. Consequently, clinically viable interventions are required to mitigate declines in muscle CSA and strength during periods of disuse. ***Purpose.*** The current study aimed to determine whether a formulation comprised of a proprietary composition of amino acids, AXA2678, would preserve muscle mass and strength in men undergoing 7d of single leg immobilization and promote return of function during 2 weeks of recovery.

Methods. 20 young healthy men (mean age 21.8 yrs) were randomly assigned (1:1) to receive AXA2678 (thrice daily) or an excipient and energy-matched placebo (PL) for 28d. Study products were given during 7d pre-immobilization, 7d of immobilization (atrophy phase) and 14d of post-immobilization (recovery phase). All subjects consumed weight-maintaining diets during the entire 28d protocol with protein at 1.0g/kg/d. Muscle biopsies were taken on d1 of the protocol, d7 (start of immobilization), d15 (end of immobilization) and d28 (post-immobilization recovery) and magnetic resonance imaging (MRI) was utilized to assess quadriceps peak CSA and Mvol. Fiber-type and CSA were assessed with immunohistochemistry. Peak torque was assessed with isometric dynamometry on d1, d8, d15 and d28.

Results. In the PL group, quadriceps peak CSA and Mvol declined significantly during immobilization (d8 vs. d15 Mvol: -3.08 ± 0.70%, *P*=0.002; peak CSA: -2.4% ± 0.78%, *P*=0.01). By contrast, peak CSA and Mvol were preserved with AXA2678 (peak CSA: -0.75 ± 0.7%, *P*=0.28; Mvol: -0.67 ± 0.60%, *P*=0.30). While muscle strength (peak torque) was reduced similarly in both groups (PL: -7.9 ± 3.74%; AXA2678: -7.14 ± 6.46%;), AXA2678 demonstrated significant recovery at d28 (13.2± 5.8%, *P*=0.006) while PL did not. Immobilization did not alter the overall fibre type distribution in AXA2678 group, however PL demonstrated a shift towards a type I fiber distribution after immobilization (PL: type I 3.52 ± 1.41% *P*=0.047; type II -2.58 ± 1.11% *P*=0.058).

Conclusions. These data demonstrate that AXA2678 prevented atrophy (both Mvol and peak CSA) and attenuated fibre type changes. AXA2678 administration could potentially be an effective therapy to preserve skeletal muscle mass and function during periods of muscle disuse. Sponsored by Axcella Health Inc.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 113

Board #41

A Rat Model Of Gulf War Illness Demonstrating Muscle Atrophy And Fatigue: Beneficial Effects Of (+)-Epicatechin

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Purpose: Gulf War illness (GWI) afflicts ~450,000 of US military personnel whom served the 1990 Persian Gulf War. GWI mainly affects nervous and skeletal muscle (SkM) systems yielding cognitive deficit, depression, muscle pain, weakness, intolerance to exercise and fatigue. Co-exposure to specific chemical agents and stress are suspected as the cause. GW personnel consumed daily pyridostigmine (PB) tablets as a prophylactic for a nerve gas attack. To prevent communicable disease infection by insects subjects were also exposed to insecticides and repellents, most commonly permetrim (PM) and N;N-diethyl-m-toluamide (DEET). Whereas knowledge is available about the effects of such treatments on neurological endpoints, nothing is known about SkM. **Methods:** We implemented a rat model of GWI to examine changes in SkM structure/function including tissue wasting pathways and evaluated the therapeutic effects of (+)-epicatechin (+Epi). Three month old male Wistar rats (n=10) were provided orally with PB 1.3 mg/kg/day, PM 0.13 mg/kg/day (back skin) and DEET 40 mg/kg/day (back skin), and physically restrained for 5 min/day for 3 weeks. An additional 1 week period was allowed to develop the intoxication profile followed by 2 weeks of either (+)-epi treatment at 0.1 mg/kg/day by gavage (n=5) or water (n=5) for chemical intoxication controls. A normal group (n=9) ran in parallel and was given vehicles and was not restrained. At 6 weeks, animals were subjected to treadmill and limb strength testing followed by euthanasia and SkM (gastrocnemius and EDL) sampling for histological, biochemical and Westerns. **Results:** GWI animals did not evidence changes in body weight or food intake. Gastrocnemius/EDL weight from GWI animals was ~30% significantly lower vs. controls, which parallel significant decreases in SkM myofiber area (~33%). Limb strength and treadmill time/distance was significantly reduced by 30-50%. Protein degradation assays (tyrosine release) yielded a significant increase of ~25% for both muscles. Gastrocnemius citrate synthase activity was significantly reduced by 60% accompanied by activation of p-SMAD2/3 (~40%) and the suppression of p-AMPK (~60%). Treatment of GWI animals with +Epi yielded a significant recovery vs. GWI of muscle strength, treadmill tests, muscle mass, protein degradation, citrate synthase activity, p-SMAD2/3 and p-AMPK to values similar to normal controls. **Conclusions:** Exposure of rodents to equivalent human doses of associated GWI chemicals can activate muscle atrophy pathways leading to the loss of organ mass/function. +Epi reverses these changes and may be considered as a means to treat humans exposed to GWI like chemicals.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 114

Board #42

Akt-mtor Pathway Contribution To Skeletal Muscle Anti-atrophy Effect Of Resistance Exercise In Tumor-bearing Rats.

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Purpose: The Akt-mTOR pathway controls the anabolic and catabolic signaling of skeletal muscle mass, resulting in the modulation of muscle hypertrophy and muscle wastage. mTOR is upregulated during hypertrophy and downregulated during muscle atrophy. Resistance exercise (RE) is known as a non-pharmacological up-regulator of Akt-mTOR signaling for skeletal muscle hypertrophy. However, the hypertrophic effect of RE and the role of Akt-mTOR signaling to prevent tumor-induced muscle wasting are poorly known. We aimed to investigate the Akt-mTOR pathway contribution to the skeletal muscle wasting prevention promoted by RE in tumor-bearing rats. **Methods:** Muscle atrophy induced by Walker-256 tumor cell injection rats were assigned into 4-week RE. Untrained rats were used as control. RE consisted of climbing a ladder apparatus with weights tied to the animal's tail. Skeletal muscle cross-sectional area was evaluated for atrophy/hypertrophy determination and locomotion capacity and muscle strength were determined as motor performance. Components of Akt-mTOR and ubiquitin-proteasome

pathways were assessed by qRT-PCR or immunoblotting. Two different subsets of rats were used to evaluate the relative contribution of mTOR inhibition (rapamycin) on RE-induced changes in muscle mass regulation and untrained and trained tumor-bearing rats' life-span. **Results:** RE prevented skeletal muscle atrophy and impaired motor performance in tumor-bearing rats. However, while RE alone up-regulated Akt-mTOR pathway components and increase muscle cross-sectional area, no changes in Akt-mTOR pathway and its downstream target p70*S6K* were demonstrated in tumor-bearing exercised rats. In addition, rapamycin treatment did not preclude RE effect on muscle mass of tumor-bearing rats, suggesting the anti-atrophy effect of RE in tumor-bearing rats is independently of Akt-mTOR pathway activation. Indeed, RE prevented increased levels of muscle Atrogin-1 and Murf-1, key regulators of muscle atrophy. RE did not improve tumor-bearing rats' life-span. **Conclusion:** RE prevents tumor-induced skeletal muscle wasting independently of Akt-mTOR activation. The RE preventive effect is probably related to its action in the downregulate of elevated key components of atrophy signaling such as Atrogin-1 and Murf-1 in tumor-bearing rats. Supported by Capes-PVE, Brazil (#88881.068035/2014-01)

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 115

Board #43

Behavioral Analysis of Wheel Running Speed and Wheel Rotations in Orchidectomized C57BL6/j Male Mice

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Routine physical activity has advantageous effects on the eleven organ systems, however, the biological regulation of this phenotypical behavior is complex. Indices of physical activity are typically measured in 24-hour epochs, however, development of inexpensive turn-by-turn wheel running systems allow for a more robust assessment of wheel running patterns. Delineating patterns in wheel running speed and rotation characteristics may provide a better understanding of the regulatory mechanisms—in particular, changes associated with alterations to sex steroid levels. **PURPOSE:** To quantify the dysregulation of wheel running speed patterns following the loss of steroids. **METHODS:** Male C57BL6/j mice (n=28) were acquired at 8 weeks of age. All mice were housed individually with access to running wheels that were monitored on a turn-by-turn basis. Mice were allowed to acclimate to the cage environment and running wheels for ten days before undergoing a surgical procedure. Mice underwent sham (control, n=12; 2 mice were removed from study for health-related reasons) or real (treatment, n=14) bilateral orchidectomy procedures to reduce circulating sex steroid levels and then were allowed ten days to recover from the surgical procedure. Mice were reintroduced to running wheels which continually monitored wheel running distance (km), duration (min), and speed ($m \cdot min^{-1}$). A single day of wheel running was used to assess 24-hour speed average (distance per unit of time for whole 24-hour period), instantaneous speed average (averaged from calculated turn-by-turn instantaneous speeds), single wheel rotations, and percentage of wheel rotations at different speeds (0-15, 15-25, 25-35, 35-45, 45 or more $m \cdot min^{-1}$). **RESULTS:** Wheel running speed calculated with 24-hour averaged data was not significantly different from wheel running speed calculated with instantaneous turn-by-turn speed data [$F(1,23)=2.92$, $p=0.1$] for either group. Single wheel rotations were not different between sham and orchidectomized treated mice [$t(23)=0.03$, p=0.97]. The percentage of wheel rotations was significantly different between sham and orchidectomized [$F(4,92)=4.4$, $p=0.002$] with a shift toward the lower speeds following the loss of sex steroids. **CONCLUSIONS:** Removal of the tissues that act as major producers of the sex steroids in mice did not affect wheel running speed when represented as a 24-hour average—using both the whole 24-hour period and instantaneous speed averaging approach—but alterations to the speed pattern, represented by the percentage of rotations at different speeds, was significantly altered following loss of sex steroids.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 116

Board #44

Cast Immobilization of Mice Hindlimb Induces Fat Tissues Loss and Glucose Metabolism Disorder

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Purpose: Skeletal muscle atrophy is successfully induced in disuse models, such as through cast immobilization. However, the effects of muscle atrophy models on adipose tissues have not been examined. We investigated whether immobilization of the hindlimbs in mice affects adipose tissue weight. **Methods:** In experiment 1, eight-week-old male C57Bl/6J mice were randomly assigned to the control group (CON; n=13) or the cast immobilization group (CAST; n=13). Cast hindlimb immobilization was performed for 14 days. Inguinal white adipose tissue (iWAT), epididymal white adipose tissue (eWAT), interscapular brown adipose tissue (BAT), and gastrocnemius (GAST), soleus (SOL), and plantaris (PLA) muscles were excised for further investigation. Western blotting was performed for quantification of oxidative phosphorylation proteins (OXPHOS). The adipose tissue was pathologically analyzed by hematoxylin and eosin staining. Intraperitoneal glucose tolerance tests and insulin tolerance tests were performed for analysis of glucose metabolism. In experiment 2, we used six, eight-week-old male C57Bl/6J mice and sciatic nerve denervation was performed. After two weeks of treatment, fat tissues and muscles were obtained and tissue masses were measured. **Results:** In experiment 1, feed consumptions were almost the same in both groups during the treatment period. Significantly low activity levels were observed in the CAST group ($P<0.05$). Both muscle and white adipose weights of the CAST were significantly lower than those of the CON group ($P<0.05$). A significantly high content of OXPHOS in eWAT was observed in the CAST group ($P<0.05$). Multiple lipid droplets in iWAT and eWAT cell were observed in the CAST group. Significantly low content of area under the glucose curve in glucose tolerance test was observed in the CAST group ($P<0.05$). In experiment 2, we found that significantly low muscle mass was induced by sciatic nerve denervation. On the contrary, loss of adipose tissues was not observed. **Conclusions:** Cast immobilization of hindlimb decreased not only skeletal muscles but also adipose tissues. The higher content of mitochondria in adipose tissues might be a possible causative factor. Extensive loss of muscle and fat tissues, accompanied by glucose metabolism disorder, suggests that cast immobilization might mimic hypermetabolic states. In addition, afferent and/or efferent nerve projections might be related in this phenomenon.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 117

Board #45

Changes in Ribosomal Content and Muscle protein Synthesis with Increasing Bouts of Electrical Muscle Stimulation

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PURPOSE: In exercise-induced muscle hypertrophy, increased rate of muscle protein synthesis has been shown to play an important part. The muscle protein synthesis is regulated by both the activation of translation and the ribosomal content (Chaillou et al. 2014; Figueiredo et al. 2015). Recently, repeated bouts of electrical muscle stimulation (EMS) training have been shown to cause an increase in ribosome content in the rat skeletal muscle (Ogasawara et al. 2015). However, it remains unclear whether the increased ribosomal content leads to the increased protein synthesis. So we investigate the relation between changes in ribosome content and muscle protein synthesis after repeated bouts of EMS training.

METHODS: Male Sprague-Dawley rats were randomly assigned into three groups: Sedentary (SED), EMS-trained with 1 bout (1B), and 3 bouts (3B). In 3B group, each bout of exercise was given every two days. The gastrocnemius muscle was subjected to EMS training consisting of 50

repetitions of maximal isometric contractions evoked by supra-maximal direct electrical stimulation. The muscle samples were taken 6h after the last session of training and subjected to the measurements of rRNA (ribosomal content) and protein synthesis (SUnSET method).

RESULTS: Ribosome content increased only in 3B group. Muscle protein synthesis was activated with EMS training, but no significant difference was observed between 1B and 3B. Mammalian target of rapamycin (mTOR) signaling pathway, a major regulator of ribosome activity, was attenuated in 3B as compared with 1B.

CONCLUSIONS: Although EMS training caused an increase in ribosomal content when the exercise bout was repeated, it failed to cause an additional increase in the muscle protein synthesis. This would be due, at least partially, to the decline in the translational efficiency through attenuation of mTOR signaling pathway.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 118

Board #46

Dietary Apple Polyphenols Increase Skeletal Muscle Capillaries In Wistar Rats

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BACK GROUND/PURPOSE: Dietary apple polyphenols (AP) have been shown to exhibit beneficial effects on muscle endurance. Fast-to-slow change in the composition of myosin heavy chains (MyHC) was known as one of the molecular mechanisms. Here, we examined the biological effects of dietary AP on muscle endurance, we evaluated the capillary density, mitochondrial content, and mitochondrial protein dynamics of gastrocnemius. Furthermore, the MyHC composition was examined, as reported by Mizunoya et al. (2015).

METHODS: Twenty-four Wistar male rats (9-week old) were maintained at 23 ± 1°C under a 12:12 light/dark cycle. All animals were fed with laboratory chow for 1 week and subsequently divided into the following three groups: 1) 5% AP group (n = 8), 2), 0.5% AP group (n = 8), and 3), the control group (n = 8). Animals were maintained on the diets for 4 weeks and the weight of each animal was recorded after every 2 days throughout the experimental period. After the experimental period, rats were dissected, gastrocnemius muscles were removed. And then, the density of capillaries, levels of mitochondrial proteins and the composition of the MyHC isoforms were analyzed.

RESULTS: We confirmed the amount of food consumed was no significantly difference. The muscle weight of the medial and lateral gastrocnemius muscle revealed no significant difference between the control, 0.5% AP, and 5% AP groups. The relative level of MyHC IIb was significantly reduced along with the compensatory increase in MyHC I and MyHC IIa levels in the group fed with 5% AP. Capillary density of the gastrocnemius increased to 17.8% in rats fed with 5% AP as compared to the control rats. No significant change was observed in the mitochondrial content and dynamics (fusion/fission) of regulatory proteins. To investigate the mechanisms underlying the increase in the capillary density, positive (vascular endothelial cell growth factor, VEGF) and negative (thronbosponsin-1, TSP-1) factors of angiogenesis were analyzed. TSP-1 expression significantly decreased in rats fed with 0.5% AP and 5% AP by approximately 25% and 40%, respectively, as compared with the control rats.

CONCLUSIONS: Dietary AP may increase the muscle capillary density by decreasing TSP-1 expression. The increase in the capillary density and the fast-to-slow change in myosin heavy chains are the main causes for muscle endurance enhancement.

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Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 119

Board #47

Dietary Exosomes Affect Growth and Skeletal Muscle Physiology in Young Male and Female Rats

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Purpose: Exosomes are nanoparticle-sized vesicles which facilitate cell-to-cell communication by transporting molecular cargo throughout the body. Of particular interest is the ability of exosomes to transport microRNA, which may regulate the metabolic pathways of different tissues. Recent studies have shown that exosomes are not only derived endogenously, but also can be obtained from exogenous sources (e.g. milk). Thus, the purpose of this study was to determine the metabolic effects of milk derived exosomes on skeletal muscle in young growing rats. **Methods:** Twenty-eight day old male (n=12) and female (n=12) Fisher 344 rats were used for this study. Half of the male (n=6) and female (n=6) rats were fed a milk based diet containing exosomes (EXO+) or a milk based diet depleted of exosomes (EXO-) for four weeks. Skeletal muscle mitochondria were isolated for respiration measures and ROS emission. Mitochondria volume was determined by measuring citrate synthase activity. Additionally, protein expression of the antioxidants superoxide dismutase 1/2 (SOD1/2), catalase (CAT), and glutathione peroxidase (GPX) and oxidative damage markers for lipid peroxidation (4HNE) and protein carbonyls (OxyBlot) were measured via Western blot. Lastly, total RNA and cross section area were determined in the gastrocnemius. **Results:** At sacrifice, male rats had higher body mass ($p<0.001$), gastrocnemius mass ($p<0.001$), subcutaneous adipose tissue mass ($p<0.001$), and liver mass ($p<0.001$) compared to female rats. There was an interaction (diet*sex) for food consumed ($p<0.001$) and feed efficiency ($p=0.003$) but mass gained was only higher in male rats ($p<0.001$). Total RNA ($p=0.001$) and cross-sectional area ($p=0.022$) of the gastrocnemius were higher in animals fed the EXO- diet. State 3 mitochondrial respiration demonstrated an interaction effect ($p=0.039$) in which EXO+ male rats had the highest respiration rate. No significant differences ($p>0.05$) were observed for ROS emission, citrate synthase activity, antioxidant protein content, or oxidative damage markers. **Conclusions:** Dietary exosomes differentially affect growth in male and female rats, without altering oxidative stress.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 120

Board #48

Effect of Nrf2 Deficiency on Age-related Changes in Skeletal Muscle Mitochondria

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PURPOSE: Oxidative stress and mitochondrial dysfunction are associated with the aging process. However, the role of nuclear factor erythroid 2-related factor 2 (Nrf2) during aging remains to be elucidated. In this study, we examined whether the lack of Nrf2, which is known as a master regulator of redox homeostasis, promotes age-related mitochondrial dysfunction and muscle atrophy in skeletal muscle.

METHODS: Aged (22 months old) Nrf2 knockout (KO) mice and young (4 months old) and age-matched (22 months old) C57BL/6J (WT) mice were used. Quadriceps femoris muscles were extracted for mitochondrial isolation, and subsequent analysis of mitochondrial respiration and reactive oxygen species (ROS) production. Gastrocnemius and tibialis anterior muscles were extracted for mRNA expression and enzyme activity analyses, respectively.

RESULTS: There was no difference in muscle weight between WT and Nrf2 KO mice. The expression of Nrf2-target antioxidant genes was decreased in Nrf2 KO mice. Mitochondrial respiration declined with aging; however, there was no difference between Nrf2 KO mice and age-matched WT mice. Similarly, cytochrome c oxidase activity was lower in aged WT and Nrf2 KO mice compared to young WT mice. The expression of Mfn2 mRNA was lower in Nrf2 KO mice compared to age-matched WT mice. ROS production per oxygen consumed in mitochondria was elevated in Nrf2 KO mice compared to other groups.

CONCLUSIONS: These results suggest that Nrf2 deficiency exacerbates age-related oxidative stress, but does not affect the decline of mitochondrial function in skeletal muscle.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 121

Board #49

Effects of Electric Pulse Stimulation and Heat Stress on Cell Injury in C2C12 Myotubes

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Exertional heat stroke is a life-threatening condition that occurs in individuals performing strenuous physical activity, usually in a hot environment with high incidence in military personnel, occupational workers and athletes. Skeletal muscle injury results in the leakage of muscle cell contents into the circulation which can lead to acute renal failure, coagulopathy and death. **PURPOSE:** To investigate the isolated and combined effects of heat stress and electric pulse stimulation on markers of cell damage, inflammation and heat shock response in cultured murine muscle C2C12 myotubes. **METHODS:** In this proof of concept study, fully-differentiated C2C12 myotubes were exposed to one of the four conditions: 1). Electric pulse (EP): cells were stimulated by EP for 12 hours (h) at 37°C, 5% CO_2; 2). Heat stress (HS): cells were cultured at 37°C, 5% CO_2 for 10 h and treated with heat stress at 43°C for 2 h; 3). EP+Heat stress (EPH): cells were stimulated by EP for 10 h at 37°C, 5%CO_2 and exposed to HS for the last 2 h of EP at 43°C, and 4). Control (CON): cells were cultured at 37°C, 5% CO_2 for 12 h. The electric pulse protocol was set at 1Hz, 11.5V, 2ms pulse width to induce contraction. Culture media and cell lysates were collected at 2, 4 and 8 h of recovery following treatment. Lactate dehydrogenase (LDH) activity in culture media was measured using a colorimetric assay. Expression of heat shock protein 72 (Hsp72) and IκB-α was measured in cell lysates using western blot. **RESULTS:** Preliminary data obtained with this model (n = 3, from independent experiments) show that LDH in culture media from EPH was higher than CON at 2 h (1.6-fold increase, $p<0.01$), 4 h (1.6-fold increase, $p<0.01$) and 8 h (1.8-fold increase, $p<0.05$) of recovery. The LDH levels from EPH were also higher than HS at 2h (1.5-fold increase, $p<0.01$) and 4 h (1.6-fold increase, $p<0.001$), and EP at 2 h (1.8-fold increase, $p<0.001$) and 4 h (1.5-fold increase, $p<0.001$) of recovery. At 8 h of recovery, Hsp72 expression in HS was higher than CON (8.6-fold increase, $p<0.01$). Induction of Hsp72 expression in EPH was 51% lower than in HS ($p<0.05$). Total IκB-α content was also lower in EPH at 8 h of recovery (0.6-fold decrease, $p<0.05$, as compared to CON). **CONCLUSION:** These preliminary data suggest that heat stress combined with electric pulse may suppress the heat shock response and induce higher levels of cell injury and inflammation compared to heat stress or electric pulse alone.
Supported by New Mexico Research Grant from the University of New Mexico.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 122

Board #50

Effects of Moderate Exercise Training on Cancer-Induced Muscle Wasting

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Purpose: Muscle atrophy is a common phenomenon in oncology context and apparently can be mitigate by exercise training. This study aimed to determine the degree of aggressiveness of cancer-induced muscle wasting in two different phenotype muscles, establishing if exercise training can attenuate this muscle dysfunction. **Methods:** Fifty Sprague-Dawley rats were randomly assigned to four experimental groups, two control groups (sedentary and exercised) and two models of breast cancer groups (sedentary and exercised) induced by *1-methyl-1-nitrosoureia* (MNU). After 35 weeks of endurance training the animals were sacrificed and gastrocnemius and soleus muscle were retrieved for morphometric and immunohistochemical analysis. **Results:** A significant reduction in cross sectional area ($P < 0.05$) was found in both muscles of sedentary animals with tumor. Interstitial fibrosis was significantly higher in gastrocnemius of sedentary tumor bearing animals ($P < 0.05$), but not in soleus. A shift from large to small fibers can be observed in gastrocnemius of sedentary animals with tumor. Long-term exercise training was able to prevent this cancer-related muscle dysfunction. **Conclusions:** Gastrocnemius muscle exhibited a very expressive reduction in cross sectional area, and a marked interstitial fibroses in sedentary animals with tumor. Soleus muscle revealed a less expressive reduction in cross sectional area, although significant, and the deposition of collagen was not different between MNU groups. These contrasting results confirm that cancer-induced muscle wasting can affect specific fiber types, and specific muscles, namely the fast glycolytic muscles and that exercise training can act to improve it.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 123

Board #51

Fatigability and Motor Unit Behavior of Lower Limb Muscles in People with Type 2 Diabetes

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People with diabetes mellitus and diabetic polyneuropathy are more fatigable for lower limb muscles during fatiguing tasks, in part due to impaired motor unit properties. Whether people with type 2 diabetes mellitus (T2D) without diabetic polyneuropathy have greater fatigability and differences in motor unit properties is unknown. **PURPOSE:** The aim was to determine the fatigability and motor unit behavior of two lower limb muscle groups (knee extensors and dorsiflexors) in people with T2D and controls.

METHODS: Sixteen people with T2D (8 men; 65.0±5.6 years; 37.8±7.8 %; 8,780±5,070 daily steps) were matched based on age, proportional body fat and physical activity with 16 healthy controls (8 men; 63.6±4.5 years; 34.4±7.0 %; 8,030±3,220 daily steps). Motor unit discharge rate (DR), coefficient of variation (CV) of DR, average torque, and CV of torque of the vastus lateralis and knee extensors or tibialis anterior and ankle dorsiflexors were quantified during submaximal contractions (10% and 40% of maximal voluntary isometric contraction (MVC)) before and after a fatiguing task. The fatiguing task for the knee extensor muscles included a six-minute dynamic, isotonic (20% MVC) fatiguing task (1 maximal kick/3 sec). The fatiguing task for the dorsiflexors was an intermittent, isometric fatiguing task (50% MVC for 6-s followed by 4-s rest until

task failure). Motor units were decomposed from high-density surface electromyography (64-channel) collected during submaximal contractions.

RESULTS: People with T2D had twice the reductions in knee extensor power (56.7±11.9 vs. 31.5±25.5% reduction, P<0.001) and 50% briefer time-to-task failure (7.3±4.1 vs. 14.4±9.1 minutes, P=0.009) relative to controls. During the 10% and 40% MVC tasks, people with T2D had greater CV of force for the knee extensors (3.70±1.48 vs. 3.31±1.18%, P=0.043 and 4.21±5.48 vs. 2.34±0.79%, P=0.005, respectively) and for the dorsiflexors (12.47±10.42 vs. 9.44±4.28%, P=0.027 and 5.31±3.51 vs. 4.20±2.17%, P=0.024, respectively) compared to controls. During the 10% and 40% MVC tasks, people with T2D had a greater CV of DR for the dorsiflexors (19.85±11.08 vs. 18.75±11.43%, P=0.002 and 25.82±10.22 vs. 23.53±9.60%, P<0.001, respectively), but not for the knee extensors (22.94±17.96 vs. 25.15±20.07%, P=0.249 and 26.19±13.70 vs. 30.48±20.00%, P=0.102, respectively) compared to controls.

CONCLUSIONS: Although people with T2D were twice as fatigable for the knee extensors and ankle dorsiflexors, the fatiguing task did not exacerbate differences between the T2D and control groups in motor unit behavior or force fluctuations.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 124

Board #52

Fecal Sex Hormone Quantification and Wheel Running Stability in Male Mice

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Understanding physical activity regulation is essential to diminish the risks associated with deadly diseases, such as heart disease, obesity, and some types of cancer. Research suggests that loss of sex steroids—testosterone and estrogen—alters physical activity patterns in mammals. The successful quantification of hormones during a wheel running task is important to track an organism's endocrine status. Ecological field techniques to quantify sex steroid levels from fecal samples are well characterized and could represent viable options to estimate the endocrine status of caged animals during behavioral analysis of wheel running. **PURPOSE:** To accurately quantify sex hormone levels in fecal material from male mice without affecting normal wheel running activity. **METHODS:** Male C57BL/6j mice (n=10) were acquired and housed individually with *ad libitum* access to food, water, and a running wheel. Mice were divided into experimental (n=5) and control (n=4, 1 removed from study for health-related reasons) groups and underwent an acclimation period (seven days) and a collection period (seven days). The experimental group underwent fecal material collections twice during the second week of study. During fecal collection, experimental mice were housed without bedding for 24 hours to facilitate recovery of fecal pellets. The fecal material was dried at 67°C for 24 hours. Following pulverization, 500mg of fecal material was added to 6 ml of 100% methanol. The samples were mixed on a nutating rocker and centrifuged. The supernatant was collected and the remaining methanol was evaporated overnight. Following the experimental period, all mice were euthanized and terminal blood draws were used to collect serum samples for sex steroid analysis. A testosterone enzyme linked immunosorbant assay kit was used to quantify testosterone concentrations in fecal material compared to blood serum testosterone concentrations. Wheel running distance (km), duration (min), and speed ($m \cdot min^{-1}$) were monitored using a turn-by-turn wheel running system during the length of the study. **RESULTS:** Wheel running distance [$F(1,7)=0.9$, $p=0.4$], duration [$F(1,7)=0.1$, $p=0.7$], and speed [$F(1,7)=0.4$, $p=0.6$] were unaffected by the fecal sampling techniques employed in this study. Fecal testosterone levels were quantified successfully in mice. **CONCLUSIONS:** Testosterone concentrations were successfully quantified from fecal material and wheel running stability was maintained throughout the entire study. The use of ecological detection techniques for quantification of fecal sex steroids levels in caged mice allows low-impact monitoring of steroid levels during wheel running.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 125

Board #53

Greater Muscle Loading During Maximal Eccentric-Concentric Training Is No More Hypertrophic than Maximal Concentric Training

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PURPOSE: High-load eccentric exercise training reputedly produces greater muscle hypertrophy than high-load concentric training, presumably from the greater loading and/or inflammation achieved by the former. We quantified the temporal effect of combined maximal voluntary eccentric and concentric exercise training on muscle cross-sectional area, volume and abundance of muscle mRNAs compared with maximal voluntary concentric training.

METHODS: Eight resistance-trained males (25.9 ± 1.6 years, BMI 23.6 ± 0.9) performed 3x30 maximal eccentric isokinetic knee extensions, interspersed with 2x30 maximal concentric knee extensions (90°/s 3x/week) for 84 days using one limb (ECC+CON), and 5x30 maximal concentric contractions (same contraction speed and frequency) with the contralateral limb (CON). Mid-thigh muscle CSA and thigh muscle volume (50 CSAs) were determined at baseline, and day (d) 7, 28 and 84 using 3T MRI. Resting vastus lateralis biopsies were obtained at baseline, on d1, and a minimum of 72 hours from the previous exercise session on d7, d28 and d84 for mRNA abundance measurement (RTPCR micro-fluidic cards). Statistical differences were determined by 2-way ANOVA; Sidak's post-hoc test performed to locate differences. Data are mean ± SEM; significance accepted at $p<0.05$.

RESULTS: Total work done during each week of training was greater in ECC+CON than CON (data not shown) and over the whole period of training (16.8 ± 2.3%; $p<0.001$). Muscle CSA increased from baseline in both limbs at d28 (CON 4.3 ± 0.9%, $p<0.05$; ECC+CON 4.0 ± 0.7%, $p<0.05$) and d84 (CON 3.9 ± 0.8%, $p<0.05$; ECC+CON 4.0 ± 1.1%, $p<0.05$). Similarly, thigh muscle volume increased from baseline at d28 (CON 3.1 ± 0.8%, $p<0.05$; ECC+CON 3.1 ± 0.4%, $p<0.05$) and d84 (CON 3.9 ± 0.8%, $p<0.05$; ECC+CON 3.4 ± 0.7%, $p<0.05$). However, there was no difference between limbs in muscle CSA or thigh volume at any time-point. Change in muscle mRNA abundance from baseline was overall greater in ECC+CON than CON at d1 and d7, with a number of cellular functions (including inflammation and morphology) identified as being altered. However, change in mRNA abundance from baseline and between CON and ECC+CON waned by d28 and thereafter.

CONCLUSIONS: Muscle mRNA responses to resistance-exercise training are transitory. Compared to maximal CON training, maximal ECC+CON exercise produces greater mRNA abundance changes over the initial week of training and greater muscle loading throughout. This is not however associated with greater muscle hypertrophy, supporting the suggestion from acute studies that muscle protein synthesis is maximal at workloads equivalent to ~80% 1 repetition max. Funded by BBSRC grant BB/I020713/1.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 126

Board #54

Honeybee Products Attenuate Capillary Regression In Skeletal Muscle Under Disuse Condition

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PURPOSE: A capillary network in skeletal muscle is essential for delivery of nutrients and oxygen. Although the loss of skeletal muscle mass is well documented under disuse condition, the muscle capillary also regress. In

addition, exercise training often is used as a countermeasure to reduce the muscle atrophy. However, the training has minimal effect on the capillary regression under disuse condition. Therefore, we investigated that honeybee products would attenuate capillary regression of skeletal muscle during disuse.

METHODS: Forty-two male Wistar rats were assigned randomly either to a control (CON), CON with propolis (PP), hindlimb unloading (HU), HU with propolis (HU+PP), HU with royal gelly (HU+RJ), or HU with DHA/EPA (HU+DHA) supplementation group for 14 days. The capillary volume and capillary-to-fiber (C/F) ratio in soleus muscle were measured using a confocal laser scanning method. The pro-angiogenic factors (VEGF, Flt-1 and KDR/Flk-1) and anti-angiogenic factor (thrombospondin-1), and oxidative stress maker (SOD-1) were also determined.

RESULTS: Unloading condition resulted in capillary regression of skeletal muscle. The capillary volume and C/F ratio in HU were lower than those in CON. PP attenuated the decrease of capillary volume and C/F ratio in HU. RJ and DHA could not attenuate the decrease of those in HU. In addition, the expression levels of VEGF and KDR/Flk-1 in PP were higher than those in HU. Furthermore, the expression levels of thrombospondin-1 and SOD-1 in PP were attenuated.

CONCLUSIONS: These data suggest that propolis may be an effective treatment to counter the detrimental effects of a chronic decrease in skeletal muscle use on the muscle capillary. *Supported by Grants-in-Aid for Scientific Research from Japanese Ministry of Education, Culture, Sports, science and Technology, and Yamada Research Grant.*

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 127

Board #55

Metabolic and Muscular Fatigue in Obese Subjects

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Purpose: Muscle fatigue is an exercise-induced reduction in the ability to voluntary produce force or power. It may arise not only because of peripheral changes at the level of the muscle, but also because the central nervous system fails to drive the motoneurons adequately2. Obese (Ob) subjects show higher isokinetic torque fatigue but same isometric stimulated fatigue compared with non-obese (NOb)1 ones. Moreover, Ob have similar peak oxygen consumption (V'O2 Peak), when expressed as absolute value but lower V'O2 Peak when the value is normalized for the lower limb fat free mass and maximal work rate3. Hence Ob show lower muscular metabolic efficiency compared to NOb.

Then, in the present study we investigated the main metabolic and muscular factors which may limit performance in Ob and NOb subjects, during maximal incremental test on Cycle Ergometer (CE) and on single leg Knee Extension (KE) ergometer.

Methods: 15 Ob (age 25±10 y, BMI 43±7 kg/m2) and 13 NOb subjects (age 27±10 y, BMI 22±3 kg/m2) participated in this study. V'O2 and Cardiac Output (CO) were measured during CE and KE. Maximal voluntary contraction (MVCs) of knee extensor muscle were performed before and immediately after the two incremental tests.

Results: Peak V'O2 (mL min-1) and CO (mL min-1) were significantly higher ($p<0.05$) in CE than KE with no differences between Ob and NOb (V'O2 CE: Ob 2.68±0.68, NOb 3.04±0.65; V'O2 KE: Ob 1.36±0.51, NO 1,15±0.26) (CO CE: Ob 20.48±6.34, NO 19.62±4.25; V'O2 KE: Ob 15.74±6.23, NO 12.00±2.45). Maximal work rate (W) was lower in Ob than NOb (191±38 vs 226±39, $p<0.05$) in CE but similar between two groups in KE (62±13 vs 61±14, $p>0.05$) The MVC reduction after CE was lower in Ob compared with NOb (14±13 vs 26±16%, $p<0.05$), while KE was the same (32±11 vs 32±18%).

Conclusions: The limiting factor during KE should reside in the muscle for both the groups, instead the performance during CE might be limited due to central mechanisms. This is particularly true for Ob where cardio respiratory system might have played a role in determining the cessation of CE as it can be evinced by a lower MVC reduction at exhaustion compared to the one produced after KE.
The study was supported by Municipalities of Gemona del Friuli (Udine, Italy)

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Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 128

Board #56

Myofibrillar Response to Low-load Blood Flow Restricted Resistance Exercise versus Heavy Resistance Exercise

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Purpose: Muscle contractile properties represent one major constituent of muscle health of great importance for muscle function and whole-body health. However, various chronic disorders may infer a decay in muscle contractile properties and compromise muscle health. While heavy-load resistance exercise (HRE) is widely appreciated to counteract such decay, low-load alternatives may be more feasible in clinical settings. This study investigated the myofibrillar response to low-load blood flow restricted exercise (BFRE) versus HRE in a randomized controlled fashion. **Methods:** 34 untrained male subjects (24±3 yr.) were randomized to 6 weeks of either BFRE, HRE or non-exercise control intervention performed 3 x week. Biopsies were collected from v. lateralis pre- and post- intervention. During the intervention, deuterium oxide was orally administered to evaluate long-term muscle protein synthesis (MPS) and RNA fractional synthesis rate (FSR) as a proxy for ribosomal biogenesis. Also, muscle fiber cross sectional area (CSA), satellite cell (SC) and myonuclear responses were evaluated by immunohistochemistry. Functional outcomes comprised dynamic strength (1RM) and isometric maximal voluntary contraction (MVC). **Results:** Both exercise regimens effectively increased long-term MPS as well as RNA FSR compared to control condition. Correlations were observed between MPS and RNA FSR ($p<0.001$) as well as RNA FSR and relative changes in total fiber CSA ($p<0.05$). No apparent increases were observed in neither fiber type-specific CSA nor myonuclear responses, with either training modality. However, when pooling exercise groups and analyzing myocellular outcomes based on clustering of low (n=13) versus high (n=9) responders with regards to changes in total fiber CSA, high responders displayed greater increases in RNA FSR, while selectively increasing overall SC content and myonuclear domain-size. Both modes of exercise increased MVC and 1RM compared to controls, with HRE accentuating the increase in 1RM compared to BFRE. **Conclusion:** We report that 6 weeks of BFRE as well as HRE, effectively augments long-term MPS and stimulates RNA synthesis, with the latter presumably indicating ribosomal biogenesis. Notably, BFRE entailed a substantially lower mechanical load compared to HRE, providing important clinical implications in settings where heavy loading may be unattainable. Supported by Novo Nordisk Foundation (NNF15OC0016674), NIH (R01-AG042569), and Aarhus University Research Foundation (AUFF-E-2O15-FLS-7-32).

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 129

Board #57

Pantothenate Kinase 4 Is A Novel Exercise-responsive Protein That Increases Glucose Uptake Into Skeletal Muscle

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PURPOSE: The signaling pathways that regulate glucose uptake during aerobic exercise are not fully elucidated. Here we investigate whether pantothenate kinase 4 (PanK4) is an exercise-responsive signaling protein that regulates glucose uptake in skeletal muscle.

METHODS: The phosphorylation of PanK4 at the Ser-63 residue (p-PanK4) was measured in skeletal muscle following aerobic exercise in humans and mice. p-PanK4 was also measured after in vitro and in situ contractions, stretch, AMPK activation and Ca2+ modulation in mouse skeletal muscle. Glucose uptake following rAAV-mediated overexpression of PanK4 in mouse skeletal muscle was determined.

RESULTS: A single bout of aerobic exercise increased p-PanK4 in both human and mouse skeletal muscle. Both in situ contractions, via electric stimulation of the sciatic nerve, and in vitro contractions increased skeletal muscle p-PanK4. In vitro, neither passive stretching nor AICAR-induced AMPK activation induced p-PanK4, while increasing cytosolic calcium concentrations augmented p-PanK4. Notably, overexpression of PanK4 was sufficient to increase glucose uptake into skeletal muscle by 80%. This effect was absent when a PanK4 mutant lacking a functional Ser-63 phosphorylation site was overexpressed.

CONCLUSIONS: PanK4 is a novel exercise-responsive protein that increases glucose uptake in skeletal muscle.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 130

Board #58

Pericyte Transplantation Improves Skeletal Muscle Recovery Following Hindlimb Immobilization

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Background: Physical inactivity and limb immobilization can result in significant losses to skeletal muscle mass and strength. Unfortunately, rehabilitation may not be sufficient to fully stimulate muscle recovery, especially in older adults. Pericytes ($NG2^+CD31\text{-}CD45^-$ (Lin^-) and $CD146^+Lin^-$) are perivascular stem/stromal cells that are able to recover injured tissues; however, their contribution and efficacy in enhancing muscle growth following immobilization is unknown. **Purpose:** The purpose of this study was to determine the contribution of pericytes to skeletal muscle recovery following hindlimb immobilization. **Methods:** 3-4 month-old male C57BL/6 mice (n=11-12) were immobilized by unilaterally stapling the foot in full dorsotibial flexion in order to atrophy the tibialis anterior (TA) muscle. After 14 days, the immobilizing staple was removed. $NG2^+Lin^-$ and $CD146^+Lin^-$ pericytes (n=5-6) or an equal volume of PBS (n=5-6) was immediately co-injected into the atrophied TA muscle. The contralateral leg received PBS injection only. Mice were remobilized for 14 days, after which TA muscles were then dissected, weighed, and frozen for histological analysis. **Results:** Myofiber cross sectional area was significantly recovered in the atrophied TA with pericyte transplantation compared to contralateral control, while deficits remained in PBS injected mice ($p=0.01$). Capillary-to-myofiber ratio and capillary density were both significantly increased with pericyte transplantation compared to contralateral control ($p<0.05$). No changes to muscle collagen content, inflammation, or muscle repair/regeneration were observed following transplantation and remobilization ($p>0.05$). Transplanted pericytes appeared to be localized to the interstitium and no evidence of fusion was present. **Conclusion:** These findings suggest that pericyte transplantation immediately prior to remobilization can significantly improve muscle recovery following disuse.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 131

Board #59

Perivascular Stem/Stromal Cell Regulation of Muscle Growth

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PURPOSE: An acute bout of resistance exercise can initiate skeletal muscle remodeling and adaptive mechanisms that can confer protection from damage and enhanced strength post-training. The myofiber may provide the primary origin for adaptation, yet multiple mononuclear cell types within the surrounding connective tissue may also contribute. The primary purpose of this study was to determine the extent to which pericytes contribute to myofiber growth in response to electrical stimulation (e-stim). **METHODS:** Mice were divided into 3 groups: total control, mice that received intramuscular (i.m.) injection of PBS, and mice that received i.m. injection of CD146+CD45-CD31- (CD146+Lin-) pericytes. Injected mice were subjected to unilateral e-stim (2x/wk for 4 wks). Gastrocnemius-soleus complexes and TA muscles were dissected 24 hr following the final session, and analyzed for fiber cross sectional area (CSA) and vascular growth. Additionally, CD146+Lin- pericytes were evaluated via multiplex flow cytometry and high throughput qPCR. **RESULTS:** Pericyte quantity was not significantly altered by acute e-stim, yet gene expression was highly upregulated. The gene signature of CD146+Lin- pericytes suggests significant involvement in extracellular matrix turnover, myogenesis, and vascular growth.. Peak torque of the CD146+Lin- pericyte transplanted mice was significantly higher compared to the PBS controls. Capillary density and capillary-to-fiber ratio were significantly elevated compared to controls ($P<0.05$). The fiber CSA of the pericyte transplanted mice was enhanced with e-stim, yet not significantly increased compared to controls. **CONCLUSIONS:** The results from this study suggest that CD146+Lin- pericytes are highly responsive to contraction, and transplantation of these cells in combination with exercise may positively influence skeletal muscle adaptation. Supported by NIH 1 R21 NS104293

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 132

Board #60

Resveratrol Improves NRF2:KEAP1 and Restores Torque Production in Alcoholic Muscle Following Injury

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Purpose: Chronic alcohol abuse may produce muscle atrophy and weakness, elevated oxidant stress, anabolic resistance, and impaired regenerative capacity following injury. Significant research efforts have implicated several signaling pathways that drive alcoholic myopathy. Unfortunately, mechanisms that regulate skeletal muscle regeneration in a model of underlying chronic alcohol abuse have not been explored. This distinction is clinically relevant as alcoholics are more likely to suffer from skeletal muscle injuries due to peripheral neuropathies and sensory decrements, discoordination and falls, or increased risky behaviors.

Methods: Male, C57BL/6 mice were provided alcohol (EtOH, 20% v/v) in their drinking water for 12 weeks. Subgroups of these alcoholic mice also had their water supplemented with resveratrol (RSV, 0.1% w/v) for 12 weeks. After 10 weeks on these treatments, tibialis anterior (TA) muscles were injured using intramuscular injections of $BaCl_2$ (1.2% v/v). Regenerating muscles were collected and processed for analyses at 7

and 14 days post-injury. Muscles were analyzed for regenerating TA fiber area and dorsiflexor torque production. Muscles were also analyzed for total antioxidant capacity and NRF2:KEAP1 content, an upstream marker of antioxidant response element (ARE) signaling.

Results: Twelve weeks of chronic alcohol ingestion reduced NRF2:KEAP1 content in the TA which may partially explain the decreased total antioxidant capacity. Further, regenerating TA fibers had decreased CSA with concomitant reduction to dorsiflexor torque production. Resveratrol increased NRF2:KEAP1 content 7 days post-injury and normalized total antioxidant capacity 14 days post-injury. While regenerating TA fiber area and dorsiflexor torque production from EtOH+RSV mice were still decreased compared to control, alcohol-naïve mice, supplementation trended to improve both outcomes when compared to untreated, alcoholic mice.

Conclusions: These data suggest that RSV may improve antioxidant status potentially by impacting the NRF2:KEAP1 relationship and help to restore normal skeletal muscle structure and function following injury in alcoholic mice. Supported by K01AA017190 to JSO.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 133

Board #61

Role Of Estrogen Receptorβ In Skeletal Muscle

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Purpose: Estrogens have crucial roles in an extensive range of physiological function regulating cellular proliferation and differentiation, development, homeostasis, and metabolism. Estrogen insufficiency induced by amenorrhea triggers various pathologies such as skeletal muscle atrophy and osteoporosis. We previously reported that estrogens were essential for maintaining muscle function with its insufficiency affecting muscle strength and regeneration in young female mice (Kitajima et al, 2016). However, it remains unclear how estrogen-insufficiency influences myofiber- and satellite cell- functions in female. Estrogen receptor (ER) exists in two main forms, ERα and ERβ which are expressed in skeletal muscle. Although ERα plays a critical role in the maintenance of muscle mitochondria, the role of ERβ in muscle is unknown. Here we comprehensively determined the function of ERβ in muscle homeostasis. **Methods:** To inactivate ERβ in myofibers or satellite cells, doxycycline-driven myofiber-specific Cre (ACTA1-rtTA;tetO-Cre) expressing mice or Pax7Cre^{ERT2} mice(Lepper and Fan Genesis 2010) were crossed with ERβ-floxed mice (termed as ERβ-mKO, ERβ-scKO, respectively). **Results:** ERβ-mKO exhibited a slight reduction of muscle mass and force generation in young female mice, whereas there was unchanged in middle-aged mice. ERβ-scKO mice displayed a severe defect in muscle regeneration with marked fibrosis and lipid accumulation after muscle injury. Ex vivo culture analysis revealed an impairment of proliferation ability in satellite cells lacking ERβ. **Conclusions:** These results suggest that ERβ of myofibers plays a role in the maintenance of muscle function in growth stage but not in post-growth stage in female mice, while ERβ in satellite cells is indispensable for muscle regeneration. This work was supported by AMED and JSPS

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 134

Board #62

Scrib Is Required For Skeletal Muscle Hypertrophy Following Mechanical Overload

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PURPOSE: Scribble (Scrib) is a major cell-polarity protein that plays a crucial role in maintaining cell adhesion and preventing outgrowth of epithelial cells. We have previously reported that Scrib controls myogenic progression of satellite cells and is indispensable for muscle regeneration (Ono et al. 2015. Cell Rep). We also revealed that Scrib protein is upregulated during myogenic differentiation. The present study is aimed to determine the function of Scrib in adult myofibers.

METHODS: We investigated the effect of ablation of Scrib on skeletal muscle using constitutive muscle-specific Scrib-deficient (Scrib-mKO) mice (*Mlc*$^{Cre/+}$;*Scrib*$^{fl/fl}$).

RESULTS: Scrib-mKO mice grew normally and did not display significant phenotypes in muscle. However, RNA-seq revealed that stimulus-responsive genes were remarkably altered in muscle lacking Scrib and so we induced chronic mechanical overload on the plantaris muscle using synergist muscle ablation. While wild-type mice exhibited an increase in cross-sectional area of the plantaris after 2 weeks of overload, the hypertrophic response was attenuated in Scrib-mKO mice. Protein synthesis and muscle hypertrophy are regulated by Akt/mTOR/S6K signaling, which was insufficiently activated in Scrib-deficient muscle following overload.

CONCLUSIONS: Scrib not only acts as a regulator of satellite cell-fate decisions, but also has an important role in mediating hypertrophic growth following mechanical overload.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 135

Board #63

Sex-Dependent Differences in Voluntary Exercise Volume and Cardiorespiratory Adaptations in Young and Aged Mice

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Previous studies have demonstrated sex and strain differences in voluntary running wheel activity in young mice. For example, across all strains studied, female mice ran on average 20% farther than males over 3 weeks with greater differences observed in C57BL mice. However, it is unknown if sex dependent differences in voluntary exercise are maintained throughout the lifespan. Further, it is unclear if differences in voluntary running distance are associated with differences in cardiorespiratory adaptations assessed by a treadmill test. **PURPOSE:** These experiments tested the hypothesis that young (3-4 months old) and aged (22-24 months old) female C57BL mice will have greater voluntary exercise volume than C57BL male mice, but both sexes will increase cardiorespiratory endurance after training. **METHODS:** Cardiorespiratory adaptations were assessed with maximal treadmill tests before and after 14 days of unlimited access to running wheels (RW, n=12-15/group) or normal cage activity (CON, n=10-12/group). During the maximal treadmill tests, speed was gradually increased until voluntary exhaustion. **RESULTS:** Both young and old females ran significantly farther than males over 14 days (Young: 69745±6743 vs. 37719±4782 AUC, Old: 30407±4227 vs. 6845±1524 AUC, respectively, $p<0.05$). In young and old mice, females ran ~50 and 75% longer than males per day, respectively. Young mice ran significantly farther than old mice independent of sex. In young CON groups, female mice maximal treadmill test time increased from 873±170 to 1089±191 seconds and decreased in males from 619±116 to 492±99 seconds. In young RW groups, female mice maximal treadmill test time increased from 803±153 to 1448±127 seconds and in males from 692±124 to 1006±185 seconds ($p<0.05$). In old CON groups, female mice maximal treadmill test time increased from 194±46 to 270±66 seconds and in males from 324±26 to 343±59 seconds. In old RW groups, female mice maximal treadmill test time increased from 371±37 to 776±99 seconds and in males from 307±26 to 469±89 seconds ($p<0.05$). **CONCLUSIONS:** These findings demonstrate that sex-related differences in running wheel exercise volume are maintained with aging; however, as a percentage of distance run the differences are increased with age. All male and female RW groups significantly increased maximal test time from pre to post. However, the greater RW distance in females was associated with greater increases in test time compared to males especially in aged mice.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 136

Board #64

Shear Elastic Modulus as a Marker of Peripheral Fatigue During Maximal Isometric Contractions in Humans

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PURPOSE: The aim of this study was to investigate whether resting *Vastus Lateralis* (VL) muscle shear elastic modulus (μ) evaluated by Share Wave Elastography is a good indicator of peripheral fatigue during repetition of isometric Maximal Voluntary Contractions (MVC) of the Knee Extensor (KE) muscles.

METHODS: Eight healthy well-trained males (29 ± 2.6 y; 74 ± 5.2 kg; 1.70 ± 0.07 m) repeated 60 isometric MVC of the KE muscles (6 x 10-MVCs; 5-s on/5-s off). Single and double electrical stimulations were delivered to the femoral nerve every ten MVCs during contractions and at rest. The amplitude and properties of the potentiated single (Tw_{pot}) and double evoked torque and the VL concomitant compound action potential amplitude were considered as indicators of peripheral fatigue. The resting VLμ was measured during a 5-s period at rest after each MVC and evoked electrical stimulation series in a potentiated state. The KE voluntary activation level was then calculated and was considered as an indicator of central fatigue.

RESULTS: Resting VLμ was also significantly decreased (-21.8 ± 3.9%; P<0.001) at the end of the fatigue protocol. It was decreased from the 10th MVC to the end of the exercise (60th MVC) for all participants, with a loss ranging from -18 to -29%. A 44% decrease in MVC was also observed after 60 repetitions (P<0.001). The potentiated doublet and the single twitch torque (Tw_{pot}) decreased by 42.5 ± 10.8% and 55.7 ± 8.8% respectively at the end of exercise (P<0.001 for both). Relative mechanical properties of Tw_{pot}, i.e., electromechanical delay (P<0.001), contraction time (P=0.004) and maximal rate of torque development/relaxation (P<0.001), were also significantly modified during exercise. The voluntary activation level was decreased by -8.7 ± 8.8% (P=0.015). **CONCLUSIONS:** This study shows that kinetics of resting VLμ is associated with changes in both voluntary and evoked torque amplitudes and electromechanical properties of the single twitch during the repetition of maximal voluntary fatiguing exercise. Changes in resting VLμ could reflect the decline in muscle function, e.g., impairments of the excitation-contraction coupling, the contractile processes and/or the elastic properties, across an increase of muscle compliance affecting directly force transmission.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 137

Board #65

Skeletal Muscle-specific Rac1 Knockdown Does Not Prevent Diaphragm Weakness In Mice With Chronic Heart Failure

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PURPOSE: Exercise intolerance and dyspnea are the main characteristics of heart failure. In patients with chronic heart failure with reduced ejection fraction (HFrEF), exercise intolerance and dyspnea are caused, in part, by diaphragm muscle weakness. The mechanisms of diaphragm weakness in HFrEF are not fully clear, but our previous study suggest that a causative role of up-regulation of NADPH oxidase 2 (Nox2) subunits and excess reactive oxygen species production. The protein Rac1 is among the Nox2 subunits required for enzyme activation and is up-regulated in diaphragm (whole tissue) of patients and mice with HFrEF. Our goal in this study was to determine the role of skeletal muscle fiber-specific Rac1 in diaphragm weakness caused by HFrEF.

METHODS: We crossed Rac1 floxed mice with skeletal muscle specific inducible Cre recombinase flanked by two mutated estrogen receptors driven by a human α-skeletal actin (HSA) promoter. To elicit skeletal muscle specific Rac1 knockdown (SkM-Rac1^{KD}), we injected a single dose of tamoxifen (40 mg/kg ip) in adult mice. Control animals received equal volume of vehicle (sunflower oil). Animals underwent sham surgeries or ligation of the coronary artery to cause myocardial infarction and induce HFrEF. We completed terminal experiments 12 weeks post-surgery in 11-13 mice per group).

RESULTS: Tamoxifen injection elicited a 30% decrease in diaphragm Rac1 protein abundance in HFrEF mice ($p < 0.05$). Animals that underwent MI surgery showed diminished fractional shortening in Controls (Sham: 37 ± 8 %, HFrEF: 21 ± 7 %; $p < 0.05$) and SkM-Rac1^{KD} (Sham: 38 ± 5 %, HFrEF: 26 ± 7 %; $p < 0.05$). HFrEF mice also had right ventricle hypertrophy evident from increased ratio of right ventricle weight-to-tibia length (mg/mm) in Controls (Sham: 1.8 ± 0.1, HFrEF: 2.4 ± 0.2; $p < 0.05$) and SkM-Rac1^{KD} (Sham: 1.8 ± 0.2, HFrEF: 2.1 ± 0.2; $p < 0.05$). HFrEF caused a similar decrease in maximal diaphragm isometric force in Controls (Sham: 27 ± 3, HFrEF: 23 ± 5 N/cm^2; $p < 0.05$) and SkM-Rac1^{KD} (Sham: 27 ± 2, HFrEF: 23 ± 2 N/cm^2; $p < 0.05$).

CONCLUSIONS: Our data show that knockdown of Rac1 in diaphragm fibers does prevent loss of specific force caused by HFrEF. These findings suggest that up-regulation of Rac1 in diaphragm muscle fibers is not required to cause diaphragm weakness in HFrEF.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 138

Board #66

Urolithin A as a Novel Intervention to Reverse Age Associated Mitochondrial Health Decline in Skeletal Muscle

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PURPOSE: Muscle health declines with aging and is accompanied by poor mitochondrial function. There is currently no effective treatment for improving the age related decline in muscle health. Strategies targeting improvements in mitochondrial health are being pursued to improve muscle function. One such novel intervention that has recently been identified is Urolithin A (UA). UA is a metabolite produced by the gut microflora upon ingestion of ellagitannins, that are abundant in pomegranates and nuts. UA induces mitophagy *in vivo* following oral consumption in worms and in rodents (Ryu et al., *Nature Medicine* 2016). In worms, UA extends lifespan, prolongs normal activity, including mobility and maintains mitochondrial respiratory capacity during aging. These effects translate to rodents, where UA improves exercise capacity in different models of age-related muscle decline.

METHODS: To further translate the reported observations in pre-clinical models, UA and it's impact on mitochondrial biomarkers were evaluated in a placebo controlled, double-blind, randomized clinical trial. 36 healthy elderly male and female volunteers (12 males and 24 females, with a mean age of 66.4 ± 4.9 years) were randomized (9 subjects/group) to receive 250 mg, 500 mg, 1000 mg of UA or placebo daily for 28 days. UA was administered orally, in fasting conditions before breakfast. Plasma and muscle biopsies were collected before and after dosing to investigate the effects of UA on muscle gene expression and on the metabolomics profile. To evaluate the impact of UA directly on the skeletal muscle, a series of genes related to autophagy/mitophagy, mitochondrial biogenesis and fatty acid oxidation were selected and assessed via qPCR. Mitochondrial abundance was also evaluated by measuring mitochondrial DNA over nuclear DNA ratio by qPCR. Microarray analysis was performed on the RNA from *vastus lateralis* and analyzed using gene set enrichment analysis (GSEA) to look for over-representation of known pathways and gene functional categories. **RESULTS:** There was a dose-dependent up-regulation for the expression of mitochondrial pathway genes after 28 days of treatment with UA along with a trend in increased mtDNA. UA treatment at 500 and 1000mg doses upregulated several mitochondrial genesets

with a FDR<0.25. In the plasma compartment, we observed a dose-dependent decrease of acylcarnitines levels (C8 to C14 and <C20), with UA treatment. **CONCLUSIONS:** These results demonstrate a successful translation of the effects of UA on mitochondrial health in elderly along with a conservation of the mechanism of action from pre-clinical models to humans.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 139

Board #67

Voluntary Wheel Running Prevents Skeletal Muscle Atrophy and Mitochondrial Dysfunction in Cancer Cachexia Mice

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PURPOSE: Cancer cachexia is characterized by systemic negative balance of protein and energy metabolism that result in involuntary progressive losses of skeletal muscle mass and metabolic dysfunction. Even though physical exercise has been suggested as an effective treatment for counteracting cachexia progression, the precise molecular regulation of muscle protein and energy metabolism remains largely unknown. For identifying the regulatory mechanisms involved in the physical exercise-mediated maintenance of skeletal muscle mass and energy metabolism, the effects of voluntary exercise in cachexia mice were investigated. **METHODS:** Cancer cachexia was induced by the subcutaneous grafting of colon carcinoma (C26) cells into the abdominal wall of 7-week old, CD2F1 male mice. Access to the running wheel was allowed immediately after tumor grafting. Four weeks following tumor grafting, animals were sacrificed, and tissue samples were collected. All experimental procedures performed in this study were approved by the Animal Ethics and Research Committee of the Health Sciences University of Hokkaido. **RESULTS:** The C26-bearing mice that did not have access to a running wheel showed a cachexia phenotype that included decreased body weight and skeletal muscle mass, and showed an increased expression of Atrogin1 protein and diminished activation of mechanistic target of rapamycin (mTOR) signaling. Expression of mitochondrial proteins involved in oxidative phosphorylation and mitochondrial fusion (Opa1 and Mfn1) were also diminished. On the contrary, the loss of muscle mass and mitochondrial dysfunction induced by C26 grafting were rescued in mice that had access to voluntary wheel running. The induction of Atrogin1 was prevented, and voluntary exercise also remedied the cachexia-induced suppression of mTOR signaling and PGC1a expression. **CONCLUSIONS:** These observations suggest that therapeutic intervention with physical exercise can release the cachexia-induced retardation of muscle protein metabolism and mitochondrial dysfunction which then contributes to the maintenance of skeletal muscle mass and function. Supported by JSPS KAKENHI Grant Number-25702041, 26560369 and 17K18040 to MM.

Hot topics in exercise physiology

Presentation Number: 140

Board #68

Translational Science at ACSM: Does the Science of Integrative Physiology Fit within ACSM's Newest Journal?

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Translational research covers a broad spectrum of science, from basic to implementation and policy change. Increasingly, scientists, clinicians, public health professionals, and funding agencies are recognizing the importance of scientific investigations that bridge traditional gaps between basic, clinical, community, and policy research. The American College of Sports Medicine (ACSM) recognizes the importance of this work and, in 2016, launched the Translational Journal of the American College of Sports Medicine (TJACSM). **PURPOSE:** We aim to inform attendees about the mission, vision, and scope of TJACSM. Further, we hope to clarify the types of research that TJACSM seeks to publish, to feature the most successful published articles to date, and to elucidate how the integrative physiology of exercise, as a content area, fits within the scope of this journal. **METHODS:** Utilizing the journal's webpage and the publisher's (Wolters Kluwer Health) annual reports, we identified information related to the journal's scope, availability and reach, and the number of reads and views of top articles. **RESULTS:** ACSM electronically publishes 24 issues of TJACSM per year and it is currently available in 2,154 institutions. The journal site had 22,879 visits during 2017 and approximately 48% of the journal's reach is outside the United States. Top viewed articles have covered topics such as the translational gap between the laboratory and playing field, the potential impact of sitting on mortality, exercise and breast cancer, and the association between aerobic fitness and academic achievement among elementary school youth. **CONCLUSION:** There is a desire to grow this journal to include all aspects of the translational science spectrum in exercise science, sports performance, and sports medicine. The integrative physiology of exercise, as an example, represents a content area that is currently under-represented in this journal but fits well within the scope of TJACSM. In addition, as an on-line journal, it provides a great deal of flexibility to respond to creative proposals. For example, scientific findings presented at this conference could be considered for a themed issue or a linked volume. Presenters are encouraged to discuss their research and ideas for innovative papers with TJACSM representatives to determine whether their work is appropriate for submission to TJACSM.

Cardiovascular exercise physiology

Presentation Number: 141

Board #1

All-Extremity Aerobic Exercise Training Improves Endothelial Function in Adults with Type 2 Diabetes

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PURPOSE: Type 2 diabetes is associated with endothelial dysfunction which predisposes patients to cardiovascular disease. Aerobic exercise may be an effective strategy for reversing endothelial dysfunction, but data in adults with type 2 diabetes are limited and conflicting. Moreover, exercise interventions commonly use lower extremity modalities. The purpose of this study was to examine the effect of all-extremity aerobic exercise on endothelial function in adults with type 2 diabetes.

METHODS: A total of 26 adults with type 2 diabetes (mean±SE: 64±2 yrs), who were sedentary, non-smokers and free of overt cardiovascular disease, participated in this clinical trial. Study participants were randomized to supervised all-extremity aerobic exercise (EX; n=15) or non-exercise control (CONT; n=11). Exercise training was performed on a non-weight-bearing all-extremity ergometer, at 70% of peak heart rate for 47 min, 4 days/week for 8 weeks. Endothelial function was assessed at pre- and post-intervention using brachial artery flow-mediated dilation (FMD) in response to reactive hyperemia (ultrasound/doppler system).

RESULTS: FMD significantly increased in EX (3.41±0.65 vs. 4.35±0.65%, P=0.004; pre vs. post) while it did not change in CONT (3.76±0.48 vs. 3.22±0.58%, P=0.1). Baseline diameter, hyperemic shear rate and systolic and diastolic blood pressure were not affected by the intervention (P≥0.5).

CONCLUSIONS: All-extremity aerobic exercise training improves endothelial function in adults with type 2 diabetes. These findings demonstrate that non-weight-bearing all-extremity exercise is an effective alternative exercise modality in this patient population and may have important implications for exercise prescription. Supported by NIH 1R21AG050203-01 to DDC.

Cardiovascular exercise physiology

Presentation Number: 142

Board #2

All-Extremity High-Intensity Interval Training Improves Carotid Arterial Compliance in Older Adults with Type 2 Diabetes

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PURPOSE: Type 2 diabetes is associated with accelerated age-related stiffening and thickening of the large elastic arteries, both independent predictors of future cardiovascular disease (CVD) events. Aerobic exercise training is an effective non-pharmacological intervention to decrease CVD risks, however, the optimal exercise training regimen for adults with type 2 diabetes is unknown. The purpose of this study was to compare the effect of all-extremity high-intensity interval training (HIIT) vs. moderate-intensity continuous training (MICT) on carotid artery structure and function in older adults with type 2 diabetes. **METHODS:** Thirty-two sedentary older adults with type 2 diabetes (mean±SE: 64±1 yrs), free of cardiovascular and other clinical disease were randomized to HIIT (n=10), MICT (n=14) or non-exercise control group (CONT; n=8). HIIT (4x4-min intervals at 90% of heart rate peak; HRpeak) and isocaloric MICT (70% of HRpeak) were performed on a non-weight-bearing all-extremity ergometer, 4 days/week for 8 weeks under supervision. Arterial stiffness was assessed using carotid arterial compliance via simultaneous diameter (ultrasonography) and pressure (applanation tonometry) measures. Arterial thickening was assessed using carotid artery intima-media thickness (IMT; ultrasonography). **RESULTS:** Carotid arterial compliance increased by ~17% in HIIT (0.103±0.009 to 0.121±0.009 mm^2/mmHg, pre- vs. post-intervention; P=0.04) while it remained unchanged in response to MICT (0.104±0.010 to 0.100±0.009 mm^2/mmHg; P=0.6) and CONT (0.096±0.013 to 0.079±0.010 mm^2/mmHg; P=0.08). Greater increases in carotid arterial compliance were associated with greater increases in peak oxygen consumption (r=0.52, P=0.003). Carotid artery IMT remained unchanged in response to the intervention (HIIT: 0.59±0.02 vs. 0.60±0.02, MICT: 0.62±0.02 vs. 0.61±0.02, CONT: 0.61±0.02 vs. 0.61±0.02; P=0.8). **CONCLUSIONS:** Carotid artery compliance improves in response to all-extremity HIIT but not MICT in older adults with type 2 diabetes. All-extremity HIIT is an effective novel strategy to decrease arterial stiffening and CVD risk in diabetes/aging which may have important implications for exercise prescription. Supported by NIH 1R21AG050203-01 to DDC.

Cardiovascular exercise physiology

Presentation Number: 143

Board #3

Cardiovascular Response To Mental Stress Is Unaffected By Recent Preeclampsia In Young Healthy Women.

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Introduction: Preeclampsia (PE) is characterized by maternal hypertension and proteinuria, affects 2-8% of pregnancies and increases the risk of chronic hypertension. PE is also associated with greater sympathetic nervous system responsiveness to stimuli. We hypothesized that cardiovascular reactivity would be increased by a recent history of PE in young, otherwise healthy women. **Purpose:** To test the heart rate (HR) and blood pressure response to an arithmetic task designed to induced mental stress. **Methods:** We measured systolic blood pressure (SBP) and HR in women with uneventful pregnancies, (C: 29±3 yrs, 25.5±4.1 kg/m^2, 15±4 months post-partum) and PE (34±6 yrs, 32.1±6.2 kg/m^2, 13±6 months post-partum) for 3-min of supine rest (BL), followed by mental arithmetic (MA), counting backwards out loud by 7 from 200 for 2 min. BL **Results:** SBP and HR were similar between groups (124±18 and 76±11mmHg and 118±11 and 74±13 bpm for C and PE, respectively). Within groups, SBP increased from BL during MA (C: Δ 7±5 mmHg, PE: Δ 8±7 mmHg, P=0.021) and HR (C: Δ 16±12 bpm, PE: Δ 11±6 bpm, P= 0.005). However, SBP or HR response to MA was unaffected by group. **Conclusions:** Our data do not support elevated pressor response to mental stress as a mechanism accounting for increased risk of chronic hypertension in women who have had PE. Paul Titus Fellowship, Department Obstetrics, Gynecology, Reproductive Sciences, Yale School of Medicine.

Cardiovascular exercise physiology

Presentation Number: 144

Board #4

Nighttime Hypertension Status and Changes in Endothelial Cell Apoptosis After AEXT

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Purpose: Office blood pressure (BP) measurements are often used in practice to diagnose patients with hypertension. However, it has been shown that office values can either be superfluously high (white-coat hypertension) or low-to-normal (masked hypertension) compared to out-of-office BP values. Therefore, 24-hour ambulatory blood pressure monitoring (ABPM) has proven to be the ideal standard for confirming a hypertension diagnosis. Physiologically, BP should be reduced during sleep and nighttime periods with values falling below 120/70 mmHg.

This BP level during sleep may be a greater predictor of cardiovascular outcomes than BP during the awake times. We examined the relationship between nighttime BP values and a novel biomarker, endothelial microparticles (EMPs), released from endothelial cells upon activation and apoptosis. This relationship was evaluated both at baseline and after a 6-months aerobic exercise training (AEXT) program. **Methods:** We recruited sedentary, middle-to-older age African American men and women that were non-diabetic, non-smoking, and free of cardiovascular, renal, and pulmonary disease. Fasted blood samples were measured for determination of circulating EMPs, and 24-hour BP measurements were undertaken at baseline and after the AEXT program. Subjects were divided into groups based on the ABPM average asleep time threshold for hypertension diagnosis (O'Brien et al 2013). Asleep time measurements were defined as occurring between 10pm and 6am. **Results:** Based on the nighttime diastolic BP criteria, the difference in circulating apoptotic EMP levels at baseline between the hypertensive and normotensive groups was not significant (p=.08). When examining the changes after training, apoptotic EMP levels significantly decreased in the normotensive group (p<.01) but not in the hypertensive group (p=.69). **Conclusions:** Our results indicate that nighttime BP values may be a significant indicator of direct endothelial cell apoptosis, and that diastolic blood pressure may give specific insight into the ability of a 6-months AEXT program to reduce endothelial cell apoptosis in our population. Further Studies are needed to confirm this relationship in various populations and to assess the effect of nighttime hypertension on additional variables. Supported by NIH Grant # R01 HL085497-01A1.

Cardiovascular exercise physiology

Presentation Number: 145

Board #5

Oxidative Stress, Inflammation and Muscle Damage Following Eccentric Cycling in COPD Patients

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PURPOSE: The purpose of this study was to compare the metabolic demand, muscle damage, oxidative stress, and inflammation following concentric and eccentric cycling in chronic obstructive pulmonary disease (COPD) patients.

METHODS: Ten moderate COPD patients (VEF_1=68.6 ± 20.4% of predicted; 68.3 ± 9.1 years old) performed 30 min of moderate concentric cycling (CONC-M) at 50% of the maximum power output (PO_{max}), an eccentric cycling bout at 50% of PO_{max} (ECC-M) and an eccentric cycling bout at 50% of peak oxygen consumption (~100% PO_{max}; ECC-H). Metabolic demand measures such as oxygen consumption, heart rate, rate of perceived exertion, blood pressure, dyspnea and saturation of oxygen were monitored during cycling. Indirect markers of muscle damage (muscle strength, soreness and creatine kinase activity; CK) were assessed before, immediately after, 24 and 48 h after each bout. Oxidative stress (TBARS), antioxidant (total antioxidant capacity [TAC]; glutathione peroxidase [GPx]) and inflammatory markers (interleukine-6 [IL-6]; tumor necrosis factor alpha [TNF-α]) were measured before and immediately after cycling from plasma.

RESULTS: Average power output of ECC-H (104.6 ± 74.2 W) was greater than CONC-M (46.3 ± 21.6 W) and ECC-M (58.8 ± 36.2 W). Metabolic demand was 35-54% lesser during ECC-M than CONC-M and ECC-H. Dyspnea was 49% and 39% lesser in ECC-M (2.3 ± 1.1) compared to CONC-M (4.5 ± 1.9) and ECC-H (3.7 ± 1.3), respectively. Systolic blood pressure increased 66% and 64% less in ECC-M (10.2 ± 11.9 mm Hg) than CONC-M (30.2 ± 12.2 mm Hg) and ECC-H (28.5 ± 8.8 mm Hg), respectively. Muscle strength decreased 17-10% greater after ECC-H than CONC-M and ECC-M immediately to 24 h after exercise. CK activity increased 24 h after ECC-H only and muscle soreness was greater after ECC-H compared to CONC-M and ECC-M. TBARS concentration decreased immediately after CONC-M (-17%; 9.2 ± 6.2 to 7.6 ± 4.9 nmol/ml), ECC-M (-13%; 10.1 ± 5.3 to 8.8 ± 5.9 nmol/ml) and ECC-H (-26%; 9.2 ± 6.1 to 6.7 ± 4.6 nmol/ml). GPx and TAC concentrations did not change after any bout of exercise. IL-6 increased 28% after ECC-H only (4.4 ± 1.8 to 5.7 ± 1.4 pg/ml), but TNF-α did not change after exercise.

CONCLUSIONS: Moderate eccentric cycling induced ~50% lesser metabolic demand, less dyspnea, systolic blood pressure increases and exertion than moderate concentric cycling and heavy eccentric cycling. All three bouts of cycling decreased oxidative stress in COPD patients. However, heavy intensity eccentric cycling induced moderate muscle damage and inflammation. The moderate intensity cycling exercise is safe with low risk of increasing inflammation and oxidative stress on COPD patients.

Cardiovascular exercise physiology

Presentation Number: 146

Board #6

Rapid Exercise Blood Pressure Responses During Mild Dehydration: Influence of Habitual Physical Activity

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Purpose: In animals, water restriction (WR) increases plasma osmolality (pOsm) and alters blood pressure (BP) regulation. In humans, exaggerated rapid BP responses during exercise is associated with many cardiovascular disease states. However, it remains unclear if WR augments rapid BP responses during static exercise in humans. Therefore, we tested the hypothesis that WR elevates pOsm and consequently augments rapid BP responses. Because high habitual physical activity (PA) is known to be cardioprotective, we also determined the role of PA in mediating dehydration-induced changes in rapid BP responses. **Methods:** Twenty-two healthy young adults (9F/13M; age: 25±1 years; BMI: 24±1 kg/m^2; BP: 108±3/59±2 mmHg) completed two hydration conditions in random order. A normal hydration (NH) and WR visit were separated by at least one week for males and one month for females. Daily water intake for the NH condition was 23mL H_2O/kg bodyweight/day for three days prior to testing. The WR condition included a stepwise reduction in water intake over three days, concluding with 16hrs of water restriction prior to testing. Beat-by-beat BP was measured continuously with finger photoplethysmography throughout a 10-min baseline and a 2-min bout of handgrip exercise (HG) at 30% MVC. To determine the rapid BP response, BP during the first 30 seconds of HG was compared to the baseline BP. To determine if PA modulates rapid BP responses, a median split was performed based on self-reported PA from a screening questionnaire. **Results:** Plasma volume, calculated from changes in hemoglobin and hematocrit, declined 5±2% during WR. POsm (289.8±0.8 vs. 292.5±1.1 mOsm/kg H_2O), urine osmolality (518±33 vs. 750±42 mOsm/kg H_2O), urine specific gravity (1.014±0.001 vs. 1.020±0.001), and thirst rating on a 0-10 scale (3±1 vs. 7±1) were higher for the WR condition (p<0.05 for all), suggesting mild dehydration. In all participants, rapid BP responses were not different between conditions (Δ mean BP NH 5±1 vs. WR 7±1 mmHg, p=0.10). However, when factoring in PA, the less active group had augmented BP rapid responses in the WR condition compared to the more active group (Less active: Δ mean BP NH 4±1 vs. WR 8±2 mmHg; More active: Δ mean BP NH 5±1 vs. WR 5±1 mmHg; interaction (condition x group) p=0.04). **Conclusion:** These preliminary findings suggest that short-term WR increases pOsm and elicits mild dehydration. Also, these preliminary findings suggest that WR augments rapid BP responses during static HG exercise in those who report being less physically active, but not those who report being more physically active. Supported by NIH Grant R01HL128388 & University of Delaware Doctoral Fellowship

Cardiovascular exercise physiology

Presentation Number: 147

Board #7

Sex Differences in Arterial Hemodynamics and Microvascular Function in Non Dialysis Chronic Kidney Disease

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PURPOSE Cardiovascular disease (CVD) is the leading cause of death in chronic kidney disease (CKD) with patients more likely to die from CVD than progress to end stage renal disease. Abnormal arterial hemodynamics contribute to CVD, a relationship that appears to be mediated by microvascular dysfunction. The contribution of sex differences in vascular function to CVD has not been fully explored in the non-dialysis CKD population. The purpose of this study was to investigate potential sex differences in arterial hemodynamics and microvascular dysfunction in Stage 3-5 CKD patients. **METHODS** Vascular function was assessed in 24 male (Mean ± SD: Age 58 ± 14 years; eGFR 54 ± 3 ml/min/1.73^2) and 12 female (62 ± 9 years; 42 ± 4 ml/min/1.73m^2) CKD patients. Aortic pressure waveforms and carotid to femoral pulse wave velocity were acquired with combined tonometry and oscillometry. Microvascular function was assessed via cutaneous vasodilation during local heating coupled with intradermal microdialysis. Skin blood flow was measured via laser Doppler flowmetry during standardized local heating (42°C). Cutaneous vascular conductance (CVC) was calculated as a percentage of the maximum conductance achieved with sodium nitroprusside infusion at 43°C. **RESULTS** There were no differences between males and females in peripheral systolic (Mean ± SEM: 144 ± 3 *vs.* 155 ± 8 mmHg; p=0.1), diastolic (86 ± 3 *vs.* 81 ± 3 mmHg; p=0.3) and central systolic (132 ± 3 *vs.*142 ± 7 mmHg; p=0.1) pressures. Central pulse pressure (45 ± 3 *vs.* 62 ± 7 mmHg; p=0.04) and the augmentation index (26 ± 3 *vs.* 35 ± 2 %; p=0.05) were higher in females compared to males. Females reported higher forward wave amplitudes (30 ± 1 *vs.* 37 ± 3 mmHg; p=0.05), reflected wave amplitudes (19 ± 1 *vs.* 26 ± 2 mmHg; p<0.01) and reflection magnitudes (63 ± 2 *vs.* 72 ± 3 %; p=0.02). There was no difference in carotid to femoral pulse wave velocity (9 ± 0.3 *vs.* 10 ± 0.1 m/s; p=0.4). Cutaneous vasodilation in response to local heating was attenuated in females compared to males (88 ± 1 *vs.* 78 ± 3 %CVC_{max}; p=0.01). **CONCLUSION** Independent of blood pressure, female CKD patients had poorer central hemodynamics and reduced microvascular function compared to their male counterparts. These differences in vascular function could accentuate the already high risk of CVD in CKD and also potentially explain the higher incidence of CKD in older females compared to males. Mechanistic insights into the observed sex disparities in CKD are warranted to provide more targeted treatments to prevent the development and slow the progression of both CVD and CKD. Supported by NIH HL113514.

Cardiovascular exercise physiology

Presentation Number: 148

Board #8

The Effects of Exercise Training on Cardiovascular- related Circulating MicroRNAs

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PURPOSE: MicroRNAs (miRNAs) are small regulatory RNAs that post transcriptionally modify mRNAs and contribute to the control of gene expression. Circulating miRNAs are significantly altered by acute exercise; however, the effect of exercise training on the circulating miRNA profile is still unclear. Therefore, the purpose of the present study was to determine the effects of endurance exercise training on the abundance of targeted circulating miRNAs and the association of changes in miRNA levels with concomitant changes in cardiometabolic traits.

METHODS: This exploratory analysis examined a subsample of 20 previously sedentary adults from the HERITAGE Family Study who completed 20 weeks of endurance exercise training. The expression of 84 miRNAs related to cardiovascular system development or diseases was measured at base line and post training by performing RT-qPCR on the Human Cardiovascular Disease miScript miRNA PCR array. Fold change was calculated as $2^{-\Delta\Delta Ct}$ using the global geometric mean signal of all detected microRNAs as the normalizer value. Paired t-tests were used to examine the effects of exercise training on individual miRNA levels.

RESULTS: Exercise training resulted in nominally significant down-regulation of five miRNAs (miR-155-5p, let-7b-5p, let-7e-5p, miR-486-5p, and miR-7-5p) compared to baseline (Fold change: 0.33-0.76, p=0.01-0.04). Enrichment analysis of these five miRNAs found that they were significantly associated (p<0.05) with over 43 different biological pathways, including fatty acid biosynthesis, hippo signaling, HIF-1 signaling, and the AMPK signaling pathways. Change in miR-486-5p expression was significantly and moderately correlated with change in small high-density lipoprotein particle concentration (r=-0.55, p=0.01) and change in low-density lipoprotein particle size (r=0.53, p=0.01). Additionally, change in miR-7-5p was significantly correlated with change in very low-density lipoprotein particle concentrations (r=-0.47, p=0.04).

CONCLUSIONS: Exercise training significantly altered the expression of specific miRNAs associated with cardiovascular disease, which was related to concomitant changes in the lipoprotein profile. Down regulation of specific miRNAs may therefore represent a mechanism mediating the beneficial effects of exercise on cardiometabolic traits. Further research is needed to understand the complete effects of exercise on the circulating miRNA profile. Supported by multiple grants: NIH P20 GM103499; NIH U54 GM104940; NIH P20 GM103528; NIH HL45670; USC Office of the Vice President for Research; NIH 1R01HL130972-01A1; and VA 2I01-BX000168-06A1

Cardiovascular exercise physiology

Presentation Number: 149

Board #9

The Effects of Sodium Supplementation on Blood Pressure Responses during Acute Submaximal Aerobic Exercise

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Purpose: Excess dietary sodium (Na^+) exaggerates BP responses during isometric exercise in rodents, however the effect of sodium on BP responses during acute aerobic exercise remain unknown. Therefore, the purpose of this study was to test the hypothesis that high dietary sodium intake will augment the BP response to acute aerobic exercise. **Methods:** Eight healthy young adults (age: 26 ± 1 years; BMI: 23.5 ± 1.0 kg/m^2) consumed a recommended sodium diet (2,300 mg Na^+/d) for 10 days on two separate occasions; participants consumed pills containing a total of either 4,000 mg Na^+ or a placebo (order randomized). Participants collected their urine for the final 24 hours of each intervention for quantification of urinary sodium excretion. On the tenth day of each intervention, participants completed 50 minutes of dynamic cycling exercise at 60% of their VO_2peak. Brachial BP was recorded via auscultation during rest before exercise and every 5 minutes during exercise. The change in plasma volume was estimated using the change in hemoglobin and hematocrit following each intervention. BP responses during exercise were compared using a two-way ANOVA with repeated measures. **Results:** The mean VO_2peak of participants was 42.2 ± 2.1 ml/min/kg and the mean power at 60% VO_2peak was matched between visits (128 ± 13 W). Urinary sodium excretion was increased following the salt pills compared to placebo (175 ± 24 vs. 279 ± 19 mmol/24 hours, p=0.008). Sodium supplementation resulted in plasma volume expansion of approximately 11 ± 3%. Despite significantly increased sodium excretion, serum sodium (140.6 ± 0.9 vs. 140.3 ± 0.6 mEq/L, p=0.68) and plasma osmolality (293.7 ± 2.1 vs. 293.0 ± 1.0 mOsm/

kg H_2O, p=0.62) were not different following sodium supplementation compared to placebo. Following sodium supplementation, systolic BP responses were augmented during aerobic exercise at 60% VO_2peak (main effect of diet; p=0.041; e.g., 10-minute time point, 37.5 ± 7.9 vs. 43.2 ± 3.9 mmHg). Mean BP responses tended to be augmented compared to placebo (main effect of diet; p=0.125) and DBP was not different between conditions (main effect of diet; p=0.546). The augmentation of systolic BP observed following sodium supplementation was correlated to plasma volume expansion (R^2=0.73, p=0.004). **Conclusion:** These preliminary data suggest that sodium supplementation increases plasma volume and augments systolic BP responses during acute submaximal aerobic exercise. Supported by NIH Grant 1R01HL128388 and ACSM Foundation Doctoral Student Research Grant #17-00521

Cardiovascular exercise physiology

Presentation Number: 150

Board #10

The Influence of Acute Dietary Sodium on Peak Exercise Blood Pressure

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Purpose: Chronic high dietary sodium augments blood pressure (BP) responses to exercise. However, the effects of a single high-sodium meal on peak dynamic exercise BP responses is unclear. Therefore, the purpose of this study was to test the hypothesis that a single high-sodium meal would augment BP responses during acute dynamic exercise. **Methods:** Eleven healthy, adults (5F/6M; age: 24±1 years.; BMI: 22±2 kg/m^2, BP: 107±3/58±2 mmHg, Mean±SEM) participated in this randomized, crossover study. Participants consumed high (1,495 mg) or low (138 mg) tomato soup and then completed a maximal graded exercise test on a cycle ergometer, 80 minutes after soup consumption. The workload began at 50 watts and was incrementally increased 25 watts every minute, until participant exhaustion. Participants were equipped with a polar monitor (Polar USA) to measure heart rate (HR). Blood pressure was measured via auscultation (Heine Gamma G7) every two minutes and was also measured on a beat-by-beat basis using servo-controlled photoplethysmography (Finometer). Visits were separated by at least one week for males and one month for females to control for the menstrual cycle. Venous blood samples were collected prior to soup consumption, and 60 minutes postprandial. **Results:** Plasma osmolality was significantly elevated following the high- compared to the low-sodium soup (Δ2.8±0.4 vs. Δ1.6±0.3 mOsm/kg H20, p<0.05). Serum sodium was significantly higher following the high-sodium soup compared to low-sodium soup (Δ1.7±0.2 vs. Δ1.1±0.2 mOsm/kg H20, p<0.05). Despite these differences, maximal systolic BP responses were not different following the two dietary conditions with brachial BP measurements (Δ56±6 vs. Δ60±5 mmHg, p=0.89), nor with beat-to-beat BP measurements (Δ58±3 vs. Δ53±5 mmHg, p=0.42). Maximal HR responses were not different under the two conditions (Δ95±11 vs. Δ101±5 mmHg, p=0.45). **Conclusion:** These preliminary data suggest that acute dietary sodium does not augment peak BP responses to maximal dynamic exercise in young, healthy humans. Supported by NIH Grant 1R01HL128388 and ACSM Doctoral Foundation Grant 17-00577.

Hot topics in exercise physiology

Presentation Number: 151

Board #11

Brain Structural Integrity in Middle-Aged Endurance Athletes

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Purpose: Brain structural integrity starts declining during middle age. Regular aerobic exercise may increase brain volume (e.g. hippocampus) and improve white matter (WM) integrity in older adults; whether this is the case in middle-aged adults remains unclear. This study addressed whether endurance training attenuates age-related reductions of brain volume and WM neuronal fiber integrity in middle-aged adults. **Methods:** Thirty middle-aged athletes (MA, 54±4 years, 15 women) who have a ≥10-year participation in endurance training were compared with 30 middle-aged sedentary adults (MS, 54±4 years, 15 women) and 30 young sedentary adults (YS, 32±6 years, 15 women). Using a 3T MRI system, brain volume was measured by high resolution T1-weighted image, and WM neuronal fiber integrity was measured by diffusion tensor imaging (DTI). The DTI data were used to calculate fractional anisotropy (FA) from the global cerebral WM skeleton and further processed by tract-based spatial statistics (TBSS) for voxelwise analysis. Peak oxygen uptake (VO2) was measured by a modified Astrand-Saltin protocol using treadmill. **Results:** Peak VO2 was greater in MA compared with MS and YS while the latter two groups showed no statistical difference. Global brain and hippocampal volumes were similar among the groups. In contrast, FA calculated from the global cerebral WM skeleton was elevated in MA and comparable to YS, suggesting that endurance training attenuates age-related reduction of neuronal fiber integrity during middle age. TBSS further demonstrated that the elevation of FA observed in MA is located primarily in the genu and body of the corpus callosum which are essential for coordinating the brain hemispheric neural network activity. **Conclusions:** Endurance training preserves brain WM neuronal fiber integrity during middle age. These salutary effects occur primarily in the anterior portions of the corpus callosum. These findings need to be confirmed in future interventional trials.

Hot topics in exercise physiology

Presentation Number: 152

Board #12

Characterizing the Aerobic and Anaerobic Energy Costs of Polynesian Dances

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Native Hawaiians and other Pacific Islanders (NHOPI) suffer a disproportionately high prevalence of cardio-metabolic disorders when compared with the U.S. general population. Further, the Centers for Disease Control has reported that 59.0% of men and 64.2% of women of the NHOPI did not meet the federally recommended levels of physical activity (PA) To address this problem, some practitioners have advocated for developing culturally-specific physical activity interventions, such as Polynesian dances within the NHOPI population. However, a direct assessment of energy expenditure (EE) for a broad range of Polynesian dances has never been reported. **PURPOSE:** This study characterized both aerobic and anaerobic energy expenditure (EE) for several Polynesian dances in a group of experienced professional Polynesian dancers. **METHODS:** Thirteen men and 17 women were tested using indirect calorimetry to assess aerobic EE (and converted to METs), and fingertip blood lactate to estimate anaerobic EE, during both resting and dancing activities. Total EE was then computed as the sum of both aerobic and anaerobic activity energy expenditure (AEE, or EE above resting). One sample t-tests compared mean MET values for each type of dance to the 3-MET and 6-MET thresholds for moderate and vigorous physical activity (MVPA), respectively (0.05 alpha with Bonferroni correction). **RESULTS:** Mean MET values for all dances, except the Maori poi balls dance (Mean±SD: 3.7±1.1 METs; P=0.340), were significantly >3.0 METs (5.9±3.1 METS; P=0.005 for Maori haka; 6.5±2.4 METs for Hawaiian hula; 6.6±1.2 METs for Samoan sasa; 9.6±1.5 METs for Samoan slap; 8.3±1.8 METs for Tahitian; 6.0±2.3 METs for Tongan; 7.0±2.6 METs for Fijian; P<0.001). Mean METs for Samoan slap and Tahitian were also significantly >6.0 METs (P=0.002 and P<0.001, respectively). Aerobic and anaerobic AEE contributed an average of 83.4% and 16.6%, respectively, across all Polynesian dances, with Hawaiian hula being the most aerobic (88.7%) and Samoan slap being the least aerobic (74.2%). **CONCLUSIONS:** This is the first study to directly

measure the EE of multiple Polynesian dances, as well as assess the contribution of anaerobic energy to the total energy cost for these dances. The Polynesian dances tested not only met the current MVPA intensity guidelines (i.e., ≥3.0 METs), each dance also had a large anaerobic EE component. These data suggest that Polynesian dancing is an appropriate mode of aerobic exercise for future programs in health promotion and disease prevention.

Hot topics in exercise physiology

Presentation Number: 153

Board #13

DNA Methylome is Conserved in Monocytes for up to 30 Days after Exertional Heat Stroke in Mice

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Exposure to exercise and extreme environments, such as exertional heat stroke (EHS), can induce a long-term epigenetic memory of stress that is stored as altered DNA-methylation and/or histone posttranslational modifications. These changes can ultimately affect gene and protein expression as well as cellular function, which may lead to greater disease susceptibility. Previously, we have observed that a single bout of EHS can drastically alter the DNA methylome in monocytes when measured after 4 days of recovery; however, whether these changes manifest into longer lasting epigenetic memories is unknown. **PURPOSE:** To determine whether a single exposure to EHS, in a preclinical mouse model, induces a prolonged epigenetic memory identified by stable alterations in DNA methylation. **METHODS:** Mice were either subjected to a standardized EHS protocol using a forced running wheel (environmental temp: 37.5°C) or a matched exercise control trial (22.5°C), N=8/group. The EHS mice achieved peak core temps of ~42.2°C, accompanied by transient loss of consciousness. Mice were sacrificed after 4 or 30 days of recovery. At both time points, cells of a monocyte lineage were isolated from bone marrow; DNA was extracted and tested using bisulfite DNA sequencing. Additionally, at 30 days, intact solei muscles were excised (N=8/group) and tested for Ca^{2+} dysregulation in response to caffeine and halothane (IVCT test) **RESULTS:** At 4 days, EHS resulted in over 136,000 differentially methylated sites (DMSs) in monocytes, while over 108,000 DMSs were observed at 30 days. A vast majority of these DMSs were found within the intron or intergenic regions of the genome, with few changes found at the promoter regions. Furthermore, conservation within the DNA methylome was observed to take place at many genes of physiological interest, including RyR 1&2, Cacna1 (s&c) (skeletal & cardiac DHPR), Camk2d, Pde4d, SERCA (1&2), NOX4, NOS1 & 2 isoforms. The IVCT test at 30 days displayed an abnormal response to caffeine in solei from EHS (6/8) vs. control (1/8) (p=0.0203; Fisher's Exact Test) **CONCLUSIONS:** The data demonstrate that EHS induces striking alterations in the epigenome that are highly conserved through 30 days. The location of the DMSs suggests prioritization of effects within the intron and intergenic regions of the DNA. Whether this is a highly calculated effort to alter expression of specific genes or a stress induced-attempt at general stabilization of the genome remains to be answered. *BK Betty Stevens; DOD Grant W81XWH-15-2-0038 The opinions or assertions contained herein are the private views of the author(s) and are not to be construed as official or reflecting the views of the Army or the DoD.*

Hot topics in exercise physiology

Presentation Number: 154

Board #14

Energy Flux Rather Than Energy Balance Predicts Children's Future BMI Classification

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The traditional Energy Balance (EB) model states that excess body weight can occur when total energy intake (TEI) exceeds total energy expenditure (TEE) - i.e., TEE-TEI>0. The controversial Energy Flux (EF) model, in contrast, suggests that low energy flux (TEI+TEE) is a better predictor of future weight gain than a negative EB. While recent evidence exists to support the Energy Flux model in adults, similar evidence in children has not been reported. **PURPOSE:** The present study used an existing dataset from an 11-week physical activity (PA) and nutrition randomized, controlled pilot study with children to determine whether Energy Flux or Energy Balance better predicted changes in BMI classification. **METHODS:** Data for 5 boys and 5 girls (Mean±SD: 7±1 yrs age) in the treatment group, and another 10 comparison group children (6 boys and 4 girls) (8±1 yrs), each with estimates for TEI and TEE, were included. Measures for TEI, TEE, and BMI were determined at baseline and at the end of the intervention. TEI was determined with the NCI ASA-24 interviewer-administered 24-hour dietary recall with each child's parents, while TEE, activity energy expenditure (AEE), and moderate-to-vigorous PA (MVPA) were all determined with 7-day wrist-worn accelerometry-based activity monitors. TEE was calculated as AEE + BMR where AEE was from an AM-specific algorithm and BMR from standard formulae. Change in body size over the intervention was calculated as a change in BMI z-score (ΔBMIz) and this was correlated with each independent variable: End measures of TEI, TEE, EB, EF, AEE, and MVPA (alpha=0.05). Standard step-forward regression analyses were also used to predict ΔBMIz with the smallest subset of independent variables (overall alpha=0.05). **RESULTS:** Post measures for EF (r=-0.45; P=0.05) and TEE (r=+0.46; P=0.04) correlated significantly with ΔBMIz, whereas correlations with TEI (r=+0.11; P=0.66), EB (r=+0.11; P=0.65), AEE (r=+0.25; P=0.29), and MVPA (r=-0.32; P=0.18) were nonsignificant. Regression analyses resulted in two similar models where combinations of both EF, TEI, and AEE, as well as EF, TEI, MVPA accounted for 83% of the variance. **CONCLUSIONS:** EF correlated significantly with ΔBMIz and significantly contributed to a multiple regression model explaining most of the ΔBMIz variance, whereas EB did neither. Further, while the current study did not use criterion measures for either TEI or TEE, the correlational results are nearly identical to an adult study using criterion measures. Thus, our results support the controversial Energy Flux model over the Energy Balance model for explaining ΔBMIz in children.
Supported by NIH award number P20GM103474.

Hot topics in exercise physiology

Presentation Number: 155

Board #15

Epigenetic and Transcriptomic Signatures of Human Slow- and Fast-Twitch Muscle Fibers across the Lifespan.

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PURPOSE: Aging skeletal muscle is characterized by a loss of muscle mass and function that is more pronounced in fast-twitch muscle fibers. Exercise can partially mitigate these effects, but little is known about how aging and exercise may impact the control of muscle gene expression through DNA methylation. We examined epigenetic and transcriptome signatures of human slow- and fast-twitch muscle fibers in lifelong

endurance exercisers (LLE; n=8, 74±1 y), age-matched healthy non-exercisers (OH; n=9, 75±1 y), and in young exercisers (YE; n=8, 25±1 y).

METHODS: Individual vastus lateralis muscle fibers were separated from a muscle bundle under a light microscope using fine tweezers. The fiber type (MHC) was determined using SDS-PAGE before fiber-type specific DNA and RNA extractions of pooled single muscle fibers. DNA methylation was assessed using Reduced Representation Bisulfite Sequencing on 32 ng of DNA. Gene expression was examined with RNA-Seq using 9 ng of RNA. Differentially methylated regions (methylation difference ≥35%, p<0.05) and differentially expressed genes (fold-change ≥1.5, FDR<0.1) between fiber types were identified in each subject cohort and overlaid to identify common genes between YE, OH, and LLE. Ingenuity Pathway Analysis software and the gene ontology database were utilized to interpret the biology of the common genes.

RESULTS: We identified 183 differentially methylated genes and 148 differentially expressed genes between fiber types, which were common in all three groups. The molecular and biological processes of these genes, such as ATP-dependent microfilament and microtubule motor activities or glycolysis,were consistent with the fiber-type functional and structural phenotypic differences.We examined the 183 differentially methylated genes with the 148 differentially expressed genes, and identified 10 genes with both gene methylation and expression differences between fiber types across all three groups. Six of them were myosin and troponin genes.

CONCLUSIONS: These data provide the first fiber-type specific gene methylation and expression signatures of healthy human skeletal muscle across the lifespan. Future analysis of the epigenetic and transcriptomic signatures specific to YE, LLE, and OH could add knowledge and further our understanding on slow- and fast-twitch fiber biology with aging and exercise. Furthermore, fiber-type specific epigenetic and transcriptomic characterization of healthy human skeletal muscles will contribute to a better understanding of age- and disease-related muscle dysfunctions. Supported by NIH grant R01 AG-038576 and Ball State University Academic Excellence Award.

Hot topics in exercise physiology

Presentation Number: 156

Board #16

Role of Nucleus Accumbens CREB and PKIα Modulation in Rescuing Low Physical Activity Motivation

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PURPOSE: As an accretion to the seminal work of the Booth lab in establishing several molecular transducers of physical activity, the current study was aimed at identifying how altering cAMP response element binding protein (CREB) activity in the nucleus accumbens (NAc) could rescue low voluntary running distance in a model of low physical activity motivation. In believing that the greater advantage for human health is in increasing the motivation to be physically active, and not in attempting to artificially mimic some of the molecular benefits of physical activity, we began selective breeding for low voluntary running (LVR) behavior in 2009. By 2012, webecame the 1st to publish data elucidating potential genetic determinants of low physical activity motivation. Building upon this work, the goal of the current study was to determine how altering CREB transcription in the NAc of LVR and wild-type (WT) rats could influence nightly voluntary running behavior. **METHODS:** Western-blotting was used to determine baseline levels of NAc CREB phosphorylation in sedentary LVR and WT rats. Bilateral NAc micoinfusion of an AAV for the overexpression of upstream CREB modulator, Protein Kinase Inhibitor Alpha (PKIα), was administered to female LVR and WT rats and wheel-running behavior was monitored. Overexpression of PKIα, and coinciding molecular markers associated with reward and motivation, were assessed via qPCR. **RESULTS:** Preliminary, unpublished results show a higher level of baseline NAc CREB phosphorylation in LVR compared to WT rats. Overexpression of PKIα significantly increased nightly running for 5 continuous estrous cycles (~3 weeks) post injection in female LVR rats, but not WT rats (Mol Neurobiol June 2, 2018). A 4-fold increase in PKIα mRNA expression was confirmed in NAc punches taken from LVR rats compared to pair matched empty vector (EV) injected controls. WT punches showed a near significant (p = 0.07) 2.5 fold increase in PKIα mRNA expression compared to EV controls. Endogenous mRNA levels for PKIα, D1, D2, and Fos were all lower in WT rats following PKIα overexpression compared to WT EV controls, as well as both overexpressed and EV LVR rats.

CONCLUSIONS: Recent results show that LVR rats have a higher baseline NAc CREB phosphorylation compared to WT rats, a state previously attributed to deficits in reward valuation and which we feel may contribute to their low motivation to be physically active. In so, we believe that modulating NAc CREB activity has the neuro-molecular potential to increase physical activity motivation when voluntary running behavior is less than "normal", as in the case of the selectively bred LVR rats tested herein.

Hot topics in exercise physiology

Presentation Number: 157

Board #17

Variability in Daily Step Counts with Shift Work-Related Circadian Rhythm Disruption

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Purpose Most mammalian circadian rhythm research has been conducted in highly controlled environments where light exposure, temperature, behavioral regularity and noise can be easily manipulated. While this provides key insights into circadian rhythm functional biology, this work is unable to guide practical health solutions for circadian-abnormal populations. Research investigating populations experiencing both significant regularity and irregularity in sleep cycles, meal times and physical activity is needed. This current study is testing the feasibility of using a commercially-available activity monitor to capture components of daily lifestyle behaviors characterizing circadian rhythm—both normal and disrupted—in a cohort of police academy trainees.

Methods Trainees were followed for 6-wk of in-class training (regular and normal circadian rhythm) and 6-wk of field training (disrupted circadian rhythm). During field training, trainees were assigned to one of four shifts that follow a 4-day on/4-day off rotation. For analysis, shifts starting at 6 AM and 10 AM were pooled (Day) and those starting at 4 PM and 8 PM were pooled (Night). Some shifts cross over two calendar days making it impossible to differentiate steps during Work vs Non-work days. Thus, only the middle 2 days of each 4-day block were used. Variability of steps/day (defined as the average standard deviation) was measured by activity monitors.

Results Data from 14 trainees (6 Day/8 Night) were analyzed. There was no difference in mean steps/day for all subjects on Work days (5413) vs Non-work days (5156) (p=0.59). However, the variability for Work (1396) vs Non-work days (2194) for all subjects was significantly different (p=0.02). When comparing Non-work days for Day vs Night, there was not a significant difference in mean steps/day (4243 vs 5765, p=0.12), but there was a trend towards significance in the variability (1768 vs 2514, p=0.10). When assessing Night shift variability, Non-work days were significantly greater than Work days (2514 vs 1484, p=0.04). For Day shift, there was no significant difference in variability observed for Work vs Non-work days.

Conclusion As expected, police academy trainees displayed greater variability in physical activity for Non-work compared to Work days. Night shift trainees displayed over 1000 steps/day higher variability on Non-work compared to Work days. As regularity and normality represent the healthiest circadian pattern, the significant variability displayed by Night shift trainees during Non-work days highlights the detrimental circadian disruption created by shiftwork.
Funded by the REACT Center, University of Alabama-Birmingham

Integrative exercise physiology and metabolism

Presentation Number: 158

Board #18

Dietary Sugar Intake Modifies Extracellular Vesicle Response to Exercise Training in Adults with Prediabetes

Natalie ZM. Eichner, Nicole M. Gilbertson, Emily M. Heiston, Luca Musante, Sabrina LaSalvia, Eugene J. Barrett, Arthur Weltman, FACSM, Uta Erdbrügger, Steven K. Malin, FACSM. *University of Virginia, Charlottesville, VA.*

PURPOSE: Extracellular vesicles (EVs) may be novel bio-activators linked to type 2 diabetes (T2D) and cardiovascular disease (CVD). Both exercise and low carbohydrate (CHO) diets modulate EVs and improve CVD risk in adults with obesity and T2D. However, the interaction of ad-libitum CHO intake and exercise training intensity on EVs in adults with prediabetes is unknown. **METHODS:** Eighteen obese adults (age: 63.8±1.5yrs BMI: 31.0±1.3 kg/m^2) were screened for prediabetes (ADA criteria: 75g OGTT and/or HbA_{1c}) and randomized to 12 bouts of supervised INT (n=10, 3 min at 90% and 50% HR_{peak}) or CONT (n=8, 70% HR_{peak}) exercise over 2-wks for 60 min/d. Ad-libitum dietary intake was recorded for 3-d before and after treatment and analyzed using ESHA. Fasting and 2-hr glucose were determined during a 180 min 75g OGTT, while insulin and arterial stiffness (augmentation index; AI) were calculated from the OGTT as total AUC. Fasted Annexin V (AV) +/- total EVs, platelet EVs (CD31$^+$/CD41$^+$), endothelial EVs (CD105, CD31$^+$/ CD41$^-$) and leukocyte EVs (CD45$^+$) were analyzed from fresh plasma via imaging flow cytometry. Fitness (VO_2peak) and body weight were also assessed. **RESULTS:** INT exercise increased VO_2peak compared with CONT training (P=0.04), although there was no effect on body weight. Independent of intensity, training significantly reduced 2-hr glucose (P=0.04), insulin $tAUC_{180}$ (P=0.05) and AI $tAUC_{180}$ (P=0.03). The intervention had no effect on platelet or leukocyte EVs, but INT exercise decreased AV- CD105 compared with CONT training (Δ= -0.2±0.2 vs. 0.6±0.15 count; P=0.04). Both INT and CONT decreased total caloric (P<0.01) and CHO intake (trend: P=0.08). However, INT training decreased, while CONT increased, sugar consumption (-27.7±7.6 vs. 27.4±17.3%, P=0.01). Interestingly, the exercise intensity effect on AV-CD105 was eliminated after co-varying for the change in sugar intake (P=0.18). This reduction in dietary sugar intake after training was linked to decreased AV+CD105 (r=0.60,P=0.01) and AV-CD45+ (r=0.61, P<0.01) as well as VO_2peak (r=-0.53, P=0.03) and fasted AI (trend: r =0.47, P=0.06). Adjusting for fitness gains strengthened the relationship between dietary sugar and AV+CD105 (P<0.01). **CONCLUSIONS:** Ad-libitum sugar consumption modifies exercise training induced effects on endothelial and leukocyte EVs in adults with prediabetes, although fitness plays a role. Future work is needed to assess how dietary sugar intake and exercise interventions interact to impact EV physiology in relation to cardio-metabolic health. Supported by UVA Curry School of Education to SKM and UVA Diabetes LaunchPad Grant to SKM and UE.

Integrative exercise physiology and metabolism

Presentation Number: 159

Board #19

Doxorubicin, Resistance Training, and Type I Muscle: Effects on Creatine Kinase and Creatine Transporter

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Doxorubicin (DOX) is an effective and commonly used anticancer drug; however, it leads to multiple side effects which include cardiotoxicity and myotoxicity. DOX alters creatine kinase (CK) and creatine transporter (CreaT) expression in cardiac muscle, and although it is suggested that DOX impairs skeletal muscle metabolism, little is known about how DOX affects CK and CreaT in type I muscle. We reported previously that resistance training before and during DOX treatment increases CreaT expression in type II muscle from rats receiving DOX, but the effects of resistance training with DOX on type I muscle have yet to be explored. **PURPOSE:** To examine the effects of resistance training before and during DOX treatment on CK and CreaT expression in the primarily type I, or slow, soleus (SOL) muscle. **METHODS:** Thirty-six male, Sprague-Dawley rats were randomly assigned to a sedentary+saline (SSS), sedentary+DOX (SSD), resistance training+saline (RRS), or resistance training+DOX (RRD) group. The resistance training groups were housed in cages where food and water were progressively raised to load the hindlimb for 10 weeks before DOX treatment and 4 weeks during DOX treatment. DOX-treated groups received 3 mg/kg DOX weekly for 4 weeks (12 mg/kg cumulative), and saline-treated groups received 0.9% NaCl as a placebo. The SOL muscle was then excised five days following the final injection, and Western blotting was performed to quantify CK and CreaT expression. **RESULTS:** A significant main drug effect was observed for CK expression with SOL from DOX-treated rats expressing lower levels of CK than saline treated rats (p=0.0474); however, no exercise effect or drug x exercise interaction was observed with CK expression (p>0.05). Furthermore, no main effects or interactions were observed for CreaT expression in the SOL (p>0.05). **CONCLUSIONS:** DOX decreased CK expression in the SOL which may lead to impaired ATP and phosphocreatine synthesis. Resistance training before and during DOX treatment, however, had no effect on CK or CreaT expression in the SOL.

Integrative exercise physiology and metabolism

Presentation Number: 160

Board #20

Effect of Electrically Evoked Local Muscle Contractions on Glucose Metabolism in High-Fat Diet-Induced Insulin-Resistant Rats

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PURPOSE: Electrically evoked local muscle stimulation (EMS) has been applied as a therapy to diabetic patients in several clinical studies. Transcutaneous EMS might improve glucose metabolism among diabetic and other patients who have difficulties with voluntary exercise, but this remains unclear. In contrast, invasive stimulation has been applied in animal studies. A non-invasive approach to EMS is required, considering the clinical application of EMS. Thus, the present study analyzed the effect of transcutaneous EMS on glucose metabolism in the rat model of insulin resistance induced by feeding with a high-fat diet.

METHODS: Experiment 1. Male Sprague-Dawley (SD) rats were randomly assigned to a control (n = 6) and a 7-day EMS (n = 6) group. The bilateral rectus femoris muscles were electrically stimulated at 0.5 Hz for 30 min/day for 7 days under anesthesia. On day 8, an euglycemic clamp (3 mU/kg/min) was placed 24 h after the last electrical stimulation. The glucose infusion rate (GIR) was determined during the last 30 min of insulin infusion when a steady state was attained. Experiment 2. Male SD rats were assigned to the groups fed either with chow (normal, n = 5) or a high-fat diet (n = 12) for 3 weeks. The latter group was further divided into a sedentary group (HFD, n = 6) and a group to which EMS was applied (HFD + ES, n = 6). The EMS protocol was the same as that described above for Experiment 1. On day 8, the 2-step euglycemic clamp (3 and 30 mU/kg/min) was placed 24 h after the last electrical stimulation. The GIR was regarded as an index of insulin action. The amounts of heat shock protein (HSP) 72 and 27 in the rectus femoris muscle were measured using western blotting.

RESULTS: The findings of Experiment 1 showed that EMS significantly increased GIR compared to the control group. The findings of Experiment 2 showed that the high-fat diet resulted in a remarkable decrease in the GIR during low-dose insulin infusion and EMS significantly increased the GIR in rats fed a high-fat diet. During high-dose insulin infusion, the high-fat diet also significantly decreased GIR compared to control rats. The decreased GIR was restored by EMS to the same level as the control group. The high-fat diet did not alter HSP72 and HSP27 expression. HSP72 expression was significantly increased in the HFD + ES group compared to the normal and HFD groups. HSP27 expression was also significantly increased in the HFD + ES group, compared to the HFD group.

CONCLUSIONS: Daily transcutaneous EMS improves glucose metabolism and increases HSP72 and HSP27 expression in insulin-resistant rats. Supported by JSPS KAKENHI Grant Nos. 17K01538 (MI) and 18K10766 (WT) from the Japan Society for the Promotion of Science.

Integrative exercise physiology and metabolism

Presentation Number: 161

Board #21

Effect of Restricted Carbohydrate Intake and Caffeineon Fat Oxidation and Performance in Moderately Trained Women

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Purpose: We aimed to elucidate whether periodized carbohydrates (CHO) intake following intense aerobic exercise enhances fat oxidation (FATox) during exercise in moderately trained women. Additionally, we investigated whether caffeine intake prior to exercise enhances time-trial performance when CHO intake was prohibited. **Methods:** In a randomised, double-blinded, cross-over, placebo-controlled design, seven moderately trained women completed three experimental trials consisting of high-intensity-training (HIT) in the evening and fat-oxidation-test (FATOX) and 20-min-time-trial (20TT) the following morning. The women received standardized, isoenergetic diets which differed in the timing of ingestion: 1) FED: 5 g $CHO \cdot kg^{-1}$ before HIT, 3 g $CHO \cdot kg^{-1}$ after HIT and placebo in the morning 1h prior to FATOX, 2) FASTEN: 8 g $CHO \cdot kg^{-1}$ prior to HIT and placebo in the morning, 3) FASTEN+CAFF: 8 g $CHO \cdot kg^{-1}$ prior to HIT and caffeine in the morning. **Results:** Based on indirect calorimetry, FATox was significantly enhanced in FASTEN+CAFF (0.56±0.04 $g \cdot min^{-1}$) compared to FED (0.46±0.03 $g \cdot min^{-1}$, p<0.03) but not compared to FASTEN (0.49±0.03 $g \cdot min^{-1}$). Maximal fat oxidation tended to be higher in FASTEN+CAFF (0.7±0.07 $g \cdot min^{-1}$) than FED (0.6±0.04 $g \cdot min^{-1}$, p=0.07) and FASTEN (0.6±0.08 $g \cdot min^{-1}$, p=0.08). Fatmax did not differ between trials (69.3-70.0% of VO_{2max}). Average power output in 20TT tended to be higher in FASTEN+CAFF (207±13W) compared to FASTEN (190±13W, p=0.06), but not compared to FED (200±10W). In conclusion, our results showed that periodized carbohydrate intake in combination with caffeine increased FATox in moderately trained women. Furthermore, caffeine seemed to be potent to counteract the decreased exercise capacity when carbohydrate was prohibited. Supported by Team Danmark and Toyota Foundation Denmark

Integrative exercise physiology and metabolism

Presentation Number: 162

Board #22

Effects of One Year Aerobic Exercise Training on Cerebral Vasomotor Reactivity in Healthy Older Adults

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PURPOSE: Aerobic exercise training (AET) may improve cerebral blood flow (CBF) regulation in older adults. CBF is sensitive to changes in arterial partial pressure of carbon dioxide (CO_2), which is referred to as cerebral vasomotor reactivity (CVMR). The purpose of this study was to determine the effects of one year AET on CVMR in healthy older adults.

METHODS: Seventy-three healthy individuals (68±5 years, 54 women) were randomized to one year of moderate-high intensity AET or stretching program. CBF velocity (CBFV) via transcranial Doppler, mean arterial pressure (MAP) via plethysmograph, and end-tidal CO_2 ($EtCO_2$) via capnograph were measured during hyperventilation (hypocapnia) and with a modified rebreathing protocol (hypercapnia). Cerebrovascular conductance index (CVCi) was calculated by CBFV/MAP, and CVMR indices were calculated by $\Delta CBFV/\Delta EtCO_2$ and $\Delta CVCi/\Delta EtCO_2$. Blood pressure responses to hypo- and hypercapnia were determined by $\Delta MAP/\Delta EtCO_2$. Cardiorespiratory fitness was assessed by peak oxygen uptake (VO_2) using a modified Astrand-Saltin treadmill protocol.

RESULTS: After one year follow-up, CVMR data were available from 13 subjects in AET program and 11 subjects in stretching program. Peak VO_2 significantly increased in AET group compared with stretching group. At rest, mean CBFV, MAP, and $EtCO_2$ remained at similar levels in both groups after the intervention. Compared with the stretching group, hypercapnic CVMR and blood pressure responses to $\Delta EtCO_2$ were significantly decreased in AET group.

CONCLUSIONS: In healthy older adults, one year AET program increased cardiorespiratory fitness and altered hypercapnic CVMRs and blood pressure response. This study was supported by NIH 5R01HL102457-04.

Integrative exercise physiology and metabolism

Presentation Number: 163

Board #23

Energy Deficit Predicts Improved Insulin Sensitivity and Adiposopathy Independent of Body Composition and VO_2peak

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PURPOSE: Weight loss and aerobic fitness (VO_2peak) each improve insulin sensitivity and adipose tissue health (i.e. adiposopathy). However, energy deficit induced by low calorie diet (LCD) and/or increased energy expenditure (EE) following lifestyle therapy may mechanistically account for this metabolic health gain. To date, it is unclear to what role energy deficit has on insulin sensitivity and adiposopathy, independent of improved body composition and VO_2peak. **METHODS:** Twenty-four women (Age: 48.2±2.4y, BMI: 37.8±1.3kg/m^2) were randomized to a LCD (n=12; mixed meals of ~1200kcal/d) or LCD combined with interval exercise (LCD+INT; n=12; 60min/d of supervised INT at 90% and 50% HR_{peak} for 3 min each, respectively). LCD+INT group received 350kcal post-exercise to equate energy availability (EA) between groups. Food logs were recorded before and during the 13-d intervention to evaluate caloric intake. Exercise EE was estimated from VO_2-HR regression analysis. Absolute (post-pre caloric intake) and relative (RMR and exercise EE relative to calorie intake) energy deficit were calculated to assess EA. VO_2peak, body composition (BodPod), adiposopathy (adiponectin/leptin), and insulin sensitivity (Matsuda Index; 2-h 75g OGTT) were also tested pre- and post-intervention. **RESULTS:** While only LCD+INT increased VO_2peak (P=0.04), LCD induced greater weight loss (*P*=0.02) versus LCD+INT. Both treatments reduced body fat (*P*<0.001), but LCD+INT tended to maintain fat free mass while LCD had a reduction (*P*=0.12). Both interventions increased insulin sensitivity (*P*=0.02) and the ratio of adiponectin to leptin (*P*=0.001). Weight loss correlated with increased insulin sensitivity (*r=-0.49*, *P*=0.02) and adiposopathy (r=-*0.53*, *P*=0.01), and enhanced adiposopathy correlated to augmented insulin sensitivity (r=0.62, *P*=0.002). Further, LCD and LCD+INT were not different in absolute (LCD -859.5±222.2 vs. LCD+INT -691.2±167.6 kcal; *P*=0.55) or relative (LCD -843.0±203.7; vs. LCD+INT -759.2±178.2 kcal; *P*=0.76) energy deficits. Absolute and relative energy deficits were linked to elevated insulin sensitivity (r=*-0.47*, *P*=0.02 and r=*-0.40*, *P*=0.05, respectively) and adiposopathy (r=*-0.49*, *P*=0.02 and r=*-0.39*, *P*=0.06, respectively), independent of weight loss, body composition changes, and increased VO_2peak as assessed by multiple linear regression. **CONCLUSIONS:** Energy deficit predicts enhanced insulin sensitivity and adiposopathy, independent of body composition and fitness These data suggest that energy deficit per se is important for reducing cardiometabolic disease risk. Funding by UVA Thelma R. Swortzel Award and Diabetes Action Research Grant.

Integrative exercise physiology and metabolism

Presentation Number: 164

Board #24

High-Fat Feeding Alters Murine Circadian Responses to Exercise

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Purpose: Circadian rhythms are ~24-hour oscillations conserved in almost all organisms and underpin the regulation of many physiological processes. The discovery of molecular clock systems in peripheral tissues (e.g., skeletal muscle) has demonstrated integration between circadian rhythms and metabolic functions. These peripheral clocks are sensitive to input from external factors such as diet and exercise; however, the combined effect(s) of these stressors on the molecular clocks control of metabolism within skeletal muscle is unexplored. **Methods:** Male C57BL/6J mice were maintained on a chow diet (CHOW; ~60% carbohydrate (CHO), 20% fat, 20% protein) for 2 weeks under a 12:12 hour light/dark cycle (Baseline). Mice were then randomly assigned to either control (CHOW, *n*=24) or high-fat diet (HFD; ~46% fat, 34% CHO, 20% protein, *n*=24) for the next 4 weeks. Within each dietary condition, mice were divided into exercise training (EX, 1hr treadmill-based high-intensity interval training 3 d/week) or sedentary control (SED; *n*=11-12 per group). All mice were housed in 24-hour darkness for the study duration. Exercise and metabolic phenotyping was performed at baseline, and at weeks 2 and 4. **Results:** Mice consuming HFD had significant increases in total body mass (BM) and body fat content compared to CHOW ($P<0.05$). However, the increase in total BM was attenuated in the HFD EX group compared to HFD SED (~20%; $P<0.05$). The changes in BM were not due to hyperphagia, as there were no differences in total food intake within the HFD groups or compared to CHOW SED over the 4-week intervention. In contrast, the CHOW EX group consumed significantly more food at weeks 2 and 4 compared to HFD SED (~26 and ~38%, respectively; $P<0.05$) and HFD EX (~19 and 28%, respectively; $P<0.05$). Despite the increase in body fat, neither HFD group developed glucose intolerance, as assessed by IPGTT. There were no differences in infrared-based activity levels after 4 weeks however the phase of physical activity rhythms (i.e. the time during which mice were active) was advanced in all groups, with a greater advance in CHOW EX compared to HFD EX ($P<0.05$). **Conclusion:** Circadian clocks are sensitive to perturbations by exercise and diet. However, when exercise is combined with a HFD during 24-hour darkness, the phase advance in physical activity patterns was attenuated compared to when mice consumed a CHOW diet. These data demonstrate the macronutrient composition of diet alters the circadian response to exercise, which has implications for the control of metabolic homeostasis. Supported by ACU FHS Research Project Grant (JW) and ACURF Program Grant (JAH).

Integrative exercise physiology and metabolism

Presentation Number: 165

Board #25

Impact of Passive Heating on Critical Torque

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PURPOSE: The hyperbolic relationship between power and duration is utilized to describe the exercise tolerance of an individual and is termed critical power or critical torque (CT). Passive heating has been shown to provide the body with sufficient stress to improve muscular function in humans. Rats that have an overexpression of heat shock protein 72 (HSP72), which is highly inducible via physiological stress (i.e. passive heating), have been observed to have an increased exercise performance. Thus, the purpose of this investigation was to determine if passive heating leads to increases in exercise tolerance in human subjects. **METHODS:** 4 healthy male subjects completed 5-min all-out tests to determine knee extension CT pre and post 11 days of passive heating. We utilized an audio file that prompts the subjects when to contract and when to relax, to ensure a duty cycle of 3-second contraction and 2-second relaxation. During the test the subjects were very strongly encouraged to maximize torque during each contraction but were not informed of the elapsed time or the number of contractions remaining. The passive heating protocol consisted of immersion up to the shoulder in a 40°C hot tub until rectal temperature reached 38.5°C or increased by 1°C for 60 minutes. **RESULTS:** Average rectal temperature change during 60 mins of passive heating was 1.45 ± 0.59 °C. CT for pre and post passive heating was 33.2 ± 19.3 kg and 35.9 ± 19.8 kg, respectively (p=0.503). 3 of the 4 subjects showed an increase in CT post passive heating. The EMG activity of the vastus lateralis m.was computed as the root mean square (RMS) of the signal. The RMS signal for the beginning of exercise was determined by the average of the first three contractions and CT RMS was determined from the average of the last six contractions. Pre and post passive heating RMS for the beginning of exercise was 125 ± 60.2 mV and 138 ± 31.4 mV (p=0.602). Pre and post passive heating RMS for CT was 120 ± 71.8 mV and 113 ± 40.5 mV (p=0.81). Torque/EMG relationship for CT pre and post passive heating was 0.31 ± 0.14 kg/mV and 0.26 ± 0.05 kg/mV (p=0.393). **CONCLUSIONS:** The trend of increased CT post passive heating indicates that the physiological stress during heating can lead to increased exercise tolerance in many subjects. Increases in exercise tolerance and performance may be facilitated through repeated bouts of passive heating.

Integrative exercise physiology and metabolism

Presentation Number: 166

Board #26

Inflammatory Response In Adipose Tissue Promoted By Acute Aerobic Exercise In PPAR-α Knockout Mice

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Purpose: Obesity is an increasing health problem and it has been demonstrated that accumulate fat in subcutaneous and visceral deposits are more prone to metabolic and cardiovascular diseases than peripheral deposits. The nuclear transcriptional factor Peroxisome proliferator activated receptor alfa (PPARα) plays a vital role in regulating genes involved in adipogenesis, lipid metabolism and inflammation. Studies have suggested that acute exercise alone can modulate PPARs expression, however PPAR-α role on exercise-mediated inflammatory response in adipose fat deposits are unknown. **Methods:** Male C57BL6/J wild-type (WT) and a PPARα knockout mice (KO) at the age of 10 weeks were randomly subdivided in non-exercising rest or submitted to acute aerobic exercise (run on treadmill performed at 60% of maximum speed for 1 hour) euthanized 2 or 24 hours after exercise session. We collected mesenteric and retroperitoneal adipose tissue and the Interleukin 6 (IL-6), Interleukin 10 (IL-10) and Tumor necrosis factor α (TNF-α) levels were evaluated by ELISA. The differences were performed by two-way ANOVA with Bonferroni post-hoc test. Moreover, the effect size (eta-squared; $\eta 2$) of each test was calculated. **Results:** In the mesenteric depots there was a significant increase in TNF-α levels 2h and 24h post-exercise (1217,414±20.8 and 615,627±13.6pg/µg protein respectively, p=0.003, η^2= 0.541) compared to rest (527,747±10.9pg/µg protein) but only in WT. Retroperitoneal depots showed no difference in cytokine production between genotypes at baseline. IL-6 levels were significantly higher 2h and remain elevated 24h post-exercise (884.7±17.8 and 485.16±12.7pg/µg protein respectively, p=0.001, $\eta 2$=0.344) when compared to rest (363.9±11.1pg/µg protein) but only in WT. Similarly, only WT showed increase in IL-10 values 2h and 24h post-exercise (19.89±2.68 to 5.09±1.16pg/µg protein, p=0.001, η^2=0.595) compared with rest (4.34±1.08pg/µg protein). **Conclusions:** The local production of IL-6 and TNF-α in WT was possibly postulated favor the lipolysis process in adipose tissue, increasing the availability of substrate to the skeletal muscles to maintain the contractile activity. PPARs play an important role inhibiting nuclear factor-kappa B activity, which impair

pro-inflammatory cytokines transcription decreasing inflammation, at the same time, increasing IL-10 in WT was an expected exercise-induced anti-inflammatory mechanism. Taken together, our data suggests that PPAR-α KO mice failed to regulate exercise-induced IL-10 production in adipose tissue, which might impair exercise benefits. Supported by FAPESP-Brazil, Grant number 2014/01246-6.

Integrative exercise physiology and metabolism

Presentation Number: 167

Board #27

Influence of Sodium Glucose Co-Transporter 2 Inhibition On The Physiological Adaptation to Endurance Exercise Training

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Metformin, arguably the most commonly prescribed anti-diabetes medication, attenuates the favorable physiological adaptations to exercise. In turn, exercise may impede the action of metformin. **PURPOSE:** To determine the influence of an alternative diabetes treatment, sodium glucose co-transporter 2 (SGLT2) inhibition, on the response to endurance exercise training. **METHODS:** Using a randomized, double-blind, repeated measures parallel design, 30 sedentary overweight and obese men and women were assigned to 12-weeks of supervised endurance exercise training, with daily ingestion of either a placebo or SGLT2 inhibitor (Dapagliflozin: up to 10 mg/day). **RESULTS:** Endurance exercise training favorably modified body mass, body composition, maximal oxygen uptake, responses to standardized sub-maximal exercise, and skeletal muscle citrate synthase activity (main effects of exercise training: all $P<0.05$); SGLT2 inhibition did not influence any of these physiological adaptations (exercise training x treatment interaction: all $P>0.05$). However, while endurance exercise training lowered fasting blood glucose and increased insulin sensitivity, SGLT2 inhibition abrogated these effects (exercise training x treatment interaction $P<0.01$). **CONCLUSIONS:** The efficacy of combining two beneficial anti-diabetes interventions, regular endurance exercise and SGLT2 inhibition, was not supported. SGLT2 inhibition neither attenuated nor augmented any of the favorable physiological adaptations to endurance exercise training, with the notable exception of abrogating the desirable changes in fasting blood glucose and insulin sensitivity. The initial health status of patients and final goals for concomitant prescription of exercise and SGLT2 inhibition may need to be considered carefully prior to commencement.

Integrative exercise physiology and metabolism

Presentation Number: 168

Board #28

Limitations to Oxidative ATP Synthesis During High-Intensity Contractions: A Hyperoxic Mitochondrial Uncoupling Hypothesis

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Oxidative metabolism is non-linearly augmented during high-intensity (HI) contractions (Cannon et al; 2014). The mechanisms behind this phenomenon are unclear but increased oxidative ATP synthesis (ATP_{OX}) and mitochondrial uncoupling are two leading hypotheses. Muscle ATP_{OX} can be measured using 31-phosphorus magnetic resonance spectroscopy by calculating the initial rate of phosphocreatine (PCr) resynthesis (V_{iPCr}) following contractions. A key distinction between the hypotheses is that the ATP_{OX} hypothesis predicts increased V_{iPCr} and the mitochondrial uncoupling hypothesis predicts decreased V_{iPCr}. **Purpose:** To quantify changes in V_{iPCr} throughout a HI contraction protocol. **Methods:** A $^{31}P/^{1}H$ surface coil was used to continuously measure intramyocellular phosphates and pH in the vastus lateralis of 3 young men (30.0±4.4 yrs, mean±SD) while contracting in a 3T MR system. Participants performed 4 rest-contract-recovery trials of maximal voluntary dynamic contractions (MVDC): 90s rest; then 24, 60, 120, or 240s of MVDCs ($120°\cdot s^{-1}$, 30° range of motion) and 7-10 min of recovery. Spectra were processed in jMRUI and analyzed using AMARES. V_{iPCr} ($mM\cdot s^{-1}$) was calculated for each trial as the change in [PCr] observed in the first 4s of recovery from the monoexponential fit of the PCr recovery curve. V_{max} ($mM\cdot s^{-1}$), *K*m, and the Hill coefficient (*n*H) were calculated for ATP_{OX} after each trial by fitting the first 60s of PCr resynthesis against the corresponding cytosolic phosphorylation potential (CPP; [ADP·Pi/ATP]) according to: $\Delta PCr=V_{max}/(1+((Km/CPP)^{nH})))$. **Results:** [PCr] and pH declined for 120s then plateaued. V_{iPCr} steadily declined beyond 60s and V_{max} was reduced beyond 24s ($p<0.01$). Muscle power output (Watts) decreased throughout the 240s trial, whereas CPP increased. **Conclusions:** The progressive declines in V_{iPCr} and V_{max} suggest that: 1) non-linear increases in oxidative metabolism observed during HI contractions cannot be explained by increases in ATP_{OX}, and 2) that HI contractions impair oxidative phosphorylation. Further, these results cannot be explained by the decline in power output, as CPP, a key driver of ATP_{OX}, increased throughout the 240s trial. We propose that mitochondrial uncoupling, due to local hyperoxia, may be responsible for altering the control of oxidative metabolism during HI contractions. That is, as O_2 delivery increases to muscle fibers with low State-3 oxidative capacity, cytosolic O_2 availability exceeds consumption, thereby inducing a temporary state of hyperoxia that stimulates the generation of reactive oxygen species and the activation of mitochondrial uncoupling proteins to avoid oxidative damage.

Integrative exercise physiology and metabolism

Presentation Number: 169

Board #29

Linear Relationship Between Muscle Oxidative Capacity Determined by NIRS and Fitness Level in Young Adults

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PURPOSE: Maximal oxygen consumption is related to structural and functional adaptations within skeletal muscle tissue, e.g. capillary density increases in response to endurance training, higher mitochondrial content in athletes compared to sedentary individuals (Hoppeler et al, 1985). Oxidative capacity is one of the main muscle metabolism components that so far have been commonly evaluated by invasive (biopsy) or expensive methods (^{31}P-MRS). Recently, a non-invasive, near-infrared spectroscopy (NIRS) based approach has been proposed to estimate skeletal muscle oxidative capacity (Motobe et al, 2004). Studies have demonstrated that this technique is able to quantitatively measure muscle oxidative capacity, which was shown to be lower in physical inactive, elderly and chronic disease populations (Adami & Rossiter, 2018). Aim of the present study was to evaluate the relationship between mitochondrial oxidative capacity of the gastrocnemius muscle and fitness level in healthy young subjects.

METHODS: Twenty-one men and three women (data are mean±SD: age 34±9 yr; body mass 70±10 kg; height 176±7 m) volunteered for this project. Each participant visited the laboratory on two separate occasions. On their first visit, an incremental exercise (INCR) test on the cycle-ergometer was performed (ramp: +20-40W/min). Gas exchanges and heart rate were continuously measured. During the second visit, *gastrocnemius* oxidative capacity was assessed twice, at rest, from the muscle O_2 consumption recovery rate constant (*k*) using a continuous-wave NIRS.

RESULTS: Average INCR peak power output was 348±114 W (range: 195-520 W). $V'O_{2peak}$ was 3.66±0.88 l/min, ranging from 31.6 to 76.5 ml/kg/min. A total of 48 $mV'O_2$ recovery kinetics assessments were performed for the study. A good test-retest reliability (CV=10.2%, ICC=0.82) and no order effect were observed between consecutive measurements. On average, *k* for $mV'O_2$ was 2.39±0.76 min^{-1}, ranging from 1.19 to 3.75 min^{-1}. A significant linear correlation between $V'O_{2peak}$ and $mV'O_2$ was observed ($r^2=0.49$, $p=0.0002$).

CONCLUSIONS: We found a significant relationship between $V'O_{2peak}$ and muscle oxidative capacity in healthy subjects with different fitness level which was similar to that found by Hoppeler and colleagues (1985) on muscle samples obtained by biopsy ($V'O_{2peak}$ ~35-58 ml/min/kg; r2=0.41). Further studies are needed to evaluate if this technique allows to detect subtle functional changes of skeletal muscle in response to interventions in healthy subjects (e.g. nitrate supplementation, chronic hypoxia) and in presence of other factors limiting exercise tolerance (e.g. oxidative stress, inflammation).

Integrative exercise physiology and metabolism

Presentation Number: 170

Board #30

Lower Temperature Reduces Oxygen Cost for Contractile Activity in Isolated Mouse Skeletal Muscle

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Purpose: Evidence suggests that the energy efficiency of key ATPases involved in skeletal muscle contractile activity are improved in a hypothermic condition. However, it is unclear how a decrease in temperature affects skeletal muscle oxygen consumption (mVO_2) induced by muscle contraction. **Methods:** Isolated mouse extensor digitorum longus (EDL) muscles were incubated in a temperature-controlled (37°C or 25°C) bath that included an oxygen probe. EDL muscles from one limb were subjected to the measurement of resting mVO_2, and the contralateral EDL muscles were used for the measurement of mVO_2 with electrically-stimulated contraction. For the resting protocol, muscles were suspended at resting tension for 15 mins with continuous oxygen recordings. For the contraction protocol, EDL muscles underwent ten electrically-stimulated isometric contractions with continuous oxygen recordings for 15 mins. The rate of oxygen disappearance was quantified as µmole oxygen per minute and normalized to the wet weight of the muscle. **Results:** Resting mVO_2 was greater at 37°C than at 25°C, consistent with the idea that lower temperature reduces basal metabolic rate. Electrically-stimulated contraction robustly increased mVO_2 at both 37°C and 25°C, which was sustained for ~3 min post-contraction. During that period, mVO_2 was elevated ~5-fold at both 37°C and 25°C. Greater contraction-induced mVO_2 at 37°C compared to 25°C occurred despite lower force generated at 37°C than at 25°C. **Conclusion:** Together, oxygen cost for muscle contraction (force-time integral per oxygen consumed) was greater at 37°C than at 25°C. Levels of high-energy phosphates were consistent with greater energy demand at 37°C compared to 25°C. In conclusion, these results indicate that muscle contraction that occurs at subnormal temperature requires less oxygen than at 37°C.

Integrative exercise physiology and metabolism

Presentation Number: 171

Board #31

Muscle Anabolism is Not Improved by High Daily Protein or Post Exercise Timing in Fit Young Males Performing Simulated Elite Athlete Training.

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PURPOSE: A great deal of variation exists in recommendations of total daily protein intake and timing of supplementation for athletes. Widely accepted recommendations promote protein intakes for strength and power athletes of 1.6-1.8 grams/kg/day and post-exercise protein supplementation. To our knowledge, no studies have investigated an interaction between supplementation timing and total daily needs in athletic populations. The purpose of this study was to determine optimal protein intake and supplementation strategy for athletic populations in a stable training phase.

METHODS: A double blind randomized controlled trial was conducted on 46 young, trained males (21.8±3.1 yr, 182.2±6.2 cm, 83.5±13.6 kg). Subjects underwent a two-week familiarization period followed by the two-week intervention period, both consisting of concurrent sprint interval and resistance exercise (60-minute session, 4x/week) with nutritional interventions of low (LO = 1.3 g/kg total mass/day, 1.9 g/kg lean mass/day) and high (HI = 2.2 g/kg total mass/day, 2.7 g/kg lean mass/day) daily protein intake and whey protein supplementation (0.4 g/kg lean mass) either immediately (IPE) or three hours delayed (DPE) post-exercise. An age and activity matched control group (CON) completed food logs but continued their normal diet (1.6 g/kg total mass/day, 2.1 g/kg lean mass/day) and exercise regimens and did not perform exercise on the experimental day. Tests of body composition (dual x-ray absorptiometry) and performance measures (lower body power, isokinetic and isometric strength, and one-repetition-maximum lifts) were conducted before and after the intervention period. Cumulative muscle protein synthesis (C-MPS) was determined using deuterium stable isotope labeling (70%^2H_2O, 3ml/kg) to measure myofibrillar fractional synthetic rates (myoFSR) during the 24-hour post-exercise window.

RESULTS: No difference in myoFSR, total body %fat, or lean mass were found among groups. Normalized myoFSR was 2.4±1.7, 1.6±1.0, 1.7±1.1, and 1.4±1.0 fold higher in LO/DPE, LO/IPE, HI/DPE, and HI/IPE, respectively, relative to CON. Thigh %fat, total thigh fat mass, and thigh cross section fat mass decreased significantly in LO/DPE compared to CON.

CONCLUSIONS: Trained individuals undergoing simulated elite athlete training exhibited no significant differences in C-MPS, lean mass accretion, or performance measures regardless of total daily protein intake or supplementation timing strategy. These data suggest that individuals in a stable training environment do not require high protein intakes or immediate post-exercise protein consumption as previously recommended.

Integrative exercise physiology and metabolism

Presentation Number: 172

Board #32

Pre-Sleep Protein-Polyphenol Supplementation Suppresses Creatine Kinase Release following Muscle-Damaging Eccentric Exercise: Preliminary Findings

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Purpose Eccentric contractions (EC) damage myofibrillar structures, requiring a prolonged (days) remodelling period accompanied by transiently weakened force production, increased soreness and appearance of muscle proteins in systemic circulation. The overnight phase comprises a substantial portion of the remodelling period, yet pre-sleep nutritional strategies to augment overnight remodelling following EC have not been investigated. We investigated the effect of consuming a protein and polyphenol supplement before sleep on the temporal recovery of knee extensor function and soreness following a bout of EC.

Methods 18 healthy males and females (22 ± 1 yrs; BMI: 24.0 ± 0.9 kg/m^2 (± SEM)) consumed a controlled isocaloric diet (1.2 g·kg^{-1} protein) and randomised to supplement with either a commercial product (Beachbody LLC) containing 20 g casein protein and 480 mg tart cherry extract (PRO; n = 9; 4 females), or, an isocaloric maltodextrin placebo (PLA; n = 9; 3 females) before sleep for 14 consecutive days. At~1900 h on day seven, subjects performed 300 maximal unilateral knee extensor EC on an isokinetic dynamometer. Total isokinetic work over 30 maximal concentric knee extensions (TW), peak isometric torque (PT) and muscle soreness (visual analogue scale (VAS) and pressure pain threshold (PPT)) were measured relative to the contralateral control limb (%con) prior to and every 24 h for 7 d following EC. Plasma creatine kinase activity (CK) was measured concurrently. Data were analysed using two-way ANOVAs.

Results EC caused a maximum decline in TW and PT of the PLA group

after 48 h (TW = 67.6 ± 5.9 %con, PT = 68.8 ± 5.3 %con, $P < 0.05$), which was similar in the PRO group (TW = 75.1 ± 3.9 %con, PT = 73.9 ± 7.0 %con, $P > 0.05$). Thereafter, temporal recovery of TW and PT was similar between groups ($P > 0.05$) and was restored by 144 h. Muscle soreness (VAS and PPT) of the PLA group peaked within 72 h of EC ($P > 0.05$) and was restored by 144 h. The VAS and PPT response were similar in the PRO group, except *vastus medialis* PPT which recovered to baseline slower than in the PLA group (PRO = 96 h, PLA = 72 h, $P < 0.05$). CK, an intramuscular enzyme that leaks from muscle tissue following structural disruption, increased > 40-fold 96 h – 144 h following EC in the PLA group ($P < 0.05$). Conversely, no change from baseline in plasma CK was observed in the PRO group ($P > 0.05$).

Conclusions The lack of increase in CK with pre-sleep casein protein is remarkable and may suggest accelerated muscle remodelling following EC-induced muscle damage. Whether pre-sleep protein-polyphenol ingestion augments adaptations to resistance exercise training requires further investigation.

Work supported by a grant from Beachbody LLC, USA

Integrative exercise physiology and metabolism

Presentation Number: 173

Board #33

Self-reported Physical Activity and Microbiome ?-diversity in Colorectal Cancer Survivors

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PURPOSE: Less diverse gut microbiota have been implicated in colorectal cancer (CRC) risk. Physical activity (PA) and body mass index (BMI) can influence gut microbiome composition and function in healthy adults, however, the relationship between PA, BMI and gut microbiome α-diversity in CRC survivors has not been examined.

METHODS: Secondary data analyses from a dietary fiber intervention; Beans/Bran Enriching Nutritional Eating For Intestinal health Trial (NCT01929122). Baseline BMI (kg/m^2) was calculated using measured height and weight. Type and duration of PA was reported using three-day logs at three time points during the one-month intervention period. MET values, corrected for height, weight, and age, were assigned to each activity based on the 2011 Compendium of PA, then multiplied by duration to compute MET-hours per week. α-diversity data was calculated from the microbiome dataset completed for the participant's baseline stool samples and was reported as the Inverse Simpson number of species plus distribution. Participants with complete PA and microbiome α-diversity data (N=14) were included in analyses. Hierarchical multiple regression examined associations between PA and α-diversity, after accounting for BMI and sex.

RESULTS: Participants (N=7 female, N=7 male), were diagnosed with stage I-III CRC, M age=62±9 years old, M BMI=27.8±5.4 kg/m^2 (71.4% overweight or obese). PA levels were M=41.8±19.0 MET-hours per week. α-diversity values were M=15.0=±4.9. BMI, sex, and PA predicted α-diversity (F[3,10]=3.98 p= 0.042, R^2= .544). BMI was significantly associated with α-diversity (b=-.593, SE=.266, t(3)=-2.23, p=.050). PA accounted for an additional 16.2% of the variance in α-diversity but was not a significant predictor (b=.118, SE=.062, t(3)=1.887, p=.088).

CONCLUSION: PA, BMI and sex accounted for 54.4% of the variance in α-diversity. Compared with PA, BMI may have a stronger and opposing relationship with α-diversity in CRC survivors. The influence of BMI and PA levels may need to be co-considered for contributions to gut microbiome species richness and diversity along with fiber intakes in CRC survivors. Longitudinal studies are needed to determine how changes in body weight and PA levels modulate gut microbiome composition and function, particularly as emerging evidences exist for host and microbial metabolism to impact risk of CRC recurrence and disease free survival.

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Integrative exercise physiology and metabolism

Presentation Number: 174

Board #34

Swimming Exercise in the Nematode Caenorhabditis elegans Promotes Mitochondrial Maintenance and Protects from Mitotoxicant Exposures

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PURPOSE: Exercise and fasting provide numerous health benefits, including reducing risk of chronic diseases during aging. However, molecular mechanisms underlying these protections have remained elusive, partly due to a high cost and time investment of mammalian long-term diet and exercise intervention studies.

METHODS: Exercise intervention was achieved by subjecting young adult *Caenorhabditis elegans* nematodes to a 6-day, twice daily swimming exercise regimen, corresponding to the entire reproductive adulthood. During exercise sessions, the animals also experienced brief, transient food deprivation. Therefore, we included a non-exercise group with the same transient food deprivation, and a control with *ad libitum* access to food, assessing mitochondrial health and sensitivity to mitochondrial toxicants consequent to these regimens.

RESULTS: Exercise, combined with food deprivation, protected against age-related decline in mitochondrial morphology in body-wall muscle. Transient food deprivation increased organismal basal respiration (20% increase, $p<0.001$); however, exercise was the sole intervention that increased spare respiratory capacity (30% increase, $p <0.05$) and proton leak (2-fold increase, $p<0.05$). We observed modestly increased lifespan in exercised animals (median lifespan 19 days) compared to both control (18 days) and transiently food-deprived nematodes (15 days; $p<0.05$). Finally, exercised animals (and to a lesser extent, transient food deprivation animals) were markedly protected against lethality from acute rotenone and arsenic exposures, both of which target mitochondria. To clarify whether exercised animals benefited simply from a further energy expenditure compared to caloric intake, we also tested animals exercising in liquid media containing bacterial food. Those animals showed no benefits in mitochondrial respiration or lifespan; however, exercise in food also resulted in maintenance of better mitochondrial networks ($p<0.01$) and dramatic protection from arsenic and rotenone exposure. In current experiments, we are investigating the impact of long-term exercise intervention on age- and toxicant-induced neurodegeneration.

CONCLUSIONS: Swimming exercise and brief food deprivation provide effective intervention in *C. elegans* through distinct mechanisms, protecting from age-associated mitochondrial decline and providing resistance to mitotoxicant exposures. This novel long-term exercise model will allow researchers to take advantage of the short lifespan and genetic power of *C. elegans* to dissect the mechanisms that mediate the benefits of exercise and dietary restriction.

Integrative exercise physiology and metabolism

Presentation Number: 175

Board #35

The Use of Cardiopulmonary Exercise Testing in Assessing Mitochondrial Dysfunction in Gulf War Illness

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PURPOSE: Gulf War Illness (GWI) is a chronic multi-symptom illness affecting veterans who served during the 1990- 1991 Gulf War, but there are currently no objective diagnostic tests. Similarities in symptoms between known mitochondrial disorders and GWI have sparked investigations regarding the integrity of the mitochondria in veterans with GWI. These studies have demonstrated the presence of mitochondrial

dysfunction in GWI, which could serve as a potential diagnostic tool. Cardiopulmonary exercise testing (CPETs) has been used effectively to distinguish patients with and without mitochondrial myopathy (e.g., exaggerated ventilatory responses), but has not been thoroughly studied in patients with GWI. The purpose of this study was to characterize CPET performance in GWI and determine whether these responses reflected mitochondrial dysfunction as well as differed from veterans without GWI.

METHODS: We recruited 24 individuals for this study, 12 met case definition status for GWI (GWI+) and 12 were considered controls (GWI-). All individuals completed spirometry followed by a maximal CPET on a cycle ergometer with metabolic gas collection. Cases and controls were matched for peak cycling power, and we compared select CPET variables at peak exercise consistent with mitochondrial disorders (i.e., VO2, VE/VO2, VE/VCO2, RER, VO2 recovery, and lactate) using a one-way MANOVA. **RESULTS:** Cases and controls were matched for peak power (125.5±29.0 vs. 125.0±28.4 watts) and were similar in demographics (age: 52.5±6.8 vs. 52.1±5.8 years; sex: 25.0 vs. 41.7 % female; body mass index: 26.8±3.9 kg/m^2 vs. 28.3±4.8 kg/m^2), and baseline lung function (FEV_1/FVC: 94.1±6.9 vs. 100.5±9.0 % predicted, FEV1: 95.2±10.6 vs. 106.5±16.4%, FVC: 101.6±11.8% vs 106.3±13.1%). For our selected CPET variables, we did not observe a multivariate effect (Wilks' $\lambda = 0.72$, $F(6, 10) = 0.656$, $p = 0.687$).

CONCLUSIONS:

In our sample, we did not observe a functional CPET phenotype consistent with mitochondrial dysfunction among veterans with GWI. This may suggest that mitochondrial dysfunction is not sufficiently present among veterans with GWI to be detected by CPET or present at all. Future studies are necessary to confirm these findings as well as explore other etiological factors that contribute to symptoms of exercise intolerance and exertional fatigue in GWI.

Integrative exercise physiology and metabolism

Presentation Number: 176

Board #36

To Investigate the Overexpression of Adiponectin Receptor 1 Mice in Aerobic Running under Normobaric Hypoxia

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PURPOSE: During the long term aerobic exercise, glucose and free fatty acid are the major energy source. Adiponectin(ADI) is one of the Adipokines, which is produced and secreted exclusively by adipocytes. It regulates the metabolism of lipids and glucose with ADI receptors. In addition to regulating the function of energy metabolism, it is also associated with inflammatory response. Some studies showed that ADI and its receptors might be related to exercise. The reason might be that exercise training could increase circulating ADI levels and its receptors express. Besides, few studies indicated that hypoxia will cause inflammatory reaction and dysregulates the production of ADI. In fact, plasma ADI levels are modulated in order to response to exercise intensities. On the contrary opinions, some studies considered that ADI might not be related to exercise because aerobic exercise did not alter plasma ADI concentration. All of these studies showed different point of views about the effect of exercise on ADI levels and its receptors. Our previous studies have found that genetically modified mice appear to have a higher maximum oxygen uptake(131.13±4.82ml/kg vs 112.38±5.53ml/kg) and longer running time than the wild mice under normobaric normoxia. However, whether overexpression of adiponectin receptor 1 (ADIR1) affects exercise ability under normobaric hypoxia is still unclear? **METHODS:** To investigate the role of adiponectin R1 receptor in regulating aerobic exercise abilityunder Normobaric Hypoxia, we used ADIR1 overexpression transgenic mice (ADIR1) and wild-type mice (Wt) to study the effect of ADIR1 on aerobic exercise ability of mice. Using metabolic system and treadmill, the VO2max and maximum running time were measured under normobaric normoxia and normobaric hypoxia Cabin and then statistically analyzed by t-test between adiponectin R1 overexpression transgenic mice and wild type mice.

RESULTS: ADIR1 mice performed better aerobic exercise ability than Wt because the ADIR1 mice had significant longer running time than the Wt mice under normobaric hypoxia (13%O_2), ADIR1 young:3025±334sec vs WT young: 2845±147sec, ADIR1 old: 2365±219sec vs WT old: 1810±651sec (25m/min running test), ADIR1 young: 4832±648sec vs WT young: 4714±380sec, at 20m/min running test ADIR1 old: 3028±675sec WT old: 2388±794sec. Additional, ADIR1 mice showed difference Respiratory Quotient(0.77 vs 0.79) in Basal metabolic rate test.

CONCLUSIONS: Our data suggested that adiponectin R1 receptor might be involved in performance of aerobic exercise ability in mice by regulating the metabolism of lipids and glucose under normobaric normoxia and hypoxia environment.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 177

Board #37

A Novel Plasma Volume Biomarker Differentiates Between Dehydration and Fluid Intake During Exercise: Preliminary Results

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Purpose: To maximise endurance exercise performance, athletes are advised to minimise dehydration via fluid consumption. Researchers have thus sought to discover the ideal composition of drinks to optimise hydration status. Calculating plasma volume (PV) loss during exercise is important to quantify dehydration. Typically, haemoglobin and haematocrit are used to calculate PV loss (Dill & Costill, 1974; DC). However, a novel set of 8 haematological biomarkers has recently been proposed to better predict PV (Lobigs *et al*, 2017; BIO). This study investigated whether BIO could detect differences in PV with various hydration strategies during prolonged exercise and a subsequent cycling performance trial. **Methods:** 14 highly-trained male cyclists (27 ± 2 yrs; 71.9 ± 2.2 kg; VO_{2max}: 67 ± 2.1 mL/kg/min (±SEM)) completed 4 experimental visits separated by ≥ 1 week. During each visit, subjects performed 90 min of steady-state exercise (SS) on a cycle ergometer at 65% VO_{2max} (201 ± 5 W) followed by a 10 min rest, and a 15-min time-trial (TT). Venous blood samples were taken every 15 mins during SS and at the end of TT. During the four visits, subjects ingested no fluid (DEH) or a 273 mL drink every 15 mins during SS. The taste- and colour-matched drinks consisted of either a hypotonic (~220 mOsmol/L) carbohydrate (9 g)-electrolyte solution (CES) (HYPO), an isotonic (~280 mOsmol/L) CES (ISO), or water (H2O). Pre-trial PV was calculated from body mass (bm), and the DC and BIO models were applied to calculate PV changes. Differences in PV and TT performance were identified using two- and one-way ANOVA, respectively. A Bland-Altman plot was used to analyse agreement between DC and BIO. **Results:** Subjects lost an average of 1.6 ± 0.1 kg bm (2.3 ± 0.1%) during SS in DEH, but not ISO, HYPO, or H2O. All groups lost ~0.4 kg bm during TT. From a similar pre-SS value, PV reduced in DEH during SS (334 ± 27 mL, P=0.003), but not in H2O, ISO or HYPO (182 ± 25, 169 ± 26, 224 ± 22 mL, respectively). PV loss of ~180 mL occurred in all groups during TT (P<0.001). Calculations of PV change using DC and BIO correlated well ($R^2 = 0.63$), but there was a 92.8 mL greater PV loss bias for BIO. 4.4% of measurements fell outside of the upper and lower 95% limits of agreement (-275 to 89.5 mL). Total work performed during TT in DEH (3.42 ± 0.11 kJ/kg) was lower than H2O, ISO and HYPO (3.65 ± 0.1, 3.69 ± 0.12, 3.64 ± 0.13 kJ/kg, respectively, $P < 0.05$). **Conclusions:** Athletes should drink either water or a CES during prolonged exercise to maintain PV and performance. Calculated PV losses using the classic DC and novel BIO methods correlate well with similar variability, however, there is little agreement. **This work was supported by a grant from Beachbody LLC, USA**

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 178

Board #38

A Single Bout Of Heat Stress Increases Mitochondria-related Genes With A Non-detectable Changes In P53 Phosphorylation And Translocation In Skeletal Muscle

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PURPOSE: We have shown heat stress induces mitochondrial biogenesis in skeletal muscle. However, its underlying mechanisms have not been clarified. Recent emerging evidence indicates that tumor-suppressor p53 involved in exercise-driven mitochondrial gene transcription in skeletal muscle. Based on these findings, we tested whether a single session of heat stress treatment activates p53 and whether the activation of p53 pathway can be a mechanism underlying heat stress-induced mitochondrial biogenesis. **METHODS:** Male ICR mice were involved. Immediately after treatment and three hours after a single bout of heat stress treatment (exposing mouse into a hot environment chamber; 40°C, 30 min), gastrocnemius muscles were collected and then examined changes in expression of mitochondrial genes and p53 activity (phosphorylation status and nuclear and mitochondrial localization). **RESULTS:** We found a single bout of heat stress increased expression of mitochondria-related genes encoded by nDNA (Cs: +21.7%, Alas: +24.8%, Tfam: +21.7% and Cytc: +22.5%, $P<0.05$) and mtDNA (Cox2: +38.5%, Nd1: +29.1% and Nd4: +40.4%, $P<0.05$) three hours after treatment. However, there are non-detectable changes in phosphorylation($P=0.84$) and sub-cellular localizations of p53 (no p53 band on western blot was observed in nuclear and mitochondrial fractions) at both immediately and 3h after heat stress. **CONCLUSION:** Heat stress activates mitochondrial gene transcription, which may not be mediated by p53 activation.

Skeletal muscle, exercise, inactivity, and signaling

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Board #39

An Iterative Interaction based Screen to Unravel FGF21 Signaling

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PURPOSE: FGF21 is an emerging hormone with important roles in glucose and lipid metabolism. Its secretion has recently been shown to be upregulated following exercise and it was shown to be required for the beneficial effect of exercise in mice during high fat diet feeding. However, the intracellular signaling pathways mediating the beneficial metabolic effects of FGF21 are still incompletely understood.

METHODS: FGF21 signals through its cognate receptor beta-klotho (KLB), causing heterodimerization with FGFR1 and subsequent signal transmission. To study the interactions between the KLB-FGFR1-complex and intracellular partners, we employ a recently described proximity labelling technique based on APEX2. A small peroxidase attached to KLB allows for rapid biotinylation of nearby proteins and subsequent immunoprecipitation and mass-spectrometric analysis, enabling us to study the signaling complexes and interactions in the presence or absence of FGF21. Identified novel interactors can be knocked out and their effect on FGF21 signal transmission studied using readouts such as lipolysis- or glucose uptake assays. Relevant functional interactors will then be APEX-labeled themselves to study downstream signaling complexes and confirm their relevance by functional studies, allowing us to unravel the intracellular signaling network of FGF21.

RESULTS: We have generated a c-terminally labeled KLB-APEX2 construct and confirmed its functional FGF21 signaling and rapid biotin-labelling of nearby proteins in HEK293 cells. We are currently establishing immunoprecipitation for subsequent proteomic analysis. **CONCLUSIONS:** This approach will identify novel interaction partners of FGF21 signaling and help elucidate the intracellular pathways involved in the beneficial metabolic effects of FGF21.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 180

Board #40

Blood-flow Restriction Resistance Exercise For Older Adults With Knee Osteoarthritis

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Purpose: To conduct a randomized, single-masked pilot study to compare the feasibility and relative efficacy of low-load resistance training with blood-flow restriction (BFR) compared to moderate-intensity resistance training (MIRT) for improving muscle strength, pain, and physical function among older adults with knee osteoarthritis (OA). **Methods:** Older adults (N=35, ≥60 years) with objectively-measured physical limitations and symptomatic knee OA were randomized to 12 weeks of lower-body MIRT or BFR. Four exercises were performed three times per week to volitional fatigue at either 60% (MIRT) or 20% (BFR) of 1RM. Study outcomes included isokinetic quadriceps extensor peak torque across three speeds of movement (60, 90, 120 °/sec), body composition, objective measures of physical function (i.e. Short Physical Performance Battery [SPPB] and fast-paced gait speed over 400 meters), and self-assessed pain via the Western Ontario and McMaster Universities OA Index (WOMAC). Data were analyzed using the intention to treat approach with adjustments for all randomized participants for visit, age, gender and baseline pain score from a visual analog scale. As a pilot study, statistical significance between groups was not anticipated. Data are presented as estimated mean differences (accounting for statistical adjustments) at 12 weeks between groups with the 95% confidence interval. **Results:** The change in knee extensor peak torque from BFR was -4.5 Nm (-11.8, 2.8) relative to the change observed from MIRT. Changes in body fat percentage and total lean mass from BFR were 1.1% (-0.3, 2.5) and -1.3 kg (-3.0, 0.4) relative to MIRT. The change in gait speed was -0.03 m/sec (-0.13, 0.06), SPPB score was -0.4 points (-1.5, 0.6), and total WOMAC score was -0.3 points (-9.3, 8.7) for BFR relative to changes induced by MIRT. **Conclusions:** Most outcome measures directionally tended to favor MIRT, though confidence intervals from this small sample suggest that further follow-up is warranted. Subsequent data analysis from will evaluate relevant demographic and training factors which may aid interpretation of these results, and will evaluate indices (e.g. adherence, exertion, perceived pleasantness) relevant to long-term adherence to the two training regimens. Ultimately, this study indicated that BFR was a safe and feasible training regimen for older adults with knee OA, and these results provide the necessary pilot data to plan a full scale trial comparing BFR and MIRT.

Research supported by the National Institute for Arthritis and Musculoskeletal and Skin Disease (1R21AR065039), University of Florida Claude D. Pepper Older Americans Independence Center (2P30AG028740).

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 181

Board #41

Central Mechanisms, Not Sex Differences, Predict Plantar Flexor Fatigue for an Intermittent Maximal Isometric Contraction Task

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PURPOSE: Females are less fatigable (measured as an acute reduction in force or power) in many upper and lower limb muscle groups (Hunter 2016). There is minimal understanding about sex differences in the plantar flexor (PF) muscles and the underlying mechanisms. Females were less fatigable in maximal dynamic shortening contractions (Lanning 2017) and after an ultra marathon (Temesi 2015), although there was no sex difference in fatigability following sustained 10-min submaximal contraction when males and females were matched for absolute strength (Hatzikotoulas 2004). The variability in findings could be due to differences in task demand (Hunter 2016) for this postural muscle group (Gimmon 2011). The purpose of this study was to determine the sex differences and mechanisms of fatigability for an intermittent isometric PF task. **METHODS:** 30 subjects (15 male) completed four baseline maximal voluntary isometric contractions (MVIC) of the PF. Peripheral electrical stimulation of the tibial nerve was performed during and immediately after baseline MVICs to determine voluntary activation (VA) [calculated as 100*(1-(superimposed twitch/potentiated twitch))] and contractile properties from the potentiated twitch. Subjects then performed intermittent MVICs, (2-s contractions followed by 2-s rests) for 4 minutes with nerve stimulation every 60 seconds. PF fatigability (FAT) was expressed as the relative drop in MVIC from pre- to post-task. **RESULTS:** Males demonstrated greater baseline MVIC torque (31.6%, p=0.035) and resting twitch amplitude (34.9%, p=0.003) than females. There were no sex differences in either baseline VA (3.6%, p=0.35), FAT (3.6%, p=0.59), change in VA from pre- to post-task (10.5%, p=0.21) or change in twitch amplitude (2.4%, p=0.96). FAT was positively correlated with the reduction in VA (r=0.62, p<.001) but not with any twitch properties. **CONCLUSIONS:** There were no sex differences in fatigability of the PF muscles. However, the reduction in neural drive to the muscle groups (central fatigue) was the greatest predictor of plantar flexor fatigability for a time-constrained intermittent maximal isometric task, with minimal contribution of muscular mechanisms. These data suggest that: (1) contrary to other limb muscles, central mechanisms were primarily responsible for fatigue in the PF muscles, and (2) taken together with other studies, the sex difference in fatigability of the PF is task dependent.

This work was supported by a Promotion of Doctoral Studies Level I Scholarship from the Foundation for Physical Therapy and the Clinical & Translational Rehabilitation Health Sciences graduate program at Marquette University.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 182

Board #42

Desensitized *GADD45a* Promoter Methylation and Gene Expression Accompany Prolonged Performance Decrements at Old Age

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PURPOSE: With aging, responsiveness to resistance-type exercise becomes more dependent on training design. Rodent studies have demonstrated that muscles of young rats exposed to 80 stretch-shortening contractions (SSCs) 2 or 3 days per week for 1 month incurred gains of 20% in muscle mass and 30% in performance regardless of the number of days per week trained. Meanwhile, given these training regimes, muscles of old rats only sustained increases in muscle mass and muscle quality following the 2 days per week training. The purpose of the present study was to determine whether apoptosis-relevant DNA methylation and gene expression profiles following an acute bout of SSCs provide insight into the age-related training response.

METHODS: Muscles of 3 months old and 30 months old Fischer Brown Norway hybrid rats were exposed to a single protocol of 80 SSCs with performance, apoptosis-related DNA methylation, and gene expression were evaluated at multiple time points between 6 and 120 hours. ANOVA was used for statistical analysis; significance was set at $p < 0.05$.

RESULTS: For non-exposed muscles of old vs young rats, growth arrest and DNA damage inducible alpha (*GADD45a*), an indicator of DNA damage, was the most differentially expressed gene (17-fold increase, $P = 0.001$). For muscles of young rats 6 hours post SSCs, the greatest fold change in gene expression (a 21-fold increase, $P < 0.0001$) was observed for growth arrest and DNA damage inducible alpha (*GADD45*a), an indicator of DNA damage. By 24 hours, isometric force output for young rats recovered to pre-SSC values and by 120 hours, *GADD45a* expression was 2-fold increased ($P = 0.02$). Decreased promoter methylation for *GADD45a* at 120 hours indicated epigenomic regulation. In contrast with young data following SSCs, *GADD45a* for old rats was not differentially methylated and expressed and muscle performance recovery required greater than 48 hours.

CONCLUSIONS: A muted responsiveness characterized by desensitized *GADD45a* gene expression potentially owing to epigenomic regulation underlies prolonged muscle weakness following SSCs and dependency on low training frequency at old age. *Disclaimer:"The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention."*

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 183

Board #43

Disruption of AMPK-Glycogen Binding In Vivo Reveals Physiological Roles in Exercise and Metabolism

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PURPOSE: The AMP-activated protein kinase (AMPK) and glycogen are essential for exercise metabolism. The energy-sensing AMPK heterotrimer contains a regulatory β subunit with a carbohydrate-binding module (CBM) that binds glycogen. However, the physiological roles of AMPK-glycogen binding in exercise and metabolism *in vivo* are unknown.

METHODS: To determine the effects of disrupting AMPK-glycogen binding, two whole-body knock-in (KI) mouse lines were generated on a C57BL/6 background to target tryptophan residues known to mediate glycogen binding in either the AMPK β1 (W100A KI) or β2 (W98A KI) subunit, predominantly expressed in liver and skeletal muscle, respectively. Whole-body metabolic and exercise phenotyping and biochemical analyses of serum and tissues were performed in male KI and wild type (WT) litter mate control mice maintained on an *ad libitum* chow diet.

RESULTS: Intraperitoneal glucose tolerance testing (2 hr, area under the curve [AUC]) revealed normal glucose tolerance in W100A mice but impaired glucose handling in W98A mice (56% increase in AUC; $P<0.05$) compared to WT, with no differences in fasting serum insulin levels between WT and KI mice. Body composition (determined from EchoMRI) showed normal whole-body fat mass and lean mass in W100A mice. Strikingly, W98A mice displayed a 42% increase in fat mass ($P<0.05$) and 5% decrease in lean mass ($P<0.05$) relative to WT. Metabolic caging experiments over three days of normal 12:12-hr light-dark cycles demonstrated no changes in cumulative food intake, O_2 consumption, indirect calorimetry or infrared-based activity levels between WT and KI

mice. Compared to WT, maximal running speed was similar in W100A but reduced by 11% in W98A mice (P=0.057). No differences were observed in submaximal running time to exhaustion or resting tissue glycogen content between KI and respective WT mice. There were no differences in epididymal fat pad mass, hindlimb muscle mass or liver and muscle mitochondrial content. Fat deposition was increased by 61% in W100A liver (P<0.05) and 54% in W98A quadricep muscle (P<0.05) versus WT, concomitant with reductions in total protein content of AMPK catalytic α and regulatory β subunits.

CONCLUSIONS: These data suggest that glycogen-bound AMPK is central to the regulation of whole-body and tissue metabolism, exercise capacity and cellular energy sensing. We reveal new insights into the physiological roles of AMPK and suggest that a loss of glycogen binding negatively impacts exercise and metabolism via reductions in the total cellular AMPK pool. This work was supported by an ACURF Early Career Researcher Grant to NJH.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 184

Board #44

Effect Of Diet Induced Obesity On Muscle Growth Following Functional Overload Surgery

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Purpose: Anabolic resistance leads to the attenuation of muscle growth under conditions of increased loading, such as recovery from disuse and functional overload (FO). Chronic exposure to high levels of fatty acids can increase triglyceride (TG) content in skeletal muscle. The impact of elevated muscle TG on skeletal muscle growth and the development of anabolic resistance is not fully known. Thus, we wanted to test what role elevated TG content plays in the development of anabolic resistance in male C57Bl/6 mice. **Methods:** Five to eight week old male C57Bl/6 mice (Charles River) and MuRF1 KO were fed either low fat diet (10% fat, LFD, D12450H) or a high fat diet (45% fat, HFD, D12451) for 22 to 29 weeks. After 20 or 25 weeks, mice from each diet were divided into either control, 14- or 30-day FO groups. All FO groups received bilateral FO of the plantaris muscle. **Results:** After 22 weeks on a HFD, both WT and MuRF1 KO mice developed insulin resistance; however, TG content was significantly (p<0.05) elevated only in WT mice. In response to 14 and 30 days of FO, the growth of the plantaris muscle was significantly (P<0.05) reduced in WT, but not MuRF1 KO mice. **Conclusions:** These results have led to the formulation of our central hypothesis that the development of anabolic resistance in diet-induced obesity is related to an accumulation of intramuscular lipids and increased of fatty acids intermediates. Supported by NIH R01 AR070031.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 185

Board #45

Effects Of Combined Antioxidant Supplementation And Resistance Exercise On Disuse Muscle Atrophy.

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Purpose: It has been shown that disuse muscle atrophy is associated with attenuation of muscle protein synthesis and elevation of muscle protein degradation. Both of these processes have been shown to relate to the accumulation of reactive oxygen species (ROS). Although one of the potent countermeasures for the disuse atrophy is resistance exercise (RE), our recent study with animal training model showed that RE with excessive frequency causes production of ROS, and may lead to attenuated protein synthesis and elevated protein degradation (Takegaki et al., 2017). Thus it was hypothesized that antioxidant supplementation can optimize the preventive effect of RE on disuse muscle atrophy. To test this hypothesis, this study investigated the effects of combination of antioxidant and RE on muscle protein synthesis and degradation in hindlimb-suspended mice muscles. **Method:** Male C57BL/6j mice were assigned to two groups:control group administered with saline and antioxidant-treated group administered with N-acetyl cysteine (500 mg/g bodyweight). In both groups, mice were subjected to a 14-day hindlimb suspension, during which sessions of RE (50 repetition of maximal isometric contractions) were given three times per week. Right leg was subjected to training and the other was used as untrained control. After the period of hindlimb suspension, samples of the gastrocnemius muscle were excised, and subjected to the measurements of protein carbonyl, muscle protein synthesis (SUnSET method) and degradation (signal transduction assays for ubiquitin proteasome pathway and autophagy). **Results:** Either RE or antioxidant administration was effective to attenuate the decrease in muscle wet weight. However, the combination of RE and antioxidant administration showed no significant difference when compared with the effect of RE or antioxidant administration alone. On the other hand, the combination of RE and antioxidant was more effective to attenuate the loss of muscle strength than RE alone. There was no significant additive effects of the combination on muscle protein synthesis, mTOR signaling, ubiquitin proteasome and autophagy, when compared to the effects of RE or antioxidant alone. **Conclusion:** The present results suggest that oxidative stress plays an important part in the disuse muscle atrophy, and RE and antioxidant are both effective to attenuate the atrophy through, at least partially, the same mechanism. RE is more beneficial than antioxidant alone because of its stronger effect to attenuate the loss in strength.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 186

Board #46

Effects of Exercise Prior to Hindlimb Unloading and During Recovery on Gastrocnemius Mass

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Purpose Our previous studies support the idea that a metabolic programme can play a major role in triggering disuse skeletal muscle atrophy. We demonstrated that gastrocnemius of mice overexpressing PGC1α is protected from disuse atrophy through the inhibition of catabolic pathways mediated by PGC1α. Since it is known that endurance exercise activates PGC-1α stimulating mitochondrial biogenesis, we hypothesized that exercise training before hindlimb suspension (HU) could prevent mitochondrial dysfunction and muscle atrophy. To test this hypothesis, the effects of physical preconditioning on muscle mass and pathways involved in its maintenance were studied. Furthermore, to verify if disuse affects muscular adaptations to exercise we applied the same volume of exercise during recovery following HU. **Methods** Six months-old male mice were divided into 4 groups: control mice (CTRL), mice subjected to 3 days HU (HU-3), mice trained for 7 days before 3 days HU (EX+HU-3), mice trained for 7 days following 3 days HU (HU-3+EX). Exercise training was performed on treadmill for 7 consecutive days. **Results** HU-3 induced a significant gastrocnemius atrophy associated with activation of ubiquitin proteasome system (UPS) (Murf1 and atrogin1 induction) and autophagy (LC3II/LC3I increase). Physical preconditioning protected gastrocnemius from disuse atrophy. Such prevention was not associated with an evident effect on mitochondrial biogenesis (no PGC1a induction in EX+HU-3 vs HU-3 group) and dynamics (no changes of profusion Mfn2, Mfn1 and Opa1 and profission DRP1 and Fis1 in EX+HU-3 vs HU-3 group). Furthermore, the catabolic pathways activation was not counteracted (persistent high levels of UPS and autophagy markers in EX+HU-3) whereas an increase of mTOR phosphorylation level was found. Conversely, gastrocnemius of mice performed exercise following HU showed a restoration of mass associated with a significant increase of PGC1? level, an improvement of mitochondrial fusion (high Mfn2 and Opa1 protein level in HU-3+EX vs HU-3), absence of catabolic pathways induction (UPS and autophagy), normalization of redox status (NRF2 mRNA decrease). **Conclusions** The same volume of endurance exercise

applied before and following HU resulted in a different muscle remodelling. Preconditioning totally protected muscle from atrophy with a mechanism that does not involve the catabolic systems inhibition via induction of mitochondrial parameters. Disuse did not compromise the muscle ability to adapt to exercise restoring muscle mass with a mechanism that mimics that found in gastrocnemius protection in unloaded transgenic mice overexpressing PGC1α

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Presentation Number: 187

Board #47

Effects Of Graded Whey Protein Supplementation On Hypertrophic Indices During Extreme Volumes Of Resistance Training

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Purpose: We examined hypertrophic outcomes of weekly graded whey protein dosing (GWP) versus whey protein (WP) or maltodextrin (MALTO) dosed once daily during 6 weeks ofresistance training (RT). **Methods:** College-aged resistance-trained males (training age=5±1 yrs; mean±SE) were assigned to WP (25g/d; n=10), MALTO (30g/d; n=10), or GWP (25-150 g/d from weeks 1-6; n=11). RT occurred 3d/wk (2 upper- and 2 lower-body exercises/d, 10 repetitions/set), and RT volume increased from 10 sets/exercise (week 1) to 32 sets/exercise (week 6). The 6-week RT program implemented was designed to involve higher RT volumes than ever investigated in this timeframe. Tests performed prior to training (PRE) and after weeks 3 (MID) and 6 (POST) included dual-energy x-ray absorptiometry (DXA), vastus lateralis (VL) and biceps brachii ultrasounds, and bioelectrical impedance spectroscopy (BIS). VL biopsies were also collected for immunohistochemical staining. Repeated-measures ANCOVAs were performed, although emphasis was also placed on effect size calculations. **Results:** The GWPgroup experienced the greatest PRE to POST reduction in DXA fat mass (FM) (-1.00 kg, d=- 0.24, $p<0.05$) and increase in DXA lean body mass (LBM) (+2.93 kg, d=0.33, $p<0.05$). DXA LBM increases (ΔLBM) occurred from PRE to MID (+1.34 kg, $p<0.001$) and MID to POST (+0.85 kg, $p<0.001$) across all groups. However, when adjusting ΔLBM for extracellular water changes, a significant increase occurred from PRE to MID (+1.18 kg, $p<0.001$), but not MID to POST (+0.25 kg; $p=0.131$). **Conclusions:** Larger effects on FM and LBM in GWP subjects indicates a need for longer-term investigations with greater sample sizes examining graded WP intakes and RT. Additionally, ECW-corrected LBM gains were largely dampened, but still positive, in resistance-trained subjects when RT exceeded ~20 sets/exercise/wk.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 188

Board #48

Effects Of High-fat Diet Induced Obesity On Contractile Function And Intracellular Ca^{2+} Release In Skeletal Muscle Of Aged Mice.

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PURPOSE: Obesity and aging are characterized by decreased muscle mass and muscle contractile function. In this study, we tested the hypothesis that a high-fat diet (HFD)-induced obesity may exacerbate contractile dysfunction and impair Ca^{2+} release in aged skeletal muscle. **METHODS:** Male C57BL/6 mice were fed a low-fat diet (LFD) or a HFD (60% kcal: fat) at 5 months of age (Young LFD/HFD) and 22 months of age (Old LFD/HFD). Skeletal muscle force was assessed by electrical stimulation ex vivo. Intracellular Ca^{2+} levels during contraction and pharmacological stimulation were analyzed by calcium imaging. **RESULTS:** Muscle force production was decreased with age and with HFD-feeding, and these effects were additive in the extensor digitorum longus muscles from the Old HFD group. With electrical stimulation, Ca^{2+} levels decreased with HFD-feeding and aging, but their effects were not cumulative. Pharmacologic activation of Ca^{2+} channels also revealed that the effect of aging on intracellular Ca^{2+} flux was greater than that of diet intervention. There was a significant correlation between low Ca^{2+} release capacity and increased intramyocellular lipid accumulation, suggesting that aging and HFD-feeding may interfere with SR Ca^{2+} kinetics. While age or diet intervention had no effect on the expression levels of Ca^{2+}-release channel (calsequestrin, dihydropryridine receptor and ryanodine receptor), there was age-dependent reduction in the calcium-binding protein into the SR lumen. **CONCLUSIONS:** These data suggest that impairment of contractile force in aged muscle is aggravated by a HFD, which may be explained by a dysfunction of SR-mediated Ca^{2+} release.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 189

Board #49

Effects Of Repetition Number On Muscle Protein Synthesis In Rodent Resistance Exercise Model

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Purpose: In general, repetition number of resistance exercise is prescribed as maximum. On the other hand, repetitions in the late phase of the exercise session tend to reduce velocity and, as a result, power output. The meaning of later low power repetitions in one exercise session is uncertain. By using our rodent resistance exercise model, we investigated effects of repetition numbers of resistance exercise on anabolic responses in rat skeletal.

Methods: Eleven male Sprague Dawley rats (n=11) were randomly assigned into low repetitions group (n=5, 5 repetitions x 5 sets) and the high repetitions group (n=6, 10 repetitions x 5 sets). Unilateral electrical stimulation of rat right gastrocnemius as a resistance exercise (isometric contraction, 80V, 100 Hz, 3 sec stimulation-7 sec rest). Left hindlimb was served as the internal control. Six hours after exercise session, we injected puromycin 15 minutes prior to dissection. Medial gastrocnemius muscles were used for biochemical analysis. Puromycin-labeled newly synthesized proteins and a post-translational modification of ribosomal proteins were measured by western blot.

Results: We found positive main effects of stimulation on protein synthesis rate and phosphorylated S6 ribosomal protein $^{ser240/244}$. However, there was no interaction between the number of repetitions and stimulation and main effect of the number of repetitions.

Conclusion: Even though exercise volume was different (5 repetitions x 5 sets vs 10 repetitions x 5sets), anabolic responses were equivalent. We speculate that repetitions with high power output are enough for inducing muscle protein synthesis.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 190

Board #50

Endurance Training Up-regulate Cellular Aldh2 Activity In Skeletal Muscle

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PURPOSE: ALDH2, a mitochondrial aldehyde dehydrogenase, plays important role in redox homeostasis as well as in an alcohol catabolism. However, specific functions and adaptabilities in skeletal muscle has been unclear. We, therefore, tested whether exercise training induces

ALDH2 adaptations in skeletal muscle. **METHODS:** Male C57BL/6J mice were divided into the sedentary control (n=6) and the endurance training group (n=6). Mice in the endurance training group were conducted treadmill running (25 m/min,60 min/day, 5 days/wk, 3 wks). Twenty-four hours after the final training session, gastrocnemius muscles were collected and then prepared for enzymatic activity assays. **RESULTS:** We first confirmed that our endurance training protocol sufficiently induced mitochondrial biogenesis, based on increased activities of citrate synthase (+37.1%,P<0.05) and cytochrome c oxidase (+93.4%,P<0.01). We found that ALDH2 activity (a capacity of aledehyde dehdrogenase) at whole-lysate level was increased by endurance training (+62.5%, P<0.05). In contrast, ALDH2 activity in isolated mitochondrial fraction showed no significant difference between the groups (P=0.40). **CONCLUSIONS:** Endurance training up-regulated cellular ALDH2 activity in skeletal muscle, concomitantly with mitochondrial biogenesis.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 191

Board #51

Exercise Attenuates Loss Of Muscle Mass During Diet-induced Weight-loss Consistent With Altered Transcriptional Networks

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The loss of muscle mass and physical function with aging may be exacerbated by obesity. Diet-induced weight-loss results in loss of fat mass (FM) and improved metabolic health, but also some loss of fat free mass (FFM), comprising mostly muscle, which may negatively impact physical function. The addition of exercise to a weight-loss intervention could preserve skeletal muscle mass in older obese adults, although data from clinical trials are scarce, and the underlying mechanisms are not known.

PURPOSE: To examine the effects of diet-induced weight loss alone (DIWL), or with the addition of exercise (WLEX), on the skeletal muscle transcriptome and changes in lean body mass in older obese adults.

METHODS: 58 older men (M) and women (W) (69±5 yrs) completed a 6-month randomized controlled trial (RCT) consisting of either Health Education Control (CON: n=20, 7M/13W), DIWL (n=19, 7M/12W), or WLEX (n=19, 7M/12W). DIWL and WLEX groups had a goal of 10% weight-loss through caloric restriction. The WLEX group completed a progressive exercise training program (4-5d/wk, 45min/session) consisting of aerobic and resistance exercise. Cardiorespiratory fitness (VO_{2max}) was determined by a graded exercise test and body composition was determined by DXA. To begin to understand the molecular mechanisms underlying changes in FFM, muscle biopsies of the vastus lateralis were obtained before and after the interventions to perform RNA-sequencing and informatics analysis.

RESULTS: The WLEX group lost more weight (-11.0%) than the DIWL (-6.8%) and CON (-1.4%) groups (P<0.05). The WLEX group also lost more FM (-9.1kg) than the DIWL (-4.9kg) and CON (-0.0) groups (P<0.05). The DIWL group, however, lost more FFM compared to the CON group (DIWL: -1.6kg vs. CON: 0.0kg; P=0.06). The addition of exercise to the weight loss intervention tended to attenuate the loss of FFM (WLEX: -1.0kg, P>0.05). VO_{2max} (ml/FFMkg/min) increased only in the WLEX group following intervention (CON: -3.8%, DIWL: -3.9%, WLEX: 9.9%; P<0.05). RNA-sequencing revealed transcriptional activation of atrophy and proteolytic pathways in the DIWL, which were not observed for WLEX. Further, the WLEX group displayed activation of angiogenesis and the IGF-Akt signaling pathway.

CONCLUSION: The addition of exercise to diet-induced weight loss results in greater weight loss with less lean mass loss and improved cardiorespiratory fitness. The effect on skeletal muscle is likely mediated by regulation of proteolytic and muscle growth transcriptional networks, suggesting these pathways may be important for preservation of muscle in older adults during intentional weight loss.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 192

Board #52

Fiber Type-Specific Activation of AMPK Following Acute High Intensity Interval Exercise in Concurrently Trained Men

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PURPOSE: AMP-activated protein kinase (AMPK) is an energy-sensing regulator of cellular metabolism that is activated during acute exercise. Previous human skeletal muscle studies analyzed AMPK activation in mixed fiber type (FT) biopsy samples, though recent investigations show that AMPK's properties are dependent on myosin heavy chain (MHC) FT (i.e., slow- vs. fast-twitch). The purpose of this study was to assess the phosphorylation of AMPK and three of its substrates (markers of AMPK activity), ACC, TBC1D1 and TBC1D4, in slow (MHC I) vs. fast (MHC IIa) skeletal muscle fibers from concurrently trained men following acute high intensity interval training (HIIT) exercise. **METHODS:** Nine concurrently trained males (age 31±2 y; height 176±8 cm; mass 81±10 kg; VO_2max 52.6±6.1 ml/kg/min) underwent a resting muscle biopsy from their right *vastus lateralis* (VL) then completed a HIIT bout consisting of 6 rounds (Intervals: 1.5 min at 90-100% VO_2max, then 2.5 min at ~40%). A second biopsy (left VL) was performed immediately after completion of the final exercise round with a third and fourth biopsy collected at 90 min and 180 min post-HIIT. Single muscle fibers were mechanically isolated for MHC analysis via SDS-PAGE to identify FT and combined into MHC I and MHC IIa pools of 5-8 fibers. FT-specific phosphorylation of AMPKα, ACC, TBC1D1 and TBC1D4 was quantified via capillary nano-immunoassay (CNIA). **RESULTS:** AMPKα phosphorylation was significantly (p<0.05) elevated (2.1-fold) between rest and 0 min post-HIIT only in MHC IIa fibers. Phosphorylation of ACC was significantly elevated between rest and 0 min for both MHC I and MHC IIa (5.1 and 8.9-fold higher, respectively) with a significant difference between MHC I and MHC IIa post-HIIT. TBC1D1 expression was significantly higher in MHC IIa vs MHC I, but with significantly higher phosphorylation in MHC I across all time points. Significant phosphorylation of TBC1D1 was also detected in MHC IIa at 180 min post-HIIT compared to rest (2.2-fold). TBC1D4 expression was significantly higher in MHC I vs MHC IIa with significantly higher phosphorylation in MHC IIa across all time points. Significant phosphorylation of TBC1D4 was also detected in MHC I at 90 min post-exercise compared to rest (1.5-fold). **CONCLUSIONS:** HIIT exercise induced *1)* FT-specific activation of AMPK, *2)* FT-specific differences in phosphorylation of AMPKα and all three substrates measured, and *3)* delayed phosphorylation responses in TBC1D1 and TBC1D4 in trained men. This knowledge enhances our understanding of the FT-specific molecular consequences of HIIT. Supported in part by a donation from Renaissance Periodization.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 193

Board #53

Influence of Creatine on AMPK and Protein Synthesis after Simulation of Exercise in C2C12 Myotubes

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AMP-activated protein kinase (AMPK) is a well-known sensor of cellular energy status, assisting in regulation of both glucose uptake and metabolism in skeletal muscle. While the understanding of its role in glucose and fat metabolism is fairly well defined, the molecule's influence over protein synthesis is less clear. Increases in the AMP/ATP ratio observed in muscle contraction lead to a phosphorylation of AMPK and a repression of the mTOR signaling pathway. Creatine, a component of the cellular energy store creatine phosphate and a commonly used ergogenic aid, may have a role in regulation of AMPK activation by

altering the cellular AMP/ATP ratio during exercise. **PURPOSE:** To determine the role of creatine supplementation on protein synthesis rates and the effects AMPK elicits on anabolism following AICAR and or Flex simulations of exercise in C2C12 myotubes. **METHODS:** Cultured C2C12 cells were supplemented with or without creatine and/or AICAR, in media enriched with 4% D20. Four hours after incubation began; half of each treatment group underwent simulated exercise using Flex (10% stretch, 1 Hz for 10 min). Cells were harvested from each pharmacological and/or exercise treatment at 30 minutes, 3 hours or 24 hours post D2O enrichment. **RESULTS:** Our results indicate that creatine supplementation augmented myotube anabolism when compared to control. When cells were incubated with creatine and AICAR, it appeared that creatine was sufficient to maintain rates of protein synthesis in the early time points, but that the positive impact of creatine had dissipated by 24h (136.1%/d, 77.5%/d, and 33%/d respectively). Generally, AICAR or Flexed groups had similar rates of synthesis and were not additive, suggesting that this mechanism of simulated exercise activates the AMPK pathway in cultured cells. Interestingly, creatine supplementation was not adequate to maintain protein synthesis in flexed cells at any time point. **CONCLUSIONS:** The negative effect of AICAR on mTOR is consistent with previous research indicating that the activation of AMPK has a negative impact on skeletal muscle outcomes. Our results indicate that the magnitude, and perhaps the duration, of anabolic outcomes may be dependent on the degree to which AMPK is activated during exercise, and may have profound implications toward the design of programs emphasizing/deemphasizing the contribution of AMPK to maintain cellular nutrient availability. These results continue to build on previous research in skeletal muscle protein synthesis and the regulatory factors affecting AMPK signal transduction and its association with anabolic function.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 194

Board #54

Mechanisms of Motor Unit Remodeling in Parkinson's Disease Human Skeletal Muscle

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Purpose: Parkinson's disease (PD) is a prevalent neurodegenerative condition manifesting in motor, (e.g., bradykinesia, tremor, rigidity) and non-motor symptoms that dramatically interfere with quality of life. Despite the significant impact of PD on motor function, its pathophysiology in limb skeletal muscles has received extremely limited attention. Previously, our laboratory has revealed an exaggerated pattern of type I myofiber grouping in skeletal muscle of PD patients that is partially reversed by 16 weeks of high-intensity exercise rehabilitation. Abnormal type I grouping arises from heightened rates of denervation-reinnervation cycling and thus is thought to result from poorly understood mechanisms that impair neuromuscular junction (NMJ) stability/integrity. The objective of this study was to leverage RNA-seq in an effort to identify known and novel molecular regulators of NMJ stability that are altered in PD muscle (in conjunction with pathological type I myofiber grouping) and are potentially responsive to high intensity exercise rehabilitation. **Methods:** A transcriptomics approach (poly-A RNA-seq) was used to map the unique gene expression signature in muscle of persons with PD, age- and sex-matched non-PD subjects (OA), and young, sex-matched adults (YA). Additionally, we examined the effect of 16 weeks of intensive exercise rehabilitation in a subset of PD individuals. Weighted gene co-expression network analysis (WGCNA) was used to group genes with highly correlated expression into modules and relate to phenotypic traits, including myofiber grouping and disease progression. **Results:** Our initial findings from RNA-seq suggest heightened basal expression of muscle development networks in PD muscle, which supports elevated denervation-reinnervation processes at NMJs. In response to high intensity exercise rehabilitation, PD muscle exhibited heightened expression of a network related to regulation of neurogenesis, suggesting that high intensity exercise may indeed induce molecular cues that contribute to reversal of pathological type I grouping. **Conclusion:** Ongoing WGCNA will provide insight into other pathophysiological manifestations of PD in skeletal muscle (e.g., functional deficits) and may have implications for current treatment paradigms in PD and the use of exercise rehabilitation as an adjuvant therapy. Supported by NIH T32HD071866.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 195

Board #55

Mitochondria And Myosin Heavy Chain In Skeletal Muscle Of Dystrophin Deficient Rat

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Purpose: Duchenne muscular dystrophy (DMD) is the severe muscle disease. Mitochondria plays important roles in the skeletal muscle homeostasis. However, it has been unclear how mitochondria contribute to pathological features in DMD skeletal muscles. Hence, we evaluated mitochondrial biogenesis, dynamics and skeletal muscle physiological characters using DMD model rats. **Methods:** DMD (n = 10, DMD group) and wild type (n = 10, WT group) Wistar-Imamichi rats were used in this study. DMD rats were dystrophin deficient rats generated by the CRISPER/Cas9 technique. For muscle functional assessments, right triceps muscles were subjected to measure isometric ankle peak torque and muscle endurance. Immediately after torque measurement (WT: n = 6, DMD: n = 6), left gastrocnemius muscle was harvested, and used for biochemical analysis (WT: n = 4, DMD: n = 4). **Results:** Isometric peak torque of the DMD was significantly lower (40%) than that of the WT group ($p<0.05$). In successive 10 times isometric contractions, torque deficit of the DMD was larger than that of the WT (first rep: 100%, 10 reps; WT: -16%, DMD: -42%, $p<0.05$). Compositions of myosin heavy chain (MHC) isoforms showed that fast-to-slow composition change occurred in DMD group ($p<0.05$). Mitochondrial biogenesis and/or content related protein expressions such as PGC-1α and OXPHOS were not different between groups. However, there were significant difference in expressions of mitochondria dynamics protein. Especially, OPA1 (fusion) and DRP1 (fission) proteins in the DMD group were higher (OPA1: 1.9-fold, DRP1: 1.9-fold, $p<0.05$) than those of the WT group. In addition, higher expressions of hexokinase II (3.8-fold) and pyruvate kinase isozymes M2 (6.0-fold) were observed in DMD group ($p<0.05$). **Conclusion:** We found that fast-to-slow MHC change occurred in DMD rats. Although changes in mitochondrial biogenesis and contents were not observed, we found that high expressions of mitochondrial dynamics protein, concomitant with higher expressions of glycolytic enzymes. Thus, we conclude that impairment of skeletal muscle mitochondria function might contribute to pathological characteristics of DMD.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 196

Board #56

Muscle Fiber-Type Specific DNA Domain with Lifelong Exercise.

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PURPOSE: Aging skeletal muscle is characterized by alterations in muscle mass and function at the whole muscle and single muscle fiber level. We present here a new method to gain insight into the DNA regulated adaptability of aging human muscle fibers and the impact of lifelong aerobic exercise (LLE). Specifically, we evaluated the muscle fiber volume to DNA content ratio (i.e., DNA domain) on a fibe-type specific basis (slow vs. fast).

METHODS: Males and females were divided into three groups: 1) old lifelong exercisers (LLEM, n=8, 74±4 y; LLEF, n=7, 72±1 y), 2) old

healthy individuals (OHM, n=9, 75±2 y; OHF, n=9, 76±1 y), and 3) young exercising individuals (YEM, n=8, 25±1 y; YEF, n=8, 24±1 y). For each subject, single muscle fibers were separated from vastus lateralis muscle bundles under a light microscope using fine tweezers. The fiber type (MHC) was determined from a segment of each fiber using SDS-PAGE before total DNA extraction from pooled muscle fibers of the same type. Fiber-type specific size (CSA), length, and volume (CSA x length) were measured. Muscle fiber-type specific volume to DNA content ratio (i.e., DNA domain) was calculated for each subject.

RESULTS: Aging led to a reduced DNA domain in both fiber types ($p<0.05$) particularly in fast fibers of both males (YEM>OHM) and females (YEF>OHF). LLE mitigated the aging-induced DNA domain reduction in males (YEM=LLEM>OHM) but not in females (YEF>LLEF=OHF). Overall, the DNA domain differences appeared to be influenced by fiber size differences across genders and fiber types ($R^2=0.40$, $p<0.01$). An increase in fiber DNA content was noticeable ($p=0.1$) in both fiber types of old males only (OHM>YEM=LLEM).

CONCLUSIONS: Aging induced a reduction of the DNA domain, particularly in fast fibers in senescent skeletal muscle of males and females (>70 y). This is completely attenuated with lifelong aerobic exercise in both fiber types but only in males. Further research is warranted to investigate the relationship between muscle fiber DNA content and the impact on skeletal muscle health with aging and lifelong aerobic exercise. Sponsored by NIH grant R01 AG-038576 and Ball State University Academic Excellence Award.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 197

Board #57

Peroxisomes In Skeletal Muscle Play An Important Role In Metabolic Adaptations To Exercise Training.

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Purpose: Several studies show the ability of the transcriptional coactivator Pgc1α to induce mitochondrial biogenesis is an important component of exercise-mediated health benefits; however, we recently showed Pgc1α also enhances peroxisomes in skeletal muscle. Since peroxisomes are involved in numerous aspects of lipid metabolism and help protect mitochondria from lipid overload, the purpose of this study was to test the effects of exercise on peroxisomal adaptations and determine the importance of this organelle in the exercise response. **Methods:** C57BL6/J mice were trained on a treadmill at low-intensity (6 weeks) and vigorous-intensity (3 week) to test peroxisomal adaptations (n=6/group). Skeletal muscle-specific peroxisome-deficient mice ($Pex5^{m-/-}$) and floxed littermates ($Pex5^{fl/fl}$) underwent four exercise modalities: voluntary wheel running (VWR; n=6/group), moderate-intensity exhaustive exercise (n=6/group), high-intensity exhaustive exercise (n=6/group), or vigorous-intensity exercise training (4 weeks; n=6/group). Blood lactate and glucose were used to confirm exercise intensity. Muscle samples were probed for substrate reserves (glycogen and triglyceride), gene/protein expression, and substrate utilization (pyruvate, leucine, palmitate, and lignocerate oxidation). **Results:** Shifts in peroxisomal fat oxidation were observed in response to an acute low-intensity exercise bout; however, training at vigorous-intensity was required to induce persistent peroxisomal adaptations. Deletion of peroxisomes in skeletal muscle did not alter self-selected activity (VWR) or run time to exhaustion at either exercise intensity; however, $Pex5^{M-/-}$ mice did exhibit a differential adaptation to exercise training vs. $Pex5^{fl/fl}$ controls. Specifically, exercise training increased leucine, palmitate (mitochondrial), and lignocerate (peroxisomal) oxidation in $Pex5^{fl/fl}$ mice, but these responses were blunted in $Pex5^{m-/-}$ mice. Alternatively, after exercise training intramuscular glycogen content in $Pex5^{m-/-}$ mice was 3-4 fold higher than $Pex5^{fl/fl}$ mice, suggesting a shift toward reliance on carbohydrate substrates. **Conclusion:** Collectively, results from this study indicate peroxisomes in skeletal muscle are recruited during exercise, but a vigorous-intensity training stimulus is required to induce persistent peroxisomal adaptations in lean, healthy mice. Peroxisomes in skeletal muscle do not appear to be critical in regulating self-selected activity or exercise tolerance in the naïve state, but play an important role in facilitating adaptations in substrate metabolism pathways in response to exercise training.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 198

Board #58

Prolonged Sitting Creates Resistance to the Metabolic Benefits of Acute Exercise (i.e.; Exercise Resistance)

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Those in a population who are the most physically inactive display a greatly elevated risk of cardiovascular disease (CVD). Generally, acute exercise improves postprandial lipemia (PPL) and insulin sensitivity (IS), risk factors for CVD. However, we have reported that prolonged sedentary behavior (e.g.; sitting) seems to prevent these healthy metabolic responses to acute exercise. **PURPOSE:** This study determined the impact of an acute bout of exercise on PPL and IS after four days of prolonged sitting (~13.5 h/day).

METHODS: Ten untrained to recreationally active men (n=5) and women (n=5) participated in this cross-over study. Prolonged sitting (SIT) without exercise was compared to prolonged sitting (~13.5 h/day) with a one-hour bout of treadmill running (SIT+EX; 67% VO_2max) performed in the evening of the 4th day. On the following morning of each trial, participants completed a high fat/glucose tolerance test (HFGTT), during which plasma was collected to analyze triglycerides, glucose, and insulin over a 6 h period.

RESULTS: No differences ($p>0.05$) were found between the two trials in the overall triglyceride, glucose, or insulin responses during the post-prandial high fat/glucose tolerance test. This lack of difference between trials came with similar physical activity (i.e.; 3,500-4,000 steps) on each day except for the one-hour bout of exercise the day before the HFGTT during SIT+EX .

CONCLUSIONS: These data suggest that physical inactivity (e.g. prolonged sitting and less than 4,000 steps) creates a condition whereby people are 'resistant' to the metabolic improvements in lipid and glucose metabolism that are normally derived from a bout of acute exercise (i.e.; exercise resistance).

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 199

Board #59

Protein Supplementation Throughout 10 Weeks of Progressive Run Training Does Not Improve Performance

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PURPOSE: Protein supplementation is proposed to promote recovery and adaptation following endurance exercise. While prior literature demonstrates improved performance when supplementing protein during, or following, endurance exercise, chronic supplementation research is limited.

METHODS: Intermediate-level runners were counter-balanced into a placebo group (PLA; n=8) or protein group (PRO; n=9) based on sex and VO2peak, and underwent 10 weeks of progressive endurance training. Prior to training, participants underwent tests for body composition, blood cell differentials, non-invasive mitochondrial capacity using near-infrared

spectroscopy, and a 5 km time trial (TT). Thereafter, progressive training commenced (10% increase in weekly volume with a recovery week following 3 weeks of training) whereby PRO supplemented with 25 g of protein following workouts and prior to sleep (additional 50 g daily). PLA supplemented similarly with a < 1 g sugar pill. Following training, participants were reanalyzed for the aforementioned tests.

RESULTS: VO_2peak and initial 5 km TT were not significantly different between groups. PRO consumed significantly more dietary protein throughout the training period (PRO = 132 g/d or 2.1 g/kg/day; PLA = 84 g/d or 1.2 g/kg/day). Running volume increased significantly over time, but was not significantly different between groups throughout training. Blood measures were unaltered with training or supplementation. Mitochondrial capacity approached significant improvement over time (time p=0.063) with no differences between groups. PLA increased lean mass 0.7 kg (p<0.05) while PRO experienced virtually no change (-0.1 kg, interaction p=0.049). PLA improved 5 km TT performance 6.4% (1 min 31 s), while PRO improved only 2.7% (40 s) (interaction p=0.080).

CONCLUSIONS: This is the first evidence to suggest long-term protein supplementation during progressive run training is not beneficial for intermediate-level runners.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 200

Board #60

Satellite Cells Mediate Muscle Fiber Size in Response to Lifelong Exercise

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There is a widely held belief that the reduction in satellite cell content with advancing age directly contributes to the progressive loss of skeletal muscle mass and function with aging (sarcopenia). However, we reported that a lifelong reduction of satellite cells did not influence the onset or progression of sarcopenia in sedentary mice. **Purpose:** The current study was undertaken to determine whether satellite cell depletion throughout adulthood negatively impacts muscle in physically active mice. We hypothesized that satellite cell depletion would diminish muscle adaptation in response to lifelong exercise. **Methods:** Thirty nine female Pax7-DTA mice were treated with vehicle (15% ethanol in sunflower seed oil) or tamoxifen (2.5mg/day) for 5 days by IP injection at 5 months of age to deplete satellite cells. Following a 2-month washout period, mice were randomly assigned to the sedentary group (locked running wheel) or the running group (free access to running wheel) at 7 months of age (n=9-10 per group). Mice were sacrificed 13 months later, at a mean age of 20 months. Wheel running activity (speed and distance) were continuously monitored and recorded throughout the experiment using ClockLab software. Thirty five mice completed the study (4 mice died over the study duration). Immediately following sacrifice, hind limb muscles were removed, weighed and frozen for immunohistochemical or microarray analyses. **Results:** Contrary to results in sedentary mice, satellite cell depletion throughout adulthood in physically active mice resulted in lower muscle fiber size in the plantaris and soleus. Both satellite cell replete and deplete mice showed a comparative oxidative fiber type shift in response to lifelong running. Microarray and subsequent pathway enrichment analysis of the plantaris and soleus muscles revealed G protein-coupled receptor (GPCR) signaling and downstream targets PI3K/AKT/mTOR to be preferentially enriched in satellite cell replete runners. **Conclusions:** These results suggest that satellite cells play a critical role in the regulation of muscle fiber size during lifelong exercise, but are not required for certain metabolic adaptations. Further, satellite cells appear to promote GPCR signaling cascades that stimulate muscle growth during exercise. These findings indicate there may be therapeutic potential in repopulating satellite cells in older adults who regularly engage, or begin to engage, in physical activity. Supported by AG060701 and AG049806 to CAP and JJM.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 201

Board #61

Single Muscle Fiber Power in Female Lifelong Exercisers

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Purpose: To examine the effects of lifelong aerobic exercise on single muscle fiber size, contractile function (strength, speed and power) and quality (normalized power) we evaluated three different female cohorts: old lifelong aerobic exercisers (LLE; n=7, 72±2y), old healthy individuals (OH; n=10, 75±1y) and young exercisers (YE; n=10, 25±1y). **Methods:** Skeletal muscle biopsies were obtained from the vastus lateralis. Myosin heavy chain (MHC) I and IIa muscle fibers were isolated and analyzed for contractile properties using the permeabilized single muscle fiber technique. Fiber size (cross-sectional area, CSA) was captured digitally, fiber force (Po) and contractile velocity (Vo) were measured using the slack test technique, and power was assessed from a series of submaximal isotonic force-velocity measurements. Fiber type (MHC) was assessed using SDS-PAGE. **Results:** MHC I power was higher (P<0.05) in LLE (13.2±0.5 $\mu N \bullet FL \bullet s^{-1}$) compared to YE (11.3±0.5 $\mu N \bullet FL \bullet s^{-1}$) with no difference compared to OH (11.7±0.5 $\mu N \bullet FL \bullet s^{-1}$). The MHC I power profile was driven by the 14% higher (P<0.05) Po observed in LLE compared to YE and OH as there was no difference in fiber size (~5,000 μm^2) or velocity (~1.10 $FL \bullet s^{-1}$) among the groups. MHC IIa power was similar in LLE (58±3 $\mu N \bullet FL \bullet s^{-1}$) and YE (61±2 $\mu N \bullet FL \bullet s^{-1}$), which was ~20% higher (P<0.05) than OH (50±2 $\mu N \bullet FL \bullet s^{-1}$). The LLE MHC IIa fiber power was driven by a 14% elevated (P<0.05) Vo compared to YE and OH. For YE, MHC IIa fiber power was driven by ~49% larger (P<0.05) and ~27% stronger (P<0.05) fibers compared to LLE and OH. MHC IIa muscle quality (i.e. normalized power) was higher (P<0.05) in LLE (18.5±0.6 $W \bullet L^{-1}$) and OH (17.3±0.5 $W \bullet L^{-1}$) compared to YE (13.5±0.5 $W \bullet L^{-1}$). **Conclusion:** Lifelong aerobic exercise resulted in a myocellular functional phenotype that enhanced (MHC I) or preserved (MHC IIa) muscle power. While there were hallmark traits of aging muscle in both LLE and OH cohorts (fiber size and quality), the >50 years of aerobic exercise resulted in unique myocellular adaptations that are likely beneficial for performance and skeletal muscle health. Sponsored by NIH R01 AG038576

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 202

Board #62

Stretch-shortening Contractions Preserves Trainability of Skeletal Muscle Performance and Augments Muscle Mass in Adult Rats

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PURPOSE: The responsiveness or trainability to resistance-type exercise training (RTET) has shown dependency on age; and, thus training design is critical. Rodent studies have demonstrated that muscles of 6-month old adult rats exposed to 80 stretch-shortening contractions (SSCs) 3 days per week for 1 month do not improve skeletal muscle performance and have an attenuated muscle mass enhancement. In comparison, 3-month old rats respond robustly to SSC RTET with ~30% increase in muscle performance and a concomitant ~20% increase in muscle mass. Thus, the purpose of the present study was to determine whether prior exposure to SSCs at a young age preserves, or even augments, responsiveness at adulthood. **METHODS:** Dorsiflexor muscles of Fischer Brown Norway hybrid rats were SSC RTET *in vivo* for 1 month on a custom-built isokinetic rodent dynamometer at 3 months and again at 6 months of age (TRT) or at 6 months of age (T). Performance for dorsiflexor muscles were analyzed temporally, and tibialis anterior muscles were harvested 3 days post-training period. ANOVA was used for statistical analysis; α was set at $p < 0.05$. **RESULTS:** SSC RTET provided no performance benefits to T

rodents. Interestingly, TRT resulted in performance increases in both static (isometric) peak force (p=0.017) and dynamic (SSC) peak force (p=0.007) during the retraining session. Further, both static and dynamic peak force were greater in the TRT versus T group (p=0.002; p=0.004, respectively). Tibialis anterior normalized muscle mass was increased in the T rodents (p<0.001); and, moreover, this response was observed for the TRT group (p<0.001). Importantly, significant differences in normalized muscle mass was observed in the TRT versus the T groups (p=0.025). **CONCLUSIONS:** An initial bout of SSC RTET at a young age preserves trainability in terms of skeletal muscle performance; and, augments the trainability of skeletal muscle mass in adulthood. Together these results advocate a means to investigate the molecular and cellular underpinning(s) of muscle memory. This project was supported by internal NIOSH funds. *Disclaimer:"The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention."*

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 203

Board #63

The Anabolic Response of C2C12 Skeletal Muscle Myotubes to Diacylglycerol Analog OAG

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PURPOSE: For years, there has been a growing interest in the role of lipids in the progression of type 2 diabetes. Specifically, molecules such as diacylglycerol have garnered attention due to their concomitant increase with the progression of insulin resistance and type 2 diabetes. We have previously demonstrated that the heightened anabolic response in muscle of diabetic rats is accompanied by elevated conventional PKC activity. These experiments aimed to further characterize the role of diacylglycerol in cellular metabolism by using the diacylglycerol mimetic, 1-oleoyl-2-acetyl-sn-glycerol (OAG) alongside mTOR inhibitors rapamycin or Torin 1.

METHODS: C2C12 myoblasts were grown and maintained in 10 cm plates with high glucose DMEM growth media until reaching ~80% confluence, at which point they were transitioned to a high glucose differentiation media to encourage myotube formation. Six days following differentiation, plates were randomly assigned to treatment groups (n=3) and treated in the presence of 4% deuterium oxide for 24 hours. Myotubes were harvested with cell scrapers in the presence of Norris lysis buffer, and cellular contents were fractionated for measures of both protein synthesis rates and anabolic signaling via western blot analysis.

RESULTS: Presence of OAG (20 μM) did not significantly alter 24 hour rates of protein synthesis (1.728%/hr) compared to controls (1.630%/hr) (p = 1.000). Rapamycin (1.333%/hr) and Torin 1 (1.187%/hr) treatments significantly reduced protein synthesis rates compared to controls (p = 0.003 and p < 0.001 respectively). However, OAG did not impact the suppressive effects of rapamycin (OAG+Rapamycin 1.380%/hr) (p=1.000) or Torin 1 (OAG+Torin 1 1.158%/hr) (p=1.000).

CONCLUSIONS: OAG is known to be a potent activator of Protein Kinase C as a cell permeable analog of diacylglycerol. Although chronic PKC activation has been implicated as a culprit for dysregulated protein anabolism with insulin resistance, these data indicate that a 24-hour incubation with OAG is not sufficient to significantly perturb fractional rates of protein synthesis in murine skeletal muscle myotubes.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 204

Board #64

The Benefits of Aqua Yoga Participation on Land Physical Measures of a Senior Residential Population.

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PURPOSE: The purpose of this study was to focus on the benefits of aqua yoga on physical land measures in a senior residence population. These measures include range of motion, muscle strength, balance, and perceived body pain.

METHODS: This was a Quasi - Experimental design using a one month wait period as the control. The Aqua Yoga intervention ran twice a week, for 8 weeks, an hour each time. Each session began with an all body warm-up, followed by range of motion activities for all joints. The class then continued with traditional yoga standing postures, challenge postures and deep yoga stretching. Each class had a traditional closing sequence. Study measures included height and weight, a VAS pain scale, the Berg Balance Scale, the YMCA sit and reach test for hamstring and low back flexibility, the Back - Scratch test for shoulder flexibility, the Modified Total Body Rotation test, the wall squat test to measure thigh strength, modified push - ups to measure arm strength, and modified sit - ups to test abdominal strength. A goniometer was used to measure ankle range of motion. Statistical analysis included standard descriptive measures, a repeated measures ANOVA was used to test within subject effect using Wilks Lambda for significance at p =0.05). Post hoc, using the Bonferonni correction for pairwise comparison.

RESULTS: 13 participants were recruited to participate in this study. One male and 11 female participated in the exercise protocol (1 female dropped before the exercise began and 1 female dropped after one month). The study participant size was limited because of the size of the pool. The mean age of the participants was 81.23 ± 6.06 and the mean BMI was in the "Overweight" range (25 -29%). Session attendance was at 85%. Results showed significant post intervention improvement in balance (P = 0.001) and significant post intervention improvement in shoulder flexibility (right side: p = 0.01; left side: p = 0.007); no significant difference in hamstring and low back flexibility but a trend toward less flexibility; no significant difference, but a trend toward improvement, in total body rotation, thigh, abdominal, and upper arm strength; no change in VAS pain; and no difference in ankle range of motion. Anecdotal evidence suggested that participants enjoyed the class, most felt stronger, some found they felt looser in their hips and were able to walk more easily, others felt it hurt their low back. **CONCLUSIONS:** Participation in eight weeks of Aqua Yoga significantly improved balance and shoulder mobility in a resident senior population. Changes in core, leg and arm strength suggest a positive trend which should be evaluated for clinical significance.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 205

Board #65

The Effects Of Prolonged Recovery After Bouts Of Resistance Exercise With Excessively Short Interval

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Purpose: Resistance exercise promotes skeletal muscle protein synthesis, and the accumulation of proteins leads to skeletal muscle hypertrophy. On the other hand, excessively shortened recovery period between bouts of exercise attenuates activation of muscle protein synthesis at an early phase of recovery after exercise. The present study aimed to investigate the effect of prolonged recovery on muscle protein synthesis after bouts of resistance exercise with excessively short interval. **Methods:** Male

C57BL/6J mice were randomly assigned into three groups: resistance-trained with 3 bouts at intervals of 72h (72H), 24h (24H), and 8h (8H), respectively. The resistance exercise consisted of 50 repetitions of maximal isometric contractions of the gastrocnemius muscle, which were elicited by transcutaneous electrical stimulation under anesthesia. Muscle samples were collected 6h(6h-post RE) and 12h(12h-post RE) after the 3rd exercise session. **Results:** At 6h-post RE, muscle protein synthesis increased in 72H and 24H, but not in 8H. However, at 12h-post RE, muscle protein synthesis increased in all groups. A significant increase in p70S6K (Thr389) phosphorylation was observed in all groups, and the magnitude of phosphorylation was increased with shortening the interval between sessions at 6h-post RE, but was similar between groups at 12h-post RE. The content of 4-hydroxynonenal conjugated protein was increased only in 8H group 6h-post RE, but returned to basal level by 12h-post RE. **Conclusion:** The present results suggest that excessively shortened recovery period between sessions attenuates activation of protein synthesis at an early phase of recovery after exercise, but regained the anabolic response at later recovery period. The suppression of protein synthesis with shortened recovery period was not associated with the suppressed mTORC1 signal, and it may have caused by the increase in oxidative stress. Supported by JSPS KAKENHI JP15H03078 to NI and JP17J05729 to JT.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 206

Board #66

Thyroid Hormone State Interacts with Chronic Motor Nerve Stimulation in Skeletal Muscle Fiber-type Transitions in a Rabbit Exercise Model

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PURPOSE: Hypo- and hyperthyroidism impair muscle function, but the impact of thyroid hormone on the response to exercise is unknown. Autophagy is necessary for the acute exercise response, but its role in exercise training (ET) is unclear. We evaluated the effects of hypo- and hyperthyroidism on autophagy, fiber type, and metabolism, in response to chronic motor nerve stimulation (CMNS) in a rabbit model of ET.

METHODS: 14 adult New Zealand rabbits were studied. 9 experienced 7-8 weeks of hypothyroidism; 3 experienced 2 weeks of hyperthyroidism; 2 were euthyroid controls. All had 21 days of CMNS to the left peroneal nerve, with 0.2·ms rectangular wave pulses at 10 Hz. Protein was extracted from EDL. Fiber type, autophagy, and protein synthesis markers were measured by WB. Metabolites were measured by mass spec.

RESULTS: In eu- and hypothyroid rabbits, CMNS increased MHC1 but did not affect MHC2a. In hyperthyroid rabbits, CMNS did not induce a fiber type change. In hypothyroid rabbits, CMNS increased activation of Akt, 70S6K, and GLUT4, suggesting enhanced insulin signaling and glucose uptake. It also increased pATGL and CPT-1α expression, suggesting it stimulated lipolysis and fatty acid oxidation, and increased p70S6K, suggesting enhanced mTOR activity and protein synthesis. In hyperthyroid rabbits, CMNS did not increase activation or expression of these markers. In hypothyroid rabbits, CMNS increased LC3II and p62 protein levels, consistent with decreased autophagy, whereas in hyperthyroid rabbits, CMNS induced LC3II toward an increase in expression without a change in p62 expression, consistent with increased autophagy. CMNS activated pAMPK and pATGL in hypothyroid rabbits suggesting increased TG lipolysis. In contrast, although baseline pAMPK and pATGL levels were increased in hyperthyroid rabbits, CMNS did not further increase their expression. Metabolomics analysis showed that CMNS increased acylcarnitine (AC) and TCA cycle fluxes accompanied by an increase in CPT1α protein expression in hypothyroid rabbits. Hyperthyroid rabbits also showed high levels of AC flux that did not increase further with CMNS whereas TCA cycle flux trended towards an increase with CMNS.

CONCLUSIONS: CMNS in hypothyroid rabbits increased MHC1a, fatty acid oxidation, and TCA flux and down-regulated autophagy, suggesting decreased autophagy may increase MHC1 production and promote fatty acid oxidation in skeletal muscle. In hyperthyroid rabbits, MHC1 and fatty acid oxidation did not increase in response to CMNS and autophagy was not blocked. Our findings show that there is a permissive muscle response to ET in the hypothyroid state that is lost in the hyperthyroid state.

Hot topics in exercise physiology

Presentation Number: 207

Board #67

Translational Science at ACSM: Does the Science of Integrative Physiology Fit within ACSM's Newest Journal?

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Translational research covers a broad spectrum of science, from basic to implementation and policy change. Increasingly, scientists, clinicians, public health professionals, and funding agencies are recognizing the importance of scientific investigations that bridge traditional gaps between basic, clinical, community, and policy research. The American College of Sports Medicine (ACSM) recognizes the importance of this work and, in 2016, launched the Translational Journal of the American College of Sports Medicine (TJACSM). **PURPOSE:** We aim to inform attendees about the mission, vision, and scope of TJACSM. Further, we hope to clarify the types of research that TJACSM seeks to publish, to feature the most successful published articles to date, and to elucidate how the integrative physiology of exercise, as a content area, fits within the scope of this journal. **METHODS:** Utilizing the journal's webpage and the publisher's (Wolters Kluwer Health) annual reports, we identified information related to the journal's scope, availability and reach, and the number of reads and views of top articles. **RESULTS:** ACSM electronically publishes 24 issues of TJACSM per year and it is currently available in 2,154 institutions. The journal site had 22,879 visits during 2017 and approximately 48% of the journal's reach is outside the United States. Top viewed articles have covered topics such as the translational gap between the laboratory and playing field, the potential impact of sitting on mortality, exercise and breast cancer, and the association between aerobic fitness and academic achievement among elementary school youth. **CONCLUSION:** There is a desire to grow this journal to include all aspects of the translational science spectrum in exercise science, sports performance, and sports medicine. The integrative physiology of exercise, as an example, represents a content area that is currently under-represented in this journal but fits well within the scope of TJACSM. In addition, as an on-line journal, it provides a great deal of flexibility to respond to creative proposals. For example, scientific findings presented at this conference could be considered for a themed issue or a linked volume. Presenters are encouraged to discuss their research and ideas for innovative papers with TJACSM representatives to determine whether their work is appropriate for submission to TJACSM.

Cardiovascular exercise physiology

Presentation Number: 208

Board #1

Acute Effects of All-Extremity Aerobic Exercise on Arterial Stiffness and Wave Reflection in Young Men

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Purpose: Arterial stiffness and wave reflection are associated with increased risk for cardiovascular disease (CVD). High-intensity interval training (HIIT) and moderate-intensity continuous training (MICT) on the treadmill have been reported to decrease CVD risks. We have recently adapted HIIT and MICT on an all-extremity non-weight-bearing ergometer to allow implementation in a larger portion of the population. The acute vascular effects of these protocols have not been investigated. Therefore, the purpose of this study was to examine the acute vascular responses to all-extremity HIIT vs. MICT in young men. **Methods:** Sixteen young men (21±2 years of age, means±SE) participated in this study. Participants were free of clinical disease and did not use tobacco products or medications. Arterial stiffness (carotid to femoral pulse wave velocity; cfPWV), wave reflection (aortic augmentation index; AIx) and central and peripheral blood pressure (aortic and brachial, respectively) were assessed using a validated cuff-based device. Measures were obtained at pre-exercise (PreE), at the end of a single session of HIIT or MICT (PostE) and following 1-hour recovery (Rec). HIIT and isocaloric MICT were performed on an all-extremity non-weight-bearing ergometer. HIIT consisted of 4x4-min intervals at 90% peak heart rate (HR_{peak}) interspersed by 3-min intervals at 70% HR_{peak} for a total of 40 min. MICT consisted of 47 min at 70% HR_{peak}. **Results:** In response to MICT, cfPWV was reduced at PostE (5.8± 0.2 vs. 5.5±0.2 $m \cdot s^{-1}$, PreE vs. PostE; P=0.003) and following 1-hour recovery returned to the PreE level (5.7±0.2 vs. 5.5±0.2 $m \cdot s^{-1}$, Rec vs. PreE; P>0.99). However, in response to HIIT cfPWV remained unchanged (P≥0.5). AIx did not change from PreE to PostE and Rec in response to HIIT or MICT (P=0.4). Aortic and brachial mean arterial pressure (MAP) responded similarly to HIIT and MICT (P≥0.1 for exercise type x time interaction); MAP was reduced following 1-hour Rec (aortic: 76±1 vs. 74±1 mmHg and brachial: 81±1 vs. 79±1 mmHg, PreE vs. Rec; P=0.03 for both). **Conclusions:** Arterial stiffness is reduced at the end of all-extremity MICT but not HIIT, whereas wave reflection is unaffected. Central and peripheral blood pressure are reduced following 1-hour recovery from all-extremity HIIT and MICT.

Cardiovascular exercise physiology

Presentation Number: 209

Board #2

Acute Vascular Effects of High-Intensity Interval Training on All-Extremity Ergometer vs. Treadmill in Young Men

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PURPOSE: Blood pressure and arterial stiffness are associated with increased risk for cardiovascular disease. High-intensity interval training (HIIT) on the treadmill is a popular and effective exercise strategy for decreasing cardiovascular disease risk. We have recently adapted HIIT on a non-weight-bearing all-extremity ergometer to reduce impact on the joints and use a large amount of muscle mass. However, the acute vascular responses to HIIT on these two exercise modalities have not been compared. Therefore, the purpose of this study was to compare the acute effects of HIIT on an all-extremity ergometer vs. treadmill on blood pressure and arterial stiffness in young men. **METHODS:** Thirty healthy young men (21.0±0.3 yrs, means±SE) completed HIIT on either an all-extremity ergometer (n=15) or treadmill (n=15). Systolic and diastolic blood pressure (SBP and DBP) and arterial stiffness (carotid-femoral pulse wave velocity; cfPWV) were assessed using a validated cuff-based device. Measures were obtained at pre-exercise, at the end of a single session of HIIT on a non-weight-bearing all-extremity ergometer or a treadmill and following 1-hour recovery. HIIT consisted of 4x4-min intervals at 90% peak heart rate (HR_{peak}) interspersed by 3-min intervals at 70% HR_{peak}. **RESULTS:** SBP increased in response to HIIT on a treadmill from pre-exercise to end of exercise (P=0.002) and returned to the pre-exercise level at recovery (P>0.99),while DBP remained unchanged (P≥0.1). However, in response to HIIT on an all-extremity ergometer, SBP remained unchanged (P>0.99), whereas DBP decreased at recovery vs. pre-exercise (P=0.04). cfPWV was not affected by HIIT on an all-extremity ergometer or a treadmill(P=0.9 for exercise modality x time and P≥0.4 for exercise modality and time main effects). **CONCLUSIONS:** HIIT, regardless of exercise modality, does not influence arterial stiffness. HIIT on an all-extremity ergometer does not result in increased SBP at the end of exercise as seen in response to HIIT on a treadmill. These findings may have important implications for exercise prescription.

Cardiovascular exercise physiology

Presentation Number: 210

Board #3

Changes in Oxygen Consumption and Left Ventricular Mass in Aerobic High School Athletes

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Purpose: In the pilot Durham Elite Athletes Study (DEAS), we investigated longitudinal changes in maximal aerobic capacity and resting heart size and function in high school cross country and track athletes.

Methods: At the beginning of each spring track season, volunteer participants from high school cross-country and track teams underwent resting echocardiograms to determine left ventricular (LV) end diastolic volume (EDV), LV end systolic volume (ESV), LV mass, and ejection fraction. We also assessed LV mass normalized to body mass. Maximal graded treadmill tests with ECGs assessed oxygen consumption measurements [VO_{2peak}, max heart rate (MHR), peak RER]. Blood variables evaluating iron status were also measured [hemoglobin (Hb), hematocrit (HCT) and ferritin]. Means and standard deviations were calculated, and paired, 2-tailed t-tests were used to detect significant changes in these variables ($p<0.05$).

Results: At baseline, participants (n=25; 15.6 ± 0.7 years) had a mean body mass of 57.0 ± 6.8 kg, HCT of 41.0 ± 2.4%, Hb of 14.2 ± 1.0 g/dL, and ferritin of 40.0 ± 28.7 ng/mL. Participants also had a mean LVEDV of 148.2 ± 21.6 mL, LVESV of 64.2 ± 15.6 mL, ejection fraction of 55.9 ± 6.1%, LV mass of 132.4 ± 26.7 g, and LV mass/body mass ratio of 0.002 ± 3.3E-4. During maximal exercise tests, participants achieved a mean relative VO_{2peak} of 59.9 ± 9.4 mL/kg/min, absolute VO_{2peak} of 3.4 ± 0.7 L/min, peak RER of 1.2 ± 0.1, and MHR of 198 ± 6.7 bpm. When assessing longitudinal changes in subsets of participants over a two year period, body mass, absolute VO_{2peak} and LV mass significantly increased by 4.2 ± 2.9 kg (n=18), 0.3 ± 0.4 L/min (n=18), and 25.0 ± 18.4 g (n=5), respectively. The LV mass/body mass ratio significantly increased by 2.0E-4 ± 3.0E-4 (n=5) during the two year follow-up. There were no significant differences in Hb, HCT, ferritin, relative VO_{2peak} or MHR.

Conclusion: As expected, high school adolescent athletes increased their body mass, LV mass, and absolute VO2peak over a two year period. Of particular interest, the LV mass to body weight ratio increased significantly from year to year, suggesting that LV mass increased at a greater rate than body mass. In this population, whether or not the greater growth of the LV in comparison to the rest of the body is a normal chronological response remains unclear. We postulate that this may reflect the additional aerobic training response that signals cardiac hypertrophy, resulting in a larger LV to body mass ratio. Therefore, our future directions include measuring these variables in a matched cohort of sedentary high school adolescents and comparing them to aerobically trained high school athletes.

Cardiovascular exercise physiology

Presentation Number: 211

Board #4

Effect of Fish Oil and Pectin on Fibrosis and Inflammation in Mouse Hearts Exposed to HZE Radiation

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Purpose: Spaceflight beyond low Earth orbit (LEO) imposes stressors on astronauts, due to the microgravity of spaceflight and tissue bombardment of galactic and solar radiation. Cardiovascular function is acutely compromised by cephalic fluid shift and disuse, while there is growing concern that the heart disease risk may be elevated by spaceflight. Indeed, high energy or heavy ion radiation (HZE) causes damage and fibrosis to the heart and vasculature; cellular mechanisms include oxidative stress, inflammation, and fibrosis. Fish oil and pectin possess antioxidant properties, elevate stress response proteins, and reduce radiation-disruption of microbiota. Fish oil and pectin attenuate radiation damage in the kidney and liver; however, their efficacy against inflammation and pro-fibrotic signaling in the heart are unknown. **Methods:** Mice were exposed to ^{28}Si and ^{48}Ti (0.5 Gy), and hearts extracted 4 wks or 8 wks after radiation exposure. Fish oil (15% by weight) and pectin (6%) in the diet were provided in one half of the irradiated mice. **Results:** HZE radiation increased damage and levels of TGF-ß and invasion of inflammatory cells. Trends in protection by fish oil and pectin were not significant. **Conclusion:** We suggest that a more targeted strategy (e.g., antioxidant) in reducing radiation-induced cardiac damage and fibrosis may be more effective than a fish oil, pectin nutraceutical approach.
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Cardiovascular exercise physiology

Presentation Number: 212

Board #5

Insulin Sensitivity is Related with Exercise Heart Rate Kinetics in Older Adults

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Hyperinsulinemia can impair ß1 adrenergic signaling in the heart via a novel mechanism involving ß2 receptors and G-protein-coupled receptor kinase 2. These findings could have important significance for the cardiovascular responses of individuals with obesity and diabetes to increased workload such as may occur in response to exercise. However, the relationship between insulin resistance and these hemodynamic adaptations remain to be addressed. **Purpose:** We examined whether or not impaired heart rate kinetic responses (Tau-HR) at the initiation of exercise was associated with insulin resistance. **Methods:** Participants for this case-control analysis were selected from a larger study based on data obtained from glucose infusion rates (GIR) from an euglycemic-hyperinsulinemic clamp. Ten participants with high insulin sensitivity (HIS) and ten with low insulin sensitivity (LIS) who were not on ß-blockade performed an 8-minute submaximal exercise test at 25 watts on an electronically-braked cycle ergometer. HR kinetics was assessed during and a monoexponential model, and the least square method was used to fit the data. The time constant and asymptote of the model were Tau-HR and HR in steady-state (HR-SS), respectively. Following this bout, maximum oxygen uptake (VO_{2max}; ml/kg of fat free mass(FFM)/min) was measured with a progressive exercise test. **Results:** HIS and LIS were of similar age (64.7±3.6 y vs. 68.4±3.7 y), body mass index (33.2±2.4 vs. 35.9.4±4.6 kg/m^2), VO_{2max} (30.7±4.4 vs. 28.8±6.6 ml/kgFFM/min), resting HR (75.0±4.4 vs. 71.9±12.8 beats/min) and maximum HR (149±14 vs. 143±28 beats/min). GIR was significantly different between HIS and LIS (10.2±1.2 vs. 3.2±0.7 mg/kgFFM/min). HIS had a faster Tau-HR than LIS (9.85±3.48 vs. 25.96±3.48 seconds, P<0.05), although similar HR-SS (149±14 vs. 143±28 beats/min; P>0.05). **Conclusions:** An impaired HR response at exercise onset may be a characteristic of insulin resistance. Additional studies are necessary to determine the mechanistic basis for this relationship between insulin resistance and impaired heart rate kinetics.

Cardiovascular exercise physiology

Presentation Number: 213

Board #6

The Effect of Aerobic Exercise on Cardiac and Metabolic Functions of High Fat Diet Aged Mice

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PURPOSE: Regular aerobic exercise has been proven to decrease the risk of cardiovascular diseases; however, whether aerobic exercise training can offset the dual effects of aging and high-fat diet remains unknown. The purposes of this study was to investigate the effect of aerobic exercise training on the cardiac and metabolic functions of the aged mice fed with high-fat diet.

METHODS: Aged C57BL/6J mice (18 months old, n = 28) were randomly assigned to one of four groups: CON (standard diet), SD+EX (standard diet with treadmill exercise), HFD (high fat diet, 46.1% of fat), or HFD+EX (high fat diet with treadmill exercise). Mice in TM groups were running on treadmill (50 minutes/day, 5 days/week for 8 weeks). The cardiac and metabolic functions of mice were measured after exercise intervention. The following measurements were performed: 1. VO_2max and maximum running speed. 2. *in vivo* cardiac function via echocardiography. 3. high-density lipoprotein cholesterol (HDL-C), Total cholesterol (TC), Triglyceride (TG) via portable blood lipid test system. Two way ANOVA was used to identify group differences. If a significant F-value was observed, the post hoc testing was performed to determine where differences existed. All results are expressed as mean ± SD. Statistical significance was set at $p <$ .05. (SPSS 18.0).

RESULTS: After 8 weeks of intervention, no signs of cardiac geometry changes were noted among groups ($p > .05$). For the *in vivo* cardiac function, the end of diastolic volume (EDV) of HFD group were significant lower than CON group (HFD, 70±3.49 uL; CON, 83.93±21.41 uL, $p < .05$). In contrast, we observed no signs of ex vivo cardiac dysfunction in HF+EX and SD+EX groups ($p > .05$). As for the metabolic functions, we observed HF diet significant affect animals' VO_2max regardless of their training status (CON, 103±9.7 ml/kg/min; HFD, 95±3.0 ml/kg/min; HFD+EX, 97±14.0, $p < .05$). As for blood lipid, we observed no significant change in TC and TG ($p > .05$). However, we observed exercise improve HDL in both exercise group when compared with CON (EX+SD, 77±17.2 mg/dL; EX+HFD, 95±7.9 mg/dL; CON, 66±32.0 mg/dL, $p > .05$).

CONCLUSIONS: Although we did not observed any metabolic function improvement in exercise training, we did found exercise training could attenuate the deterioration in cardiac function and improve plasma lipid profile in the elderly mice.

Cardiovascular exercise physiology

Presentation Number: 214

Board #7

The Effect of an Acute Bout of Cycling on Monocyte Adhesion Molecules: A Pilot Study

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Integrins, such as β1 integrin very late antigen-4 (VLA-4) and β2 integrin CD11c/CD18, play a key role in monocyte adherence to the endothelium. During transient states, e.g. the postprandial period, and in chronic disease states, e.g. the metabolic syndrome, monocytes have been shown to upregulate integrins resulting in an increased adherence to the endothelium, further progressing the development of atherosclerosis. It is well established that both an acute bout and chronic aerobic exercise exert cardioprotective effects, however limited data on the effect of exercise on monocyte adhesion molecules exists. **PURPOSE:** To investigate the acute effects of a moderate bout of exercise on surface receptor expression of CD11c and VLA-4, and monocyte lipid uptake in young, fit individuals. **METHODS:** Six physically active, fit (VO2peak 45.8±4.0 mL O2/kg/min) individuals (age 24.7±1.1) performed 30 min of cycling at 60%VO2peak. Blood samples were obtained pre-exercise (PRE), immediately after (POST) and 1 h (1HR) post-exercise. Whole blood was fixed and stained with Nile Red and antibodies against CD14, CD16, CD11c and VLA-4 for analysis via flow cytometry. Classical monocytes were determined based on CD14 and CD16 expression. A second cohort (N=5) of individuals, with similar demographics, underwent the same exercise protocol and monocytes, isolated from PBMCs, were cultured and allowed to differentiate into macrophages. Cells were fixed and stained for antibodies against CD86 and CD206 to identify M1 and M2 macrophages, respectively. **RESULTS:** No significant changes in Nile Red staining, along with VLA-4 and CD11c receptor expression were observed at POST. However, both CD11c [MFI: 6888.75±1007.95 vs 5327.67±989.83, p=0.002] and VLA-4 [5531.25±416.17 vs 5101.08±349.59, p=0.030] receptor expression decreased at 1HR in comparison to PRE. Interestingly, monocyte lipid uptake, as indicated by Nile Red staining, increased at 1HR compared to PRE values [8560.00±2675.82 vs 11666.3±3415.72, p=0.039]. Furthermore, there was a non-significant trend toward a reduction in M1 macrophages at 1 HR in comparison to PRE [CD86%: 14.38±1.96 vs 5.05±1.69, p=0.144]. **CONCLUSION:** An acute bout of moderate intensity exercise transiently decreases monocyte adhesion molecules 1 h post-exercise in young, fit individuals. Future research is warranted to better understand the effect of exercise on monocyte adhesion following a meal. More specifically, exercising at an optimal intensity and time prior to a meal may induce a cardioprotective benefit to the known effect of a Western Diet on the development of cardiovascular disease.

Cardiovascular exercise physiology

Presentation Number: 215

Board #8

The Influence of Habitual Physical Activity on Blood Pressure Variability

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Purpose: Recent evidence suggests that blood pressure (BP) variability, as assessed using the Average Real Variability (ARV) index, provides prognostic information to 24-hour ambulatory BP monitoring. Elevated ARV is predictive of target end-organ damage and cardiovascular events. Physical activity (PA) is important for BP and cardiovascular health. However, the influence of habitual PA on ARV has not been studied. Therefore, the purpose of this investigation was to determine the influence of habitual PA on ARV derived from 24-hour ambulatory BP monitoring. **Methods:** Twenty-seven healthy adults (14F/13M; age: 26±1yrs; BMI: 24±1kg/m2 BP: 111±2/64±2 mmHg, mean±SEM) underwent 24-hour ambulatory BP monitoring after abstaining from caffeine and alcohol for ≥ 12 hours and exercise for ≥ 24 hours. All participants were normally hydrated and ate similar, recommended sodium diets. Habitual PA was assessed via seven days of accelerometry. A median split was performed to divide participants into less active and more active groups based on their average daily steps and moderate to vigorous PA (MVPA). Additionally, correlation analysis was performed to determine associations between PA and ARV. **Results:** Data are presented as less active (n=13) vs. more active (n=14). ARV of BP readings during waking hours are reported here. As expected, there was a significant difference between groups for average daily step count (6249±442 vs. 11,634±715 steps/day, p<0.01) and MVPA (60±4 vs. 119±6 min/day, p<0.01). Systolic BP ARV was similar between PA groups for both average daily step count (10.9±0.8 vs. 10.2±0.5 mmHg, p=0.44) and MVPA (10.3±.8 vs. 10.6±0.5 mmHg, p=0.77). Diastolic BP ARV was similar between PA groups for both average daily step count (8.4±.4 vs. 8.3±0.4 mmHg, p=0.87) and MVPA (8.2±0.4 vs. 8.5±0.4 mmHg, p=0.49). There was no correlation between systolic BP ARV and average daily step count (r=0.18, p=0.36) or MVPA (r=0.07, p=0.73). There was also no correlation between diastolic BP ARV and average daily step count (r=0.17, p=0.40) or MVPA (r=0.13, p=0.53). **Conclusion:** Our preliminary suggest that habitual PA does not influence 24-hour ambulatory BP AVR in young normotensive adults.

Supported by NIH Grant 1R01HL128388, ACSM Research Endowment Award #16-00213, and AHA 18POST34060020

Cardiovascular exercise physiology

Presentation Number: 216

Board #9

The Physiological Effects of a Combination of HIIT and Steady State Exercise: Does Sequence Matter?

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PURPOSE: Recent investigations have examined the effects of steady-state (SS) and high-intensity interval training (HIIT) on cardiovascular and metabolic responses. Lack of time is cited as a common reason why individuals do not meet the recommended ACSM physical activity guidelines (150 minutes/week of moderate-intensity or 75 minutes/week of vigorous-intensity). To our knowledge, no study has examined the cardiovascular, metabolic and perceptual responses of SS + HITT versus HIIT + SS versus SS only (control). **METHODS:** 14 healthy (male=7, female=7; mass: 65.8 ± 11.7 kg, height: 166.8 ± 10.1 cm, body fat: 17.1 ± 6.2%) college-aged volunteers participated in this randomized, cross-over study. Each participant performed an individualized maximal aerobic capacity test on a treadmill for the determination of VO_2max (44.6 ± 5.2 ml/kg/min) and maximal velocity (Vmax) reached during the aerobic capacity test. Each participant then performed 3 different intensity protocols (1. SS only - 55% Vmax, 2. HIIT + SS - 85% Vmax+ 55% Vmax, 3. SS + HIIT - 55% Vmax+ 85% Vmax) in a randomized fashion. All exercise portions of a trial were 20 minutes in duration, performed at 3% grade and consisted of a 5-minute warm-up and 3-minute cool-down. The HIIT bouts were 30 seconds work and 30 rest (3 mph) lasting a total of 10 minutes in each trial, with SS being performed for the other 10-minute period. Excess post-exercise oxygen consumption (EPOC) was also measured for 20 minutes post-exercise. Oxygen consumption (VO_2) and heart rate (HR) were continuously collected and monitored during each training protocol with rating of perceived exertion (RPE) being collected, pre, mid and post exercise. A two-way repeated measures ANOVA (SPSS v21.0; $p < 0.05$) was used to examine differences between protocols. **RESULTS:** There was no significant difference for average energy expenditure, EPOC, SBP or RPE between any of the three exercise conditions ($p > .05$). There was a significantly higher average HR in the HIIT + SS in comparison to SS only (167.0 ± 12.5 bpm vs 153.0 ± 12.8 bpm) ($p < .05$). There was a tendency towards a higher average VO_2 during the HIIT + SS condition, but this difference was not significant ($p = .081$). **CONCLUSIONS:** The order of HIIT and SS in an acute bout of exercise elicits similar cardiovascular, metabolic and perceptual

responses. An inclination towards a greater physiological stimulus with the HIIT + SS protocol was observed but the results suggest that the order of these modalities for exercisers should be based on personal preference and to facilitate adherence. More research is needed to determine if the HIIT bouts prior to SS exercise may provide a long-term enhanced physiological outcome.

Cardiovascular exercise physiology

Presentation Number: 217

Board #10

Vascular Function is not Adversely Affected by a High-Intensity Interval Training Session in Older Adults

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PURPOSE: Aging is associated with arterial stiffening, early return of the reflected pressure wave, and elevated central blood pressure which increase the risk for cardiovascular disease (CVD). Recently, there has been growing interest in high-intensity interval training (HIIT) as a strategy for decreasing CVD risks, but concerns remain regarding potential adverse vascular responses to HIIT in older adults. The purpose of this study was twofold: 1) to investigate the acute vascular responses to HIIT in older adults and 2) to compare the acute vascular responses to HIIT in older vs. young adults. **METHODS:** A total of 30 young (21.4±0.4 yrs; means±SE) and 27 older adults (66.0±1.1 yrs), free of CVD, participated in this study. Central systolic and diastolic blood pressure (aortic; AoSBP and AoDBP), wave reflection (augmentation index; AIx) and arterial stiffness (carotid to femoral pulse wave velocity; cfPWV) were assessed using a validated cuff-based device. Measures were obtained at pre-exercise, at the end of a single session of HIIT on the treadmill, and following 1-hour recovery from HIIT. HIIT consisted of 4x4-min intervals at 90% peak heart rate (HRpeak) interspersed by 3-min bouts of active recovery at 70% of HRpeak. **RESULTS:** AoSBP was decreased at recovery vs. pre-exercise and end of HIIT in older adults (P≤0.005). However, in young adults, AoSBP was increased at end of HIIT (P<0.0005) and returned to the pre-exercise level at recovery (P>0.99; P=0.003 for agextime interaction). AoDBP was increased at end of HIIT and returned to the pre-exercise level at recovery in older adults (P≤0.01). In young adults, AoDBP was also increased at end of HIIT (P=0.001), but remained elevated at recovery (P=0.2). AIx was decreased at recovery vs. pre-exercise in older adults (P=0.01) and the response was similar vs. young adults (P=0.08 for agextime interaction). cfPWV remained unchanged in response to HIIT in older adults (P=0.7) and the response was similar vs. young adults (P=0.4 for agextime interaction). **CONCLUSIONS:** In older adults, vascular function is not adversely affected following a single session of HIIT. Arterial stiffness is unaffected, whereas, central blood pressure and wave reflection are reduced following recovery from HIIT.

Hot topics in exercise physiology

Presentation Number: 218

Board #11

Exercise Therapy and Radiation Therapy (EXERT) for Cancer: A Systematic Review

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PURPOSE: The benefit of adding exercise therapy (ET) to cancer patients receiving radiation therapy (RT) is unclear, and current guidelines by ASTRO, ESTRO, and NCCN do not recommend concurrent ET+RT. Our goal is to determine the impact of concurrent ET+RT with respect to (1) acceptability, feasibility, and safety; (2) patient reported outcomes (PROs); and (3) physical function and body composition.

METHODS: A PICOS/PRISMA/MOOSE selection protocol was used to systematically search PubMed for prospective randomized controlled trials evaluating concurrent ET+RT. We extracted characteristics of patients, cancer, treatment, outcomes, and toxicity. Physical function was defined as improvements in strength or range of motion. Body composition was defined by bone mineral density or blood markers. Statistical significance for improvement was defined by p<0.05.

RESULTS: 190 articles were screened, and 25 studies were included, with 2,090 patients. The most common cancers were breast (1461 patients, 70% of patients), prostate (401, 19%), and spinal metastases (180, 9%). The most common types of exercise intervention were resistance training (651, 31%), combined aerobic/resistance (592, 28%), yoga (477, 23 %), and aerobics (370, 18%). 18 studies had supervised; 9 studies had home interventions. The median session duration was 1 hour (IQR 0.75-1 hour), performed for a median of 3 times/week (IQR 3-3.25) for a median of 8 weeks (IQR 6-12). *Objective 1.* Among 3,458 patients approached for ET intervention, 2,343 (68%) accepted, of which 2,090 (89%) completed ET+RT. There was 1 adverse event secondary to ET. *Objective 2.* Health perception improved in 3/3 studies; QOL improved in 12/13 (unchanged in 1/13); pain improved in 4/4; fatigue improved in 13/15 (unchanged in 2/15); mood improved in 9/10 (unchanged in 1/10); anxiety improved in 7/8 (unchanged in 1/8); sexual function improved in 1/1; cognition improved in 4/4. *Objective 3.* Physical function improved in 16/16 studies. Body composition improved in 6/6 studies.

CONCLUSIONS: Combined ET+RT is safe and well-tolerated with statistically significant improvements in PROs, physical function, and body composition and no increase in adverse events. Integration of ET+RT in guidelines is warranted.

Hot topics in exercise physiology

Presentation Number: 219

Board #12

Exercise Training Is Associated with Decreased Exercise-Induced Pain and Down Regulation of Acid Sensing Ion Channels (ASICs)

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Purpose: Exercise is an effective therapy for many pain-related conditions, and also there is a difference in pain perception between athletes and deconditioned people. The mechanisms underlying these benefits of exercise are poorly understood. Many of these pain conditions are associated with elevated levels of metabolites, inflammatory factors and other chemicals which can activate receptors on peripheral sensory neurons, such as ASICs and Transient Receptor Potential Vanilloid 1 (TRPV1). Interestingly, high-intensity exercise can also induce release of protons, metabolites, and inflammatory factors, which are known to activate ASICs and TRPV1 and induce pain and fatigue. To understand a potential role of ASICs in the beneficial effects of exercise, we tested if ASICs expression is altered after exercise training. **Methods:** C57BL/6 mice were divided into sedentary (SED), low intensity training (LIT) and high intensity interval training (HIIT) groups. HIIT was trained on treadmill every other day for 4 weeks (4 bouts of 6 min intervals at 80-90% of maximum velocity (V_{max}) with 4 min of active rest), whereas LIT trained at 40-50% of V_{max} for the same distance as HIIT group. SED mice were placed on a non-moving treadmill for similar periods of time. After 4 weeks of exercise training, all groups underwent an incremental treadmill test. Dorsal root ganglia (DRG) were collected 48 hours after exercise, and mRNA levels of ASICs and TRPV1 determined by RT-qPCR. In a separate group of mice, we measured muscle withdrawal threshold at baseline and following maximal exercise before and after 8 weeks of HIIT. **Results:** HIIT group had higher exercise performance compared to LIT and SED, while there was no difference between LIT and SED groups ($p < 0.05$). Body composition, as measured by NMR, did not change between groups after 4 weeks. HIIT group showed reductions of ASIC1b, ASIC2, ASIC3, TRPV1 mRNA levels in DRG. LIT group showed an upregulation of ASIC3 and ASIC1a in DRG. Exercise-induced pain was diminished after 8 weeks of HIIT ($p < 0.05$). **Conclusion:** HIIT improves performance, reduces

exercise-induced pain and downregulates ASICs and TRPV1 in muscle afferents, which might contribute to enhanced performance by diminishing pain and fatigue. Moreover, diminishment of these sensory pathways might contribute to benefits of exercise in disease conditions by reducing deleterious sympathoexcitation. Supported by NIH and VA.

Hot topics in exercise physiology

Presentation Number: 220

Board #13

From Heat Stroke to Heat Sepsis - A Journey of More Than 2000 Years

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The Dual Pathway Model (DPM) of heat stroke suggests that heat stroke is triggered by two separate pathways. The first pathway is due to heat sepsis, as an extension of exercise-induced endotoxemia. The second pathway in the DPM is due to the direct toxic effects of heat on the cytoskeletal structure of cells in major organs. **Purpose:** This presentation aims to discuss the roles of immune disturbances in the mechanisms of heat stroke. **Discussion:** Heat stroke is an ancient condition, dating back more than 2000 years. For centuries, scholars subscribe to the central role of heat in the mechanisms of heat stroke and attributed the pathophysiology of heat stroke to the effects of heat toxicity, which includes circulatory shock, cell death, multi-organ failure and central nervous system dysfunction. This heat-centred model of heat stroke underpins the current strategies for preventing and mitigating the risks of heat stroke in public health, occupational, sports and military settings. However, heat stroke continues to be reported in civilians, labourers, military service personnel and athletes in present time. Recent evidence suggests that immune disturbances, in the forms of endotoxemia and systemic inflammation, may be the primary driver of exertional heat stroke when core temperature (Tc) is <~ 42°C. For example, anesthetized rodents were protected from lethal heat stress when endotoxemia was inhibited, while 25% - 65% of animals with heat-induced endotoxemia died of heat stroke. In field experiments, healthy runners tolerated Tc of up to 41.7 °C with no symptoms of heat stroke. Mild endotoxemia was also detected in healthy runners with significant increases in the concentrations of anti-inflammatory (IL-10, IL-1ra) and inflammatory responsive (IL-6), but not in pro-inflammatory (TNF-α and IL-1β) cytokines. **Conclusion:** These results suggest that humans can tolerate a higher level of heat stress than previously postulated and that heat alone does not fully explain the mechanisms of heat stroke. Other mechanisms related to exercise-induced changes in gut permeability and endotoxin translocation may play important roles in triggering the mechanisms heat stroke. A higher level of heat tolerance may be associated with immune functions that can prevent or protect against endotoxemia and systemic inflammation during intense physical exertion

Hot topics in exercise physiology

Presentation Number: 221

Board #14

Metformin to Augment Strength Training Effective Response in Seniors

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PURPOSE: Loss of muscle mass with aging leads to frailty and numerous metabolic consequences. Resistance training is the most effective method to increase skeletal muscle mass and strength in the elderly; however, the response to resistance training in older individuals is variable and sometimes completely absent. We hypothesized that metformin would augment elderly participants' response to training.

METHODS: At two study sites using a double-blind study design, generally healthy (mean BMI 26.3 ± 0.32 SEM, range 18.6-33.9), elderly (mean age 70.4 ± 0.48 SEM, range 64-91) participants were randomized to metformin or placebo and all performed resistance training for 14 weeks. One hundred and nine participants were randomized and 94 completed the study. Results were analyzed per-protocol.

RESULTS: Analysis of muscle fiber cross sectional area in vastus lateralis muscle biopsies showed that there was no difference in growth response between treatment groups. DXA showed that training led to increased lean mass in both treatment groups ($P < 0.0001$ for effect of exercise); however, the metformin group gained less lean mass than the placebo group ($P < 0.01$ for effect of treatment group). Similarly, thigh CT scans indicated that the placebo group gained more normal density muscle than the metformin group ($P < 0.01$). The placebo group also decreased low density muscle to a greater extent than the metformin group ($P < 0.01$). Preliminary RNAseq analyses of RNA isolated from vastus lateralis muscle biopsies from 30 participants (15 metformin and 15 placebo) pre and post training suggest that metformin blunted signaling pathways normally associated with muscle hypertrophy. However, other pathways involving extracellular matrix remodeling and metabolism, specifically activated by metformin, may contribute to growth.

CONCLUSIONS: These data indicate that adjuvant metformin treatment does not enhance the hypertrophic response to resistance training in healthy elderly individuals. Supported by the NIH R01AG046920-05.

Hot topics in exercise physiology

Presentation Number: 222

Board #15

No Effect Of Menstrual Cycle Phase On Endurance Training-induced Mitochondrial Dynamics

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Purpose: Mitochondria are dynamic organelles in skeletal muscles, which are critical in physical performance. In response to both endogenous and exogenous stimuli, mammalian mitochondria undergo dynamic structural remodeling via fusion and fission events (mitochondrial dynamics) that support biogenesis, maintain functional integrity, and assist in the removal of dysfunctional organelles. Exercise training may promote these processes, conferring positive impacts on skeletal muscle contractile and metabolic functions. Estradiol stimulates mitochondrial biogenesis in skeletal muscles. However, the effect of the menstrual cycle phase on endurance training-induced mitochondrial dynamics has not been studied. The aim of this study was to determine the effect of endurance training on mitochondrial dynamics-related proteins and the effect of the menstrual cycle phase on endurance training-induced mitochondrial dynamics. **Methods:** Female Wistar-Imamichi rats, with a menstrual cycle of 4 days were studied. The menstrual cycle phase of each rat was presumed by performing vaginal lavage. They were divided into four groups: proestrus + sedentary (PS), proestrus + endurance training (PT), estrus + sedentary (ES), and estrus + endurance training (ET). Animals of each endurance training group performed treadmill running (25.7 m/min, 30-120 min, 8.5 degree, 8 weeks). The frequency of endurance training was once in 4 days (15 sessions in total). Immediately after the last training session, the red portion of the gastrocnemius muscle was excised to quantify the expression levels of mitochondrial dynamics-related proteins by Western blotting analysis and to measure citrate synthase (CS) activity to confirm the validity of endurance training. **Results:** After 15 sessions, the CS activity increased in both training groups, suggesting that endurance training was enough to increase mitochondrial enzyme activity. The endurance training increased Drp1 protein, which regulates mitochondrial fission in both training groups. However, there was no effect of the menstrual cycle phase on endurance training-induced Drp1 expression. No statistically significant differences detected in other mitochondrial dynamics-related proteins, i.e., Mfn2, total-, L- and S- Opa1, p-Drp1^{ser616}, and p-Drp1^{ser637}. **Conclusion:** Our results suggest that endurance exercise stimulation in female rats may be able to promote mitochondrial fission, but the phase of the menstrual cycle may not contribute to changes in the mitochondrial dynamics.

Hot topics in exercise physiology

Presentation Number: 223

Board #16

Skeletal Muscle-specific Il-6 Secretion Regulates Leukocyte Trafficking In Female Mice During Septic Shock

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PURPOSE: In skeletal muscle specific IL-6 knockout mice (skmIL-6KO), we have observed alterations in a variety of circulating chemokines and cytokines during septic shock. We hypothesize that these responses affect the recruitment and trafficking of leukocytes into infected tissues and therefore influence host defense. **METHODS:** Female IL-6 floxed mice (N=9-10 per group) were bred with muscle-specific CRE mice. Recombinase activity in muscle was induced in adults by IP injections of the estrogen receptor modulator, raloxifene. Results were compared directly to vehicle-injected strain-matched controls.To resolve confounding effects of raloxifene and activation of recombinase, results were compared with CRE only mice, treated with raloxifene or vehicle. Septic shock was induced by injection of IP cecal contents from donor mice. Cell differential counts were performed on blood, peritoneal lavage (PL), spleen and bone marrow. **RESULTS:** In PL, 6 hours after cecal slurry injection, total leukocyte counts were unaffected. However, the %neutrophils was elevated from 21% in controls to 37% (P<0.0002) in skmIL-6KO. Lymphocytes dropped from 15 to 5% (P<0.002) and basophils dropped from 3.8 to 2% (P<0.01). At 12 hrs post cecal slurry injection, total leukocytes remained unchanged between skmIL-6KO and controls, but in PL neutrophils remained elevated (59% vs 45%, P=0.05), %lymphocytes were unchanged, but %monocytes increased from 9 to 13%, (P = 0.02); %eosinophils and %basophils were reduced (P < 0.03 and <0.02, respectfully). There were no statistically significant differences between groups in the cell differential counts in blood, bone marrow or spleen. There were also no differences cell differentials in any tissue between raloxifene-treated and untreated CRE mice. **CONCLUSIONS:** Skeletal muscle IL-6 plays an important role in the regulation of inflammatory cells and in the timing of their recruitment to the primary site of infection (i.e. the peritoneum in the cecal slurry model). This appears to be specific to skeletal muscle IL-6 secretion and not to potential confounders of muscle CRE activation or raloxifene treatment. Supported by NIGMS R01GM118895-01 and the BK and Betty Stevens Endowment

Hot topics in exercise physiology

Presentation Number: 224

Board #17

Suppression of Skeletal Muscle Interleukin-6 Alters Circulatory Cytokine Response to Sepsis in Female Mice

Orlando Laitano, Gerard P. Robinson, Christian K. Garcia, Alex J. Mattingly, Kevin O. Murray, Laila H. Sheikh, Tara Aboumahboub, Shannon M. Wallet, Thomas L. Clanton. *University of Florida, Gainesville, FL.*
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Interleukin-6 (IL-6) is one of the major cytokines released by skeletal muscle in response to blood pathogens. Nevertheless, the contribution of IL-6 secreted by skeletal muscle (skmIL-6) to innate immunity is not well understood. **PURPOSE:** In this study we utilized a floxed IL-6 knockout mouse crossed with a skeletal muscle inducible CRE mouse to evaluate the contribution of skeletal muscle IL-6 secretion to the overall response to sepsis. **METHODS:** Polymicrobial sepsis was induced using intraperitoneal injection of a standardized dose of cecal slurry (CS) collected previously from donor mice. Twenty-four animals were studied at 6 and 12 hours after CS injection and plasma cytokines were measured using Luminex multiplex array. Female mice in which the recombination of CRE was induced with raloxifene (skmIL-$6^{-/-}$) were compared to sham strain-match controls (skmIL-$6_{+/+}$). **RESULTS:** At the 6-hour time-point after CS injection, the skmIL-$6^{-/-}$ mice demonstrated significant reductions in INF-δ (skmIL-$6^{+/+}$ = 21 ± 8 vs. skmIL-$6^{-/-}$ = 7 ± 4 pg/ml, P < 0.01), IL-5 (skmIL-$6^{+/+}$ = 232 ± 43 vs. skmIL-$6^{-/-}$ = 139 ± 52 pg/ml, P < 0.02), IL-9 (skmIL-$6^{+/+}$ = 128 ± 82 vs. skmIL-$6^{-/-}$ = 22 ± 31 pg/ml, P < 0.02), IL-10 (skmIL-$6^{+/+}$ = 10846 ± 4080 vs. skmIL-$6^{-/-}$ = 3350 ± 1456 pg/ml, P < 0.05), MIP-1α (skmIL-$6^{+/+}$ = 1054 ± 398 vs. skmIL-$6^{-/-}$ = 477 ± 570 pg/ml, P < 0.05), MIP-1β (skmIL-$6^{+/+}$ = 2576 ± 613 vs. skmIL-$6^{-/-}$ = 1432 ± 808 pg/ml, P < 0.05), and TNFα (skmIL-$6^{+/+}$ = 77 ± 40 vs. skmIL-$6^{-/-}$ = 29 ± 10 pg/ml, P < 0.01). At 12 hours, the only observed effect was a reduction in RANTES (skmIL-$6^{+/+}$ = 61 ± 7 vs. skmIL-$6^{-/-}$ = 37 ± 7 pg/ml, P < 0.05). **CONCLUSIONS:** Inhibition of IL-6 production by skeletal muscles suppresses a variety of cytokines in the circulation including TNFα and a number of chemokines required to provide immunity against polymicrobial sepsis. Importantly, most of the observed changes occurred 6 hours after induction of polymicrobial sepsis which is consistent with skeletal muscle IL-6 being required for the early innate immune response in this model. These effects appear to be independent of the influence of raloxifene, the estrogen receptor activator, or CRE activation. *Supported by NIGMS R01GM118895-01*

Hot topics in exercise physiology

Presentation Number: 225

Board #18

The Acute Effects of Beta-Alanine on Exercise Performance Variables

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Beta-Alanine (BA) is converted to carnosine which serves to lower acid levels in the muscle by acting as an intramuscular buffer to H+ ions. BA supplementation may increase carnosine synthesis in muscle, leading to reduced muscle fatigue with exercise. **PURPOSE:** To determine the effects of an acute dose of BA (4 grams, 30 min before testing) on muscular power, muscular endurance and aerobic performance. **METHODS:** 21 recreationally active men (24.5±1.5yrs, 1.8±0.1m, 79.2±9.3kg) and 15 women (25.7±2.2yrs, 1.6±.0.1m, 55.1±8.1kg) participated in a placebo controlled, double blind cross-over design study. Subjects were tested on 3 separate days with a 24-hour washout period between test visits. Visits consisted of 4 tests done in the following order: vertical jump on a jump mat, repetition of 70% leg press and chest press max until failure, and a 4-kilometer time trial (4km) on a cycle ergometer. The first testing visit established the 1-repetition maximum on the leg and chess press and familiarization with testing procedures. Subjects were randomized to BA or placebo on the 2nd and 3rd visit. Comparisons of the effects of BA and placebo on exercise test values were made using two-way ANOVA with repeated measures (p<0.05). **RESULTS:** BA showed a significant increase from baseline in the number of reps performed on both the leg press (15.7±5.5 vs. 22.9±7.3 repetitions, p<0.001) and chest press (12.0±5.8 vs. 17.7±5.4 repetitions, p<0.001). Placebo showed a small non-significant increase from baseline in the number of reps performed on both the leg press (15.7±5.5 vs. 17.3±5.3 repetitions, p=0.055) and chest press (12.0±5.8 vs. 12.6±5.6 repetitions, p=0.059). The increases in the BA group were statistically different from the change in the placebo group (leg press, p<0.001 and chest press p<0.001). BA showed a significant increase from baseline in aerobic power (132.0±49.1 vs 144.0±48.8 Watts, p<0.001) during the 4km. Placebo showed a small non-significant increase from baseline in aerobic power (132.0±49.1 vs 134.3±49.4 Watts, p=0.080) during 4km. The increase in aerobic power in the BA group was statistically different from the change in the placebo group (p<0.001). **CONCLUSION:** A single 4 gram dose of BA improves muscular endurance and aerobic power in recreationally active young men and women.

Hot topics in exercise physiology

Presentation Number: 226

Board #19

Transcriptome Response to Resistance Exercise in Slow- and Fast-Twitch Skeletal Muscle Fibers with Lifelong Exercise

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Purpose: Aging skeletal muscle is characterized by a loss of mass and function, which is more pronounced in fast-twitch muscle fibers. However, little is known about the potential benefits of lifelong exercise on myocellular biology and the response to exercise. Using an anabolic exercise challenge (resistance exercise, RE) we examined the transcriptome response in slow- and fast-twitch muscle fibers from 3 different cohorts: Old lifelong exercisers (LLE; n=8 M, 74±4 y), old healthy individuals (OH; n=9 M, 75±2 y) and young exercising individuals (YE; n=8 M, 25±1 y). **Methods:** Skeletal muscle biopsies were obtained from the vastus lateralis before and 4h after an acute bout of RE (3 x 10 bilateral knee extensions at 70% of 1-RM). Single muscle fibers were separated from muscle bundles under a light microscope, and then the fiber type (MHC) was determined using SDS-PAGE. Total RNA extraction was performed on pools of muscle fibers of the same type from each subject and time-point, generating 100 fiber-type specific samples. Gene expression was evaluated using RNA-Seq and the data were analyzed using DESeq2. Differential gene expression cut-offs to determine the response to RE were set at a fold-change of >1.5 and FDR<0.1. The GO database was used to find enriched biology in the datasets. **Results:** Regardless of age or training status, fast-twitch muscle fibers were more responsive to the RE bout (YE: 47 genes, LLE: 228 genes, OH: 567 genes) compared to slow-twitch muscle fibers (YE: 25 genes, LLE: 60 genes, OH: 50 genes). Within fast-twitch fibers, the untrained OH had the greatest number of genes responding to RE, but the least categories of enriched biology (EB). The YE had the shortest list of responsive genes but the most categories of EB, with the LLE group falling in between. When comparing RE-responsive genes across groups, 30 genes emerged as the fast-twitch RE transcriptome signature including EB such as skeletal muscle differentiation and development, circadian rhythm, and transcription. There was no EB detected among the slow-twitch fibers in any group. **Conclusions:** These novel fiber-type specific RNA-Seq data provide unique insight into the exercise-induced skeletal muscle biology. The transcriptome data show that fast-twitch muscle fibers are more responsive than slow-twitch fibers to an RE stimulus. Interestingly, a hierarchical pattern emerged in the enriched biological response of the fast-twitch muscle fibers to exercise (YE>LLE>OH) providing insight into the potential skeletal muscle health benefits at the genetic level with lifelong exercise, which warrants further investigation. Sponsored by NIH R01 AG038576 and BSU Academic Excellence Award.

Integrative exercise physiology and metabolism

Presentation Number: 227

Board #20

Caloric Restriction Improves Skeletal Muscle P:O Ratio but not Whole-body Exercise Efficiency

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Purpose: To compare changes in cellular and whole-body efficiency in individuals that underwent caloric restriction (CR) versus control. **Methods:** This analysis included, twenty-one (13 F, 8 M) sedentary, normal weight (24.9±1.8 kg/m^2), middle-aged (40.4±6.7 y) individuals from the Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy (CALERIE) phase 2 trial. Subjects were randomized to 25% CR (CR: n=14) or an *ad libitum* control group (AL: n=7) for 2 years. At baseline and months 12 and 24, subjects underwent a VO_2peak (Cornell incremental treadmill) test. Resting O_2 uptake, ATPflux and ATPmax in the *vastus lateralis* (optical spectroscopy and by ^{31}P-magentic resonance spectroscopy) and P:O ratio (ratio of ATPflux to O_2 uptake) were assessed. Exercise efficiency was calculated during the treadmill test as the inverse slope of the relationship (delta efficiency, ΔE) between VO_2 and power output both expressed in kcal/min. **Results:** At the whole-body level, VO_{2peak} and ΔE did not differ at baseline between CR and AL (35.4±8.6 vs. 31.6±4.5 ml/kg/min, p=0.2 & 12.5±1.9 vs. AL: 13.5±1.9 %, p=0.29, respectively). VO_2peak decreased at month 12 to 24 only within AL by ~17% (p=0.01) with no changes in any time within or between groups for ΔE. There were no associations between these exercise variables at baseline; however, ΔE negatively correlated with VO_2peak at month 12 (R^2=0.23, p=0.03) and month 24 (R^2=0.21, p=0.04). At the cellular level, ATPmax did not differ at baseline between CR and AL (0.8±0.3 vs. 0.9±0.3 mM/s, respectively, p=0.34) nor at months 12 or 24 indicating no within or between group differences in mitochondrial capacity. P:O was not different between groups at baseline (p=0.63). However, P:O increased from months 12 to 24 in CR by ~22% (p=0.01), with no such difference observed in AL (p=0.09). At baseline, P:O and ATPmax both positively correlated (R^2=0.33, p=0.006, R^2=0.28, p=0.02, respectively) with VO_2peak but this correlation dissipated at months 12 and 24 (p=0.18). Changes in weight did not associate with the above outcomes at any period. **Conclusion:** An improved P:O ratio may constitute a more efficient flux through the electron transport chain as an adaptive mechanism to conserve energy during CR, without any observed changes in *in vivo* mitochondrial capacity (ATP generation). Thus, chronic CR (>1 year) may be a viable exercise mimetic at the cellular level; however, this does not translate to improvements in mechanical efficiency during exercise. Supported by NIH (R01 AG029914 & U01 AG020478 to E.R.), and in part by P30DK072476 (Pennington/Louisiana NORC) & U54 GM104940 (Louisiana Clinical and Translational Science Center).

Integrative exercise physiology and metabolism

Presentation Number: 228

Board #21

Effects of Constant Scattering on Muscle Oxygenation Measurements During Ischemia and Vascular Reperfusion

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Purpose: Frequency-domain near-infrared spectroscopy (FD-NIRS) measures absolute concentrations of deoxygenated and oxygenated heme (deoxy-[heme] and oxy-[heme], respectively) by continuously measuring dynamic changes in tissue optical properties (i.e. scattering and absorption). Continuous-wave near-infrared spectroscopy (CW-NIRS) relies on the assumption that tissue scattering remains unchanged. During incremental cycling exercise, interpretation of muscle oxygenation characteristics is altered when assuming a constant tissue scattering. The purpose of this study was to determine if assuming constant scattering would alter muscle oxygenation measurements during ischemia and vascular reperfusion. We hypothesized that assuming constant scattering would significantly alter muscle oxygenation measurements.

Methods: 21 subjects (21.8 ± 1.9 yr, 175 ± 8 cm, 74.3 ± 17.5 kg) completed three vascular occlusion tests consisting of 1 minute of baseline, 5 minutes of arterial occlusion, and 3 minutes of recovery following reperfusion. FD-NIRS was used to measure deoxy-[heme], oxy-[heme], total-[heme] and tissue oxygen saturation (S_tO_2) with and without constant scattering.

Results: Assuming constant scattering led to an overestimate of deoxy-[heme] and underestimate of S_tO_2 at baseline, the end of occlusion, reperfusion and recovery (all $p < 0.001$). Total-[heme] was not different at any time point ($p > 0.05$). The magnitudes of change in deoxy-[heme], oxy-[heme] and S_tO_2 during occlusion and reperfusion were significantly

greater when constant scattering was assumed ($p < 0.001$). The rate of tissue re-saturation (S_tO_2 slope 2) was significantly overestimated when scattering was assumed constant (5.2 ± 2.6 vs. 7.8 ± 4.7%/s; $p < 0.001$).

Conclusion: Muscle oxygenation measurements during ischemia and vascular reperfusion were altered when holding scattering constant. These differences in NIRS methodologies may lead to inaccurate interpretations of muscle oxygenation when dynamic changes in tissue optical properties are not measured.

Integrative exercise physiology and metabolism

Presentation Number: 229

Board #22

Effects of Exercise or HFD in Mice Lacking Cannabinoid 1 Receptors Within Steroidogenic Factor 1 Neurons

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The transcription factor Steroidogenic Factor 1 (SF1) is exclusively expressed in the ventromedial hypothalamus (VMH). We recently found that that deleting SF1 from the VMH blunts improvements in body composition in response to exercise training. The cannabinoid 1 receptor (CB1R) is widely expressed in the periphery and the nervous system. Whole body deletion of CB1R protects against high fat diet (HFD) induced obesity and insulin resistance. However, the exact cites of CB1R action in regulating metabolism are poorly defined. Among neuronal populations, CB1R expression is high in the VMH. Notably, CB1R is a putative direct transcriptional target of SF1. Therefore, the **PURPOSE** of these studies was to determine the role of CB1R within SF1 expressing neurons (SF1-neurons) of the VMH in regulating metabolic responses to exercise training or HFD feeding. **METHODS & RESULTS:** Utilizing CRISPR/Cas9 technology we inserted flanking loxP sites into the CB1R allele *(Cnr1)* of mice to allow for site specific deletion of CB1R from SF1-neurons ($CB1R^{SF1\text{-}KO}$). Chow fed $CB1R^{SF1\text{-}KO}$ mice and their littermate controls ($CB1R^{flox}$) either remained sedentary or performed 9 weeks of treadmill exercise training (15m/min for 1h, 10% incline, 5 days/week). We also assessed the role of CB1R in SF1-neurons with HFD feeding. $CB1R^{SF1\text{-}KO}$ had similar body weights to control groups in response to exercise training, or when fed HFD or chow. Notably, with HFD feeding glucose tolerance was improved for $CB1R^{SF1\text{-}KO}$ mice compared to control groups. One week of CB1R inverse-agonists treatment similarly reduced body weight in HFD fed control and $CB1R^{SF1\text{-}KO}$ mice. We found that CB1R inverse-agonists treatment improved glucose tolerance in control, but not $CB1R^{SF1\text{-}KO}$ mice. We also performed hyperinsulinemic-euglycemic clamps to assess insulin sensitivity in HFD fed $CB1R^{SF1\text{-}KO}$ and control mice. Basal hepatic glucose production in $CB1R^{SF1\text{-}KO}$ was lower, accounting for the improved glucose homeostasis. **CONCLUSION:** Our results indicate that CB1Rs of the VMH are critical for regulating whole body glucose homeostasis. In addition, CB1Rs within SF1-neurons are not required to regulate body weight in response to either exercise training or HFD feeding. NIH **R01-DK100659 to JKE**. NIDDK **K01-DK111644 to CMC**.

Integrative exercise physiology and metabolism

Presentation Number: 230

Board #23

Elevated Whole-Body Production of Citrulline & Arginine in High Active Mice: A NO-vel Finding

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Physical activity is associated with attenuating the incidence of hypokinetic related diseases and its worldwide economic burden on health care cost. However, the mechanisms regulating physical activity remain unclear, specifically, the mechanistic interactions between arginine (ARG)/citrulline (CIT) metabolism that affects nitric oxide (NO) production and therefore potentially regulates physical activity. Although differences in total ARG and CIT plasma concentrations have been observed in different mouse strains, it is unknown if whole body production (WBP) of ARG and CIT and *de novo* ARG are altered.

PURPOSE: To assess ARG and CIT metabolism by measuring WBP and *de novo* ARG production in mice previously classified as either low-active (LA; C3H/HeJ) or high-active (HA; C57L/J).

METHODS: 12-week-old male LA (n=23) mice (body weight: 25.8 ± 1.2g; lean mass: 21.0 ± 1.1g; fat mass: 2.5 ± 0.5g) and HA (n=20) mice (body 27.5 ± 1.2g; lean mass: 22.5 ± 1.3g; fat mass: 2.5 ± 0.7g) were used. Under anesthesia, a pulse of stable tracers (L-[Guanido-$^{15}N_2$]-arginine, L-[5-^{13}C; 4,4,5,5-d_4]-citrulline) were administered via a right jugular vein catheter. Subsequently blood samples were taken (Time: 1,3,5,7,10,15,20,25,30, and 40 mins). Plasma enrichments and concentrations of ARG and CIT were determined by LC-MS/MS. WBP along with CIT to ARG conversion (*de novo* ARG) were calculated. Fitting and statistical analysis (unpaired student *t*-tests) were performed using GraphPad Prism 7 software. Data are expressed as mean ± SE.

RESULTS: The HA mice showed higher WBP values for CIT (42.71 ± 1.44 vs. 33.34 ± 1.28 µmol/kg lbm/h, $p<0.0001$), for ARG (436.39 ± 18.7 vs. 332.01 ± 9.83 µmol/kg lbm/h, $p<0.0001$), and for *de novo* ARG production (58.82 ± 2.52 vs. 45.27 ± 2.36 µmol/kg lbm/h, $p=0.0001$).

CONCLUSIONS: The observed changes in the CIT ARG pathway suggest modified/higher NO production in HA active mice, potentially linked to their drive for greater physical activity levels.

ACKNOWLEDGMENTS: Study was funded by a research development grant from the Vice-President of Research, Texas A&M University.

Integrative exercise physiology and metabolism

Presentation Number: 231

Board #24

Endurance Exercise Training Prevents Doxorubicin-induced Mitochondrial Dysfunction of the Liver

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PURPOSE: Doxorubicin (DOX) is a highly effective chemotherapeutic agent used in the treatment of a broad spectrum of cancers. However, clinical use of DOX is limited by irreversible and dose-dependent hepatotoxicity. Damage to the liver occurs in nearly 40% of patients receiving DOX and can result in serious complications, including liver failure and death. The liver is the primary organ responsible for the clearance of antineoplastic agents, and evidence indicates that hepatotoxicity occurs as a result of increased mitochondrial free radical production during DOX metabolism. In this regard, it is well known that endurance exercise training is sufficient to reduce oxidative stress and protect against DOX-induced cytotoxicity. Therefore, the purpose of this study was to determine if short-term exercise preconditioning is sufficient to protect against DOX-induced liver mitochondrionopathy.

METHODS: Four-month old female Sprague-Dawley rats were randomly assigned to one of four groups: 1) sedentary, treated with saline (SED-SAL); 2) sedentary, treated with DOX (SED-DOX); 3) exercise trained, treated with saline (EX-SAL); 4) exercise trained, treated with DOX (EX-DOX). Exercise trained animals underwent 5 days of treadmill running habituation followed by 10 days of running for 60 min/day (30 m/min; 0% grade). Following the last training bout, exercise-trained animals and sedentary animals were injected with either DOX (20 mg/kg; ip) or saline (equal volume to DOX). Two days following drug treatment the liver was removed and mitochondria were isolated.

RESULTS: DOX administration resulted in a significant reduction in mitochondrial coupling. Specifically, the respiratory control ratio of SED-DOX animals was reduced compared to all other groups (SED-SAL = 5.55 ± 0.39; SED-DOX = 3.94 ± 0.29; EX-SAL = 5.67 ± 0.38; EX-DOX = 5.12 ± 0.39), and was associated with changes in citrate synthase protein expression (SED-SAL = 1.0 ± 0.06; SED-DOX = 0.82 ± 0.05; EX-SAL = 1.03 ± 0.07; EX-DOX = 0.93 ± 0.08). Further, our results demonstrate that DOX significantly affects protein acetylation as acetylated lysine was significantly increased (SED-SAL = 1.0 ± 0.19; SED-DOX = 3.98 ± 0.27; EX-SAL = 1.46 ± 0.36; EX-DOX = 2.04 ± 0.64) and Sirt3 was significantly decreased (SED-SAL = 1.0 ± 0.09; SED-DOX = 0.69 ± 0.08; EX-SAL = 1.14 ± 0.09; EX-DOX = 1.16 ± 0.08) in SED-DOX animals.

CONCLUSIONS: These findings suggest that DOX administration results in liver mitochondrionopathy and that exercise preconditioning is sufficient to prevent mitochondrial dysfunction.

Integrative exercise physiology and metabolism

Presentation Number: 232

Board #25

Exercise Affects Histone Modification of Colorectal Tissue in BALB/c Mice

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PURPOSE: Epidemiological studies have demonstrated that regular physical exercise prevented the incidence of colon cancer, even though the mechanisms involved are unclear. We investigated the effects of exercise on colon tumorigenesis in association with inflammatory cytokine and histone modification in azoxymethane (AOM)-injected mice. **METHODS:** BALB/c mice (7-week-old) were randomly assigned to control (CON), AOM, and AOM with exercise (AOM/Ex) groups, and the 2 latter groups were intraperitoneally injected with AOM (12.5 mg/kg of body weight) once a week for 2 weeks. After the first AOM injection, the mice performed running exercises on a motorized treadmill 5 times per week for 6 weeks. During the first 2 weeks, the level of exercise was gradually increased from running for 15 min at a speed of 15 m/min to running for 30 min at 20 m/min, which was then maintained for the following 4 weeks. Next, the mucosal surface of the colon was stained with methylene blue and mRNA and protein levels were determined via RT-PCR and western blot analysis. Statistical significance was established at $p < 0.05$. **RESULTS:** Aberrant crypt foci (ACF) are one of the earliest histopathological manifestations of colon cancer. ACF developed in the AOM and AOM/Ex groups; however, their incidences were lower in the AOM/Ex group when compared to the AOM group. Moreover, histone 3 lysine 27 acetylation (H3K27ac) was downregulated and TNF-α and iNOS mRNA levels were upregulated in the AOM group than AOM/Ex group. **CONCLUSIONS:** Exercise prevents colon tumorigenesis, at least partly, the suppression of iNOS and TNF-α expression via histone modification. This work was supported by Japan Society for Promotion of Science (JSPS) KAKENHI Grant No. 16K16564. Grant from the MEXT-Supported Program for Strategic Research Foundation at Private University also supported this research.

Integrative exercise physiology and metabolism

Presentation Number: 233

Board #26

Exercise-Induced Improvements in Muscle Mitochondrial Capacity In Vivo Are Retained *In Vitro* in Primary Human Muscle Cells

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Purpose: Life-long exercise training is associated with high muscle mitochondrial function which increases exercise capacity and reduces metabolic disease risk. Short-term (weeks) training induces improvements in these same parameters. Nascent myogenic progenitor cells (HSkMC) are a critical component of skeletal muscle plasticity, particularly in response to exercise. We investigated the ability of short-term and life-long exercise training to imprint HSkMC with metabolic and epigenetic modifications. **Methods:** 17 individuals with type 2 diabetes (T2D) performed a 10-week supervised, progressive, aerobic training protocol (50-70% VO_2peak for 4 days/week on a treadmill). We also included a cohort of BMI-matched non-diabetic individuals (n=8) and highly active individuals (n=7). *In vivo* mitochondrial function (PCr recovery via ^{31}P-MRS) and a biopsy of the *v. lateralis* for high-resolution respirometry and establishment of HSkMCs were performed pre-training in all three groups and post-training in the individuals with T2D. Global DNA methylation was also performed in the pre-training HSkMC. **Results:** Active individuals had the highest rates of muscle mitochondrial function *in vivo* compared to individuals with type 2 diabetes (T2D; $p<0.001$) and without (ND; $p<0.05$). This pattern was retained in the muscle tissue (Active vs. ND, $p<0.0001$; Active vs. T2D, $p<0.0001$) and HSkMC (Active vs. ND, $p<0.05$; Active vs. T2D, $p<0.01$) derived from the same individuals and quantified via high-resolution respirometry (mitochondrial function). 10 weeks of aerobic training improved mitochondrial function in the muscle tissue ($p<0.05$) and in the HSkMC ($p<0.05$) from the individuals with T2D, almost to the levels observed in the Active individuals. > 3,400 CpG sites were differentially methylated in HSkMC from Active vs. individuals with T2D prior to training with ~64% of these sites being hyper-methylated in the individuals with T2D vs. Active. Pathway enrichment analyses annotated these differentially methylated CpG sites to genes involved in lipid metabolism and mitochondrial function. Training-induced improvements in muscle mitochondrial function *in vivo* were significantly related with the pre-training DNA methylation profiles of the HSkMC in the T2Ds. **Conclusions:** These data illustrate that HSkMC can retain a training-induced phenotype and are capable of metabolic imprinting, in terms of mitochondrial function. These are seminal observations, as HSkMC undergo proliferation and differentiation in media void of the hormonal and neural influences present *in vivo*, which suggests that the adaptations observed are of a genetic and/or epigenomic origin.

Integrative exercise physiology and metabolism

Presentation Number: 234

Board #27

General Health Characteristics and Training Profile of Lifelong Exercisers

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Purpose: As part of a larger investigation into the potential benefits of lifelong aerobic exercise, this portion of the study describes the general health characteristics of the participants. To accomplish this, we examined young exercisers (YE; 25±1y; *n*=20, 10F), lifelong exercisers (LLE; 74±2y; *n*=28, 7F), and age-matched non-exercisers (OH; 75±1y; *n*=20, 10F). On average, LLE exercised 5d/wk for 7h/wk for 52±1y. Based on intensity, males were further subdivided into performance (LLE-P,

n=14) and fitness (LLE-F, n=7). The females ranged from performance to fitness. Upon extensive screening, 16% of interested individuals were admitted, demonstrating the selectivity of the investigation. **Methods:** The exercise history and general health profile of the subjects were evaluated using various measurements including: anthropometric data, resting and exercising cardiovascular data, blood chemistries, a body composition assessment (DXA) scan, and a medical and exercise history questionnaire. **Results:** In males, LLE demonstrated superior values to OH in several general health measures (HDL, triglycerides, %fat) (P<0.05), with only percent body fat lower in LLE females compared to OH (P<0.05). Intensity appeared to only effect blood glucose and hematocrit in males as LLE-P had superior values to LLE-F (P<0.05). **Conclusion:** Lifelong aerobic exercise appears to improve general health characteristics only in males, as there were no differences in blood chemistries in lifelong exercising females. This may suggest a potential physiological sex difference in response to lifelong training, or perhaps may be due to differences in exercise training history. These data further support the cardiovascular and skeletal muscle health profiles in our companion abstracts. Supported by NIH AG038576

Integrative exercise physiology and metabolism

Presentation Number: 235

Board #28

Heat Stress and the Velocity-Duration Relationship: Implications for Middle Distance and Endurance Running Performance

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Tolerance to high-intensity running is constrained by a hyperbolic velocity-duration relationship. Measuring the parameters (curvature constant, D′ and asymptote, critical velocity) is essential for a rigorous characterization of exercise tolerance. Evidence for the effects of thermoregulatory stress on middle-distance running performance is equivocal – likely do to the complexities of the velocity-duration relationship not being taken into account. **PURPOSE:** We aimed to 1) characterize the velocity-duration relationship for elite performances across a wide range of event distances and heat indices, and 2) measure the effects of heat stress on the velocity-duration relationship in amateur competitive and recreational runners. **METHODS:** Performance and weather data were collected from 129 elite athletic events (400 to 10,000 m), including the Olympic Games and the World Championships, to develop velocity-tolerable duration relationships across four heat index ranges (12 to 34°C). Additionally, we recruited 15 participants (4 women, 23 ± 6 yr, 177 ± 8 cm, 69.4 ± 12.6 kg) to complete a series of constant-velocity running bouts to intolerance in 3 heat indices produced in a temperature and humidity controlled environmental chamber (heat indices for COOL: 20°C, WARM: 38°C, HOT: 55°C). **RESULTS:** Following the records analysis, mean D′ and critical velocity were 120.6 ± 1.5 m; 6.34 ± 0.04 m/s for elite men and 129.1 ± 13.1 m; 5.58 ± 0.082 m/s for women. There was no interaction of heat index and event distance on elite mean running velocity (men: p<0.89; F(12,78) = 0.53; women p<0.08; F(12,70) = 1.74), nor a main effect of heat index on running velocity (men: p<0.44; F(3,52) = 0.92; women (p<0.63; F(3,19) = 0.58). However, in our laboratory experiment, critical velocity in COOL (3.52 ± 0.86 m/s) was greater than that during WARM (3.39 ± 0.82 m/s) and HOT (3.29 ± 1.05 m/s; F(2,28) = 4.06; p<0.03) with no effect of heat stress on D′ (F(2,28) = 2.67; p<0.09). **CONCLUSION:** Thermoregulatory stress up to a heat index of 34°C does not appear to negatively impact elite running performance in 400 to 10,000 m events. However, data are lacking from elite events in which the heat index was greater than 35°C. This may soon change with events being scheduled in some of the hottest environments (2019 IAAF World Championships, Doha, Qatar). In amateur competitive and recreational runners, heat stress as little as a 38°C heat index negatively affected critical velocity. Thus, even during relatively short and middle distance events where fluid loss is not a primary concern, heat stress may negatively impact performance.

Integrative exercise physiology and metabolism

Presentation Number: 236

Board #29

Identifying Predictors of the Change in VO2max in Response to HIIT Prescribed according to Ventilatory Threshold

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Many participants demonstrate no change in maximal oxygen uptake (VO_2max) in response to moderate intensity continuous training (MICT) (Bouchard et al 1999) or high intensity interval training (HIIT, Astorino & Schubert 2014). Approximately 50 % of this non-response is hereditary (Bouchard et al 1999) and the other 50 % is likely related to participants' habitual physical activity, diet, sleep, and traits of the training regime (Mann et al. 2015). In unfit adults, Wolpern et al. (2015) showed that MICT prescribed according to ventilatory threshold (VT) led to lower onset of individual non-response than when prescribed using heart rate (HR). **PURPOSE:** To examine correlates of change in VO_2max in response to low volume HIIT prescribed using VT. **METHODS:** Fourteen active (age and VO_2max = 27 ± 8 yr and 38 ± 4 mL/kg/min) men and women performed baseline testing including a VO_2max test on a cycle ergometer to determine peak power output and VT. Subjects also performed a 5 mi cycling time trial (TT) over three separate days. Subsequently, they underwent 9 sessions of HIIT consisting of 8 – 10 60 s bouts at work rate of 130% VT with a 75 s recovery. Training elicited an intensity = 90 ± 5 %PPO. VO_2max and TT were assessed within 96 h post-training. Controls (CON) of similar age and fitness (n=14, age and VO_2max = 22 ± 3 yr and 40 ± 5 mL/kg/min) completed all sessions of baseline testing separated by 3 wk. **RESULTS:** Baseline VO_2max (r = 0.13, p = 0.50) and absolute work rate attained during HIIT (r = 0.32, p = 0.27) were unrelated to the change in VO_2max, although peak heart rate attained during HIIT (r = 0.62, p = 0.02), change in VT (r = 0.52, p = 0.005), and change in TT performance (r = -0.48, p = 0.01) demonstrated significant associations. Data showed a significant groupXtime interaction for change in VO_2max (38 ± 4 mL/kg/min to 41 ± 5 mL/kg/min vs. 40 ± 5 mL/kg/min to 41 ± 6 mL/kg/min, p = 0.003) and TT (936 ± 80 s to 913 ± 78 s vs. 915 ± 99 s to 928 ± 88 s, p = 0.007) between HIIT and CON. With 2Xtypical error = 0.12 L/min for VO_2max and 21 s for TT, 57 % of participants showed meaningful increases in VO_2max and TT in response to HIIT. Two of 14 participants exhibited no change in any variable. **CONCLUSION:** Data show that 9 sessions of personalized HIIT significantly increases VO2max and this change is positively related to absolute cardiorespiratory strain and enhanced cycling performance and VT which are determined by oxidative capacity. Yet, this change in VO2max was unrelated to baseline fitness, which opposes previous results. Further study is merited to understand predictors of training responsiveness.

Integrative exercise physiology and metabolism

Presentation Number: 237

Board #30

In Vivo Muscle Oxidative Capacity Differs with Contraction Mode and Energetic Demand

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Skeletal muscle oxidative capacity can be measured *in vivo* from the rate constant (k_{PCr}) of the monoexponential recovery of phosphocreatine (PCr) following a brief contraction using ^{31}P-magnetic resonance spectroscopy. Although the ATP cost of contraction differs by contraction mode, the effect of contraction mode on k_{PCr} is not known. **Purpose:** To investigate whether isometric and dynamic contractions yield different k_{PCr} values in healthy adults. **Methods:** 7 adults (4 men, 28.9±3.3 yrs, mean±SD) were positioned supine in a 3T MR system with their dominant leg strapped at the ankle, knee, and hip to a custom-built knee extension ergometer. A

dual-tuned ^{31}P-^{1}H surface coil was secured over the vastus lateralis using inelastic straps. Torque-time integrals were measured in all participants during 24-s maximal voluntary isometric (MVICs) and dynamic (MVDCs) contraction protocols. Following 2 "warm-up" contractions, intramyocellular [PCr] and pH were measured continuously during 90s rest, each contraction protocol, and 7 min of recovery. All MVDCs were completed at 120°.s^{-1} over a 30° range of motion, with 1 contraction every 2s. The order of contraction modes was randomized. Spectra were processed in jMRUI v6.0beta and analyzed using AMARES. k_{PCr} was quantified by fitting the observed PCr recovery with a monoexponential: $PCr(t)=PCr_{End} + Amp*(1-Exp^{(-k*t)})$. **Results:** Baseline [PCr] (38.9±1.0 vs. 38.9±0.8 mM) and pH (7.03±0.02 vs. 7.04±0.02) did not differ between the MVIC and MVDC protocols (p>0.05). The decline in [PCr] (38.1±10.4 vs. 49.1 ±9.5% baseline, p=0.01) and pH (6.98±0.07 vs. 7.07±0.05, p=0.02) at the end of contractions was greater for the MVIC than the MVDC protocol, respectively. The total torque-time integral was greater in the MVIC than MVDC protocol (5,577±1,592 vs. 451±163Nm.s, p=0.001), whereas the torque produced per ATP was lower during the MVDC than the MVIC protocol (12.9±2.9 vs. 131.6±23.5 Nm/ATP/s, p=0.001). k_{PCr} was faster following the MVDC protocol (0.027±0.004 vs. 0.022±0.005s^{-1}, p=0.01). **Conclusions:** Maximal dynamic contractions elicited greater k_{PCr} than isometric contractions, consistent with the greater overall ATP cost of dynamic contractions. These results indicate that contraction mode is an important consideration for studies designed to measure muscle oxidative capacity *in vivo* using k_{PCr}, in that oxidative capacity may be underestimated when using isometric contractions. Supported by a UMass Amherst *Institute for Applied Life Sciences* Pilot Grant.

Integrative exercise physiology and metabolism

Presentation Number: 238

Board #31

Ischemic Preconditioning Does Not Affect Performance in Young Healthy Females during Maximal Arm Cycle Ergometry

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Ischemic preconditioning (IPC; a series of occlusion-reperfusion cycles) prior to exercise has been reported to improve performance in cycling modalities. **PURPOSE:** The purpose of this study was to examine the effect of IPC on blood flow, muscle oxygenation, and performance variables in young healthy female participants during 3 min of maximum effort arm cycle ergometry.

METHODS: Twenty young healthy female participants performed 3 min of maximum effort arm cycle ergometry preceded either by three cycles of IPC (50 mmHg above systolic) or SHAM (20 mmHg absolute). During both IPC and SHAM, blood flow was assessed in the right brachial artery using high resolution ultrasound, and muscle oxygenation was recorded in the left triceps muscle using near infrared spectroscopy (NIRS). Total revolutions were counted during the 3-min exercise period at a fixed resistance.

RESULTS: Blood flow (N=20) was zero during the occlusion phases of the IPC cycles. During the reperfusion phase of the occlusion-reperfusion cycles of IPC, blood flow was significantly greater in comparison to SHAM (MEAN: IPC = 1.08 ± 0.48 L/min; SHAM = 0.46 ± 0.22 L/min; PEAK: IPC = 4.65 ± 1.87 L/min; SHAM = 0.57 ± 0.29 L/min. Muscle oxygenation and deoxygenation (N=5) patterns during IPC corresponded to blood flow changes. During exercise, HHb increased with no differences between conditions (20-40s IPC $\bar{x}$ = 12.4 ± 7.6 a.u.; SHAM $\bar{x}$ = 13.0 ± 7.5 a.u.), and remained elevated until the completion of exercise (160-180s IPC $\bar{x}$ = 10.0 ± 8.1; SHAM $\bar{x}$ = 9.1 ± 6.6). HbO_2 initially decreased with no differences between conditions (20-40s IPC $\bar{x}$ = -4.9 ± 9.6 a.u.; SHAM $\bar{x}$ = -5.5 ± 6.7 a.u.), and returned towards baseline by the completion of the exercise bout (160-180s IPC $\bar{x}$ = 1.0 ± 6.8 a.u.; SHAM $\bar{x}$ = 3.6 ± 10.4 a.u.). Relative peak power (IPC = 1.81 ± 0.39 W/kg; SHAM = 1.82 ± 0.34 W/kg), relative end power (IPC = 0.95 ± 0.18 W/kg; SHAM = 0.94 ± 0.18 W/kg), total work (IPC = 13,842 ± 3,365 J, SHAM = 13,856 ± 2,799 J), and fatigue index (IPC = 51.6 ± 13%, SHAM = 50 ± 12%) were not different between IPC and SHAM.

CONCLUSIONS: For the first time, blood flow and muscle oxygenation were recorded during multiple IPC cycles prior to exercise. Both mean and peak blood flow were zero during occlusion and increased above SHAM during reperfusion. As expected, muscle deoxygenation increased during occlusion and increased during reperfusion with muscle oxygenation going in the opposite direction. Despite these changes in both blood flow and muscle oxygenation during the IPC cycles, IPC did not impact the oxygenation/deoxygenation responses during maximal effort arm cranking or the performance itself.

Integrative exercise physiology and metabolism

Presentation Number: 239

Board #32

Metabolic and Skeletal Muscle Molecular Responses to a NASA Exercise Paradigm

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Purpose: Findings from a recent 70-day bed rest investigation suggested intermittent exercise testing in the control group may have served as a partial countermeasure for skeletal muscle size, function, and fiber type shifts. The purpose of the current study was to investigate the metabolic and skeletal muscle molecular responses to the testing protocols. **Methods:** Eight males (29±2y) completed Muscle Power (6x4 sec; peak muscle power: 1369±86W) and VO_2max (13±1min; 3.2±0.2L/min) tests on specially designed supine cycle ergometers during two separate trials. Blood catecholamines and lactate were measured pre, immediately post, and 4h postexercise. Muscle homogenate and muscle fiber type specific (Type I and Type IIa) mRNA levels of exercise markers (myostatin, IκBα, myogenin, MuRF-1, ABRA, RRAD, Fn14, PDK4) and myosin heavy chain (MHC) I, IIa, and IIx were measured from vastus lateralis muscle biopsies obtained pre and 4h postexercise. **Results:** The Muscle Power test altered (p≤0.05) norepinephrine (124%), epinephrine (145%), lactate (300%), and muscle homogenate mRNA (IκBα, myogenin, MuRF-1, RRAD, Fn14). The VO_2max test altered (p≤0.05) norepinephrine (1394%), epinephrine (1412%), lactate (736%), and muscle homogenate mRNA (myostatin, IκBα, myogenin, MuRF-1, ABRA, RRAD, Fn14, PDK4). In general, both tests influenced Type IIa muscle fibers more than Type I with respect to the number of genes that responded and the magnitude of response. Both tests also influenced MHC expression in a muscle fiber type specific manner. **Conclusion:** These findings provide unique insights into the adaptive response of skeletal muscle to small doses of exercise and will help shape future exercise countermeasures for long duration spaceflight. Supported by NASA NNX11AJ62G.

Integrative exercise physiology and metabolism

Presentation Number: 240

Board #33

Post-exercise Insulin Sensitivity is Unrelated to Metabolic Flexibility or Fat Oxidation Capacity in Lean Humans

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Purpose: A single session of moderate-intensity exercise is sufficient to improve insulin sensitivity in most humans; however, the determinants of such improvement are not fully understood. The purpose of this study was to determine if the improvement in insulin sensitivity in the hours after acute exercise is related to baseline insulin sensitivity, metabolic flexibility or skeletal muscle fatty acid oxidation capacity among sedentary lean adults. **Methods:** Sedentary lean adults (n=14 (4M/10F), BMI 22.2 ± 2.1 kg/m^2, VO_2max 32.2 ± 4.5 ml/kg/min) completed two metabolic study visits in a randomized crossover design. Trials were identical other than completing 1 hour of moderate intensity cycling exercise (65% VO_2max)

or remaining sedentary. Vastus lateralis muscle biopsies were obtained 15 min post-exercise or sedentary rest for determination of mitochondrial fatty acid oxidation capacity via high-resolution respirometry. Insulin sensitivity was determined via steady-state glucose infusion rate during the final 30 min of a 3-hour hyperinsulinemic-euglycemic clamp beginning 2 hours post-exercise. Metabolic flexibility was measured as the change in respiratory exchange ratio during steady-state hyperinsulinemia compared with sedentary fasting. **Results:** Insulin sensitivity was significantly improved after a single session of moderate-intensity exercise compared with sedentary rest (+12 ± 16.5 %, *P*=0.03 vs. rest); however, exercise-induced changes in insulin sensitivity were variable, ranging from +40% to -27% compared with rest. Such changes in insulin sensitivity were not related to baseline measures of insulin sensitivity (r^2=0.14, *P*=0.19), metabolic flexibility (r^2=0.06, *P*=0.42) or mitochondrial fat oxidation capacity (r^2=0.03, *P*=0.55). Further, mitochondrial fat oxidation capacity (during palmitoyl-carnitine supported oxidative phosphorylation) was unchanged following acute exercise compared with rest (*P*=0.77). **Conclusion:** A single session of moderate-intensity exercise is sufficient to improve insulin sensitivity in the hours after exercise in most sedentary lean adults; however, there is considerable variation in the response to exercise. Such variance was not explained by baseline insulin sensitivity, metabolic flexibility or capacity for fatty acid oxidation. Thus, commonly implicated determinants of insulin sensitivity in obese individuals appear unrelated to the improvement in insulin sensitivity after exercise in sedentary lean humans.

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Integrative exercise physiology and metabolism

Presentation Number: 241

Board #34

Serum MOTS-C is not Associated with Age and Cardiorespiratory Fitness

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It is well known that exercise reduces the risk of chronic disease and may attenuate the aging phenotype. Mitochondrial dysfunction is a primary hallmark of the aging process and is implicated in a number of chronic diseases. Recently, a mitochondrial-derived peptide was discovered, mitochondrial open reading frame of the 12S rRNA-c (MOTS-c) and represents a new class of circulating signaling molecules associated with function and attenuation of age-related diseases, such as insulin resistance. However, it is unknown whether cardiorespiratory fitness and/or age alters circulating concentrations of MOTS-c. **PURPOSE:** The current study aimed to investigate blood serum MOTS-c concentrations in humans in divergent populations based on age and cardiorespiratory fitness. **METHODS:** Forty-two participants were recruited and separated into four categories determined by age and maximal oxygen consumption (VO_2max). Participants were divided into two primary categories determined by age: Older Group (n=15) ages 55-70 year and Younger Group (n=27) ages 18-30 yr. These primary groups were subdivided based on their VO_2max and classified as either "active" (older active, VO_2max ≥30mLO2/kg/min [OA] and younger active, VO_2max ≥35mLO2/kg/min [YA]) or "inactive" (older inactive [OI] and younger inactive [YI]). [MOTS-c] was detected using a specific enzyme-linked immunosorbent assay kit. Independent student's t-test and Pearson correlation were performed using a statistical software package (SPSS 22). **RESULTS:** Average serum MOTS-C concentration was not different between the Older (387.7±59.0ng/mL) vs Younger (407.2±80.0 ng/mL; p= 0.481) groups. Also, average serum MOTS-C concentration was not different between OA versus OI (380.9±40.7 vs 393.7±73.9 ng/mL; p= 0.346) and YA versus YI (385.2±84.1 vs 368.7±100.4 ng/mL; p= 0.382) groups. There were no correlations between serum MOTS-c concentration and VO_2max (r=-0.007). **CONCLUSION:** These results indicate that age and VO_2max do not affect blood MOTS-c concentration.

Integrative exercise physiology and metabolism

Presentation Number: 242

Board #35

Submaximal Exercise at Moderate Altitude (2600 m) in Andean Healthy Young Women: Native and Acclimatized

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PURPOSE: Andean natives (Quechua) living at high-altitude exhibit specific genetic and/or developmental adaptations at rest and during exercise when compared to lowlanders acclimatized to the same altitude (higher hemoglobin concentration, lower hypoxic ventilatory drive, lower resting and exercise ventilation, higher alveolo-capillary diffusing capacity and preferential carbohydrate substrate utilisation). Moderate altitude (2600 m, barometric pressure 560 mmHg) affects oxygen delivery systems in healthy subjects (e.g. maximal oxygen consumption decreases about 11%). It has not been established for admixed Andean population, born and raised at moderate altitude, if some of the already postulated adaptations for Quechua, at least as a result of developmental altitude adaptations, are functional and can be evidenced during exercise.

METHODS: Two groups of healthy, non-athlete young women, who were permanent residents in Bogotá (2600 m), group 1 natives (n = 34, born and raised between 2500 and 2800 m, age 21.6 ± 1.9 yr, BMI 21.4 ± 1.5) group 2 acclimatized (n = 29, born and raised below 500 m, age 20.3 ± 4.3 yr, BMI 21.6 ± 1.7), exercised at constant submaximal low-intensity exercise using an electronically braked-cycloergometer (50 w@65 rpm for 15 min). Oxygen consumption (VO_2), carbon dioxide production (VCO_2), respiratory exchange ratio (RER), ventilation (VE) and heart rate (HR) were measured breath-by-breath by gas-analyzer and 12-lead electrocardiography; ear-lobe capillary lactic acid concentration (LAC) was sampled every 2.5 min. Mean and standard deviation of the last 10 minutes of the exercise phase were computed. Only subjects who fulfilled the following three criteria during the last 10 minutes of the exercise phase were included in the analysis: RER values below 1.0, a difference of less than 1 mmol/L between highest and lowest LAC value, and keeping cycling frequency between 60 and 70 rpm.

RESULTS: Cardiorespiratory and metabolic parameters were similar in native and acclimatized women, respectively: VE (31 ± 4 vs 33 ± 4 L/min), VO_2 (965 ± 86 vs 938 ± 56 mL/min), VCO_2 (866 ± 75 vs 867 ± 57 mL/min), RER (0.90 ± 0.05 vs 0.93 ± 0.04), HR (123 ± 14 vs 136 ± 14 bpm), and LAC (1.76 ± 1.0 vs 1.90 ± 0.92 mmol/L).

CONCLUSIONS: At moderate altitude, native and chronic acclimatized healthy young women performed similarly in main cardiorespiratory and metabolic parameters during steady state low-intensity cycling, suggesting that the postulated developmental adaptations in admixed Andean populations has no effect on oxygen transport or utilisation systems at the workloads administered in this study.

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Integrative exercise physiology and metabolism

Presentation Number: 243

Board #36

The Effect of Acute Glutamine Supplementation on Markers of Immune Function and Stress After Repeated Firefighting Simulations

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Purpose: Wildland firefighters (WLFFs) perform physically demanding work in extreme environmental conditions (heat and pollution), which puts them at an increased risk for heat and fatigue-related injuries. Further, WWLFs typically work long shifts (12h), which are repeated on consecutive days until fire suppression is complete. The combination of heat stress and environmental hazards induces oxidative stress and inflammatory responses. Glutamine is a non-essential amino acid

that has been shown to activate the heat shock protein (HSP) which is known to blunt oxidative stress and inflammation. Thus, glutamine supplementation may protect WLFFs from oxidative damage and reduce inflammation during and after firefighting. The purpose of this study was to determine the effect of glutamine ingestion on oxidative stress, inflammation and markers of fatigue after repeated exposure to simulated wildland firefighting conditions. **Methods:** Eleven physically active subjects (7 male, 4 female) performed baseline testing followed by glutamine (Gln) and placebo (Pla) supplementation trials. Subjects ingested glutamine (0.15g/kg) or placebo before and after repeated bouts (separated by 24h) of firefighting simulations, in a heated environmental chamber (35°C). Markers of thermal stress, biological stress, and fatigue were measured at baseline, pre, post 4h and 24h post-exercise in each trial. **Results:** Glutamine levels were increased prior to exercise on both days for Gln vs. Pla trials ($p<0.05$). HSP70 was elevated on the second day of the Gln trial ($p<0.05$), which correlated with lower levels of physical fatigue. The accumulation of HSP70 was accompanied with a significantly lower fold increase in the inflammatory marker, IκBα. **Conclusion:** The ingestion of an acute glutamine supplement prior to repeated firefighting simulations appears to upregulate the heat shock response at the post-simulation time points and blunt inflammation as evidence by lower I?B? protein levels. These findings suggest that oral glutamine supplementation may be beneficial for WLFFs before and during fire suppression.

Integrative exercise physiology and metabolism

Presentation Number: 244

Board #37

The Effects of Rest Interval on Neuromuscular Activity

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Abstract

Purpose: Research has demonstrated the rest time intervals affect mechanical and physiological variables, which in turn, may reduce power output during the bench press exercise performed at 40% of the 1 repetition maximum. However, previous research has not taken neural measurements to explore the impact of rest time intervals on muscular electrical. **Methods:** The study followed a within-subjects study design that examined the effects of a 1-minute res interval on neuromuscular activity. Each participant attended 2 sessions within the same week. The first sessions consisted of a 1RM test (bench press). The second sessions consisted of the subject performing a bench press strength training protocol that was 5 sets of 8 repetitions using 40% of the subject's 1RM. Subjects rested 1-minute between each of the 5-sets. Mean and maximum muscular electrical activity of the right and left pectoralis major and lateral head of the triceps using surface electromyography (EMG). **Results:** 12 subjects with an average age of 23 yrs. of age took part in this study. A repeated-measures ANOVA showed that 1-minute rest interval caused a significantly lower mean electrical activity in the right triceps between sets 2 and 5, $p <.05$. There were no other differences in mean and maximum neuromuscular activity between sets for the left and right pectoralis major and lateral head of the triceps brachi. **Conclusion:** This study provides evidence that the decreases in power observed during 1-minute rest interval during the bench press performed exercise performed at 40% 1-RM may not be caused by changes in neuromuscular activity (neural fatigue). Previous research suggest that the decrease in power may be caused by mechanical and physiological variables.

Integrative exercise physiology and metabolism

Presentation Number: 245

Board #38

The Impact of Amino Acid Consumption on Resistance Exercise-Mediated Adaptive Responses in Young Adult Females

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Purpose: Exercise-induced increases in collagen synthesis are blunted in women when compared to men. This lack of response may contribute to the apparent lack of tendon adaptations to chronic exercise previously noted in women. Novel interventions are needed to enhance tendon exercise response in women. We propose that a novel formulation of amino acids augmented with collagen specific amino acids glycine, proline, and leucine, which is a potent stimulator of protein synthesis can impact tendon response to acute exercise in women. Thus, the purpose of this study was to determine the impact of a post-exercise provision of oral amino acid augmented with leucine, proline, and glycine, on post-exercise Achilles peritendinous levels of the collagen synthesis stimulating growth factor, IGF-1 and a key protein regulation matrix degradation, matrix metalloproteinase-9 (MMP-9) in young women. **Methods:** Seven healthy young (25±5 yrs.) women engaged in two calf press resistance exercise sessions (8 sets of 15 repetitions of calf presses, 70% of 15RM). Following each exercise session, a microdialysis fiber was inserted anterior to the Achilles tendon. Samples were collected at 30-min intervals for 6-hrs. Ninety minutes after the completion of the exercise bout, subjects consumed a placebo or AA beverage in a double-blind placebo-controlled manner. Peritendinous amino acid levels were evaluated using HPLC, while IGF-1 and MMP-9 concentrations were measured via ELISA. **Results:** In general, peritendinous amino acid levels increased during the AA beverage condition. However, peritendinous levels of IGF-1 and MMP-9 were not influenced by AA consumption ($P>0.05$) **Conclusions:** The results of these data demonstrate that an oral bolus of AA increases AA concentrations in the peritendinous region of the Achilles tendon. However, IGF-1 and MMP-9 remained unchanged. This study uniquely examined the effects of AA on tendon post-exercise production of key regulators of tendon extracellular matrix. Further analysis of other key proteins is necessary to accurately detail the effects of AA consumption following exercise on tendon in women.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 246

Board #39

Acute Heat Stress Under Fed State Stimulates Muscle Protein Synthesis In Mouse Soleus Muscle

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PURPOSE: Muscle protein turnover is largely affected by nutrition. We previously showed that acute heat stress under fasting activates protein synthesis related intracellular signaling in animal and human skeletal muscle. However, the effects of nutritional state (fasting or feeding) during heat stress on muscle protein synthesis remain unclear. Thus, we investigated the effects of nutritional state on acute heat stress-induced mammalian target of rapamycine (mTOR) activation and muscle protein synthesis in mice. **METHODS:** C57BL/6 male mice (8 weeks-old) were fasted for 6 h (FT) or fed normally (FD) before the start of heat stress experiment. Mice were exposed to hot environment (41°) for 1h. For in vivo measurements of protein synthesis, mice were anesthetized and then given an intraperitoneal injection of 0.040 μmol/g puromycin 15 min before removal of soleus muscle. The soleus muscles (n=3/each time point) were quickly removed before, 1h and 6h after heat exposure and frozen in liquid nitrogen for western blotting analysis. **RESULTS:** Heat stress in FD condition significantly increased mTOR phosphorylation at 1h after heat stress ($p<0.05$), but there was no change in FT condition after HS. At 6h after heat stress, mTOR phosphorylation in FD condition

was significantly higher than that in FT condition ($p<0.05$). Heat stress in both FT and FD condition significantly increased p70s6k phosphorylation at 1h after heat stress ($p<0.05$). However, p70s6k phosphorylation in FD condition was significantly higher than that in FT condition at 6h after heat stress ($p<0.05$). 4E-BP1 phosphorylation in FD condition was significantly increased 1 and 6 h after heat stress ($p<0.05$), and was significantly higher than that in FT condition at 6h after heat stress ($p<0.05$). Puromycin-labeled peptides (protein synthesis) in FD condition was significantly increased 6 h after heat stress ($p<0.05$), and was significantly higher than that in FT condition at 6h after heat stress ($p<0.05$). **CONCLUSIONS:** Acute heat stress under fed state stimulates muscle protein synthesis rate via prolonged activation of mTOR signaling. This work was supported by JSPS KAKENHI Grant Number JP16K16565.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 247

Board #40

Aging Increases LINE-1 Expression And Integration In Rodent Skeletal Muscle Tissue

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PURPOSE: Long interspersed nuclear element-1 (LINE-1 or L1) is a class 1 transposable element know as a retrotransposon. LINE-1 is termed a genomic parasite due to its reverse transcription machinery, and ability to randomly copy and paste itself back into the genome. Studies have shown that there are an estimated 500,000 copies of LINE-1 accounting for roughly 17-18% of the total human genome. However, only around 100 of the 500,000 copies are functionally active. Additional studies have shown that LINE-1 activity increases with age, and due to LINE-1's ability to randomly insert itself into the genome this may negatively impact overall health. Specifically, LINE-1 mutations in the genome have been linked with multiple cancers and genetic diseases (e.g cases of Duchene muscular dystrophy). Furthermore, LINE-1 in mice has been shown to increase in aged skeletal muscle. However, there is no current research regarding the effects of aging on LINE-1 activity in rat skeletal muscle tissue. Therefore, the purpose of this study was to identify the effects of aging on LINE-1 activity markers in rat skeletal muscle tissue. **METHODS:** Sedentary male fischer 344 rats were fed ad libitum and were aged to 3, 12, and 24 months (n=9 per age group) and then sacrificed. With LINE-1 having multiple gene families, primer sets for qPCR were designed for the youngest most active form of LINE-1 (L1.3), and older LINE-1 elements (L1.Tot). Gastrocnemius skeletal muscle was harvested and analyzed for LINE-1 mRNA (L1.3 and L1.Tot), inhibitors of LINE-1(TREX1 and PIWIL2) mRNA, LINE-1 genomic DNA (L1.3 and L1.Tot) and ORF1p protein markers. **RESULTS:** L1.3 mRNA significantly increased with age ($p=0.003$), and was higher at 24 months compared to 3 months ($p<0.01$). Similarly, L1.Tot mRNA significantly increased with age ($p=0.003$), and was also higher at 24 months compared to 3 months ($p<0.01$). L1.3 integration into the genome was significantly higher at 24 months compared to 3 months ($p=0.021$), whereby there was a 3.4% increase in L1.3 within the genome at 24 months. Furthermore, ORF1p protein expression significantly increased with age ($p<0.001$), and was higher in both the 12 and 24 months compared to 3 months ($p<0.05$). However, both LINE-1 mRNA inhibitors and L1.Tot genomic DNA were not significantly different. **CONCLUSION:** It appears that LINE-1 expression increases with age, which presumably leads to increased LINE-1 genomic integration in rat skeletal muscle tissue. Therefore, the increased LINE-1 expression and integration could potentially be contributing to the aging phenotype in skeletal muscle (e.g sarcopenia or cachexia), however, more research is needed to validate this hypothesis.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 248

Board #41

Alteration Of Plasma Membrane Phospholipid Composition Increases Insulin Signaling And Microdomain Clustering In Skeletal Muscle

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PURPOSE: Aberrant lipid metabolism has been linked to skeletal muscle insulin resistance, which is a precursor to type 2 diabetes, the 7th leading cause of death in the United States. The exact molecular mechanisms that promote skeletal muscle insulin resistance remain unclear. Our previous study suggested that obesity alters skeletal muscle lysophospholipid metabolism in humans. This study sought to identify whether the alteration of lysophospholipid metabolism is sufficient to affect the insulin signaling pathway in skeletal muscle.

METHODS: Lysophosphatidylcholine acyltransferase 3 (LPCAT3), the major lysophospholipid acyltransferase in skeletal muscle, was inhibited (LPCAT3 KD) in C2C12 cells, and cells were fully differentiated to myotubes. Phospholipid membrane composition, physical characteristics of phospholipid membranes, microdomain formation, and insulin sensitivity were measured in LPCAT3 KD cells.

RESULTS: C2C12 cells with LPCAT3 KD exhibited increased levels of lysophospholipids, consistent with the idea that LPCAT3 is a major lysophospholipid acyltransferase in skeletal muscle cells. Knockdown of LPCAT3 promoted a robust increase in the insulin signaling cascade at the level of the insulin receptor. Furthermore, plasma membrane microdomain clustering was increased with LPCAT3 KD, consistent with subcellular localization of the insulin receptor.

CONCLUSIONS: Together, these data suggest that altering LPCAT3 expression in skeletal muscle is sufficient to modulate the plasma membrane phospholipids to increase microdomain formation, and that such increase is responsible for the enhancement of insulin receptor signaling. Funding Sources: NIH DK107397, DK109888

Skeletal muscle, exercise, inactivity, and signaling

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Board #42

Comparison of Cell Culture Harvesting Protocols and Bestatin Application in Murine Muscle Tissue

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PURPOSE: Determine if there is a difference between myofibrillar fractional synthesis rates (FSR) of murine myotubes with differing harvest protocols and with the application of bestatin, an aminopeptidase inhibitor.

METHODS: C2C12 cells were grown in 10cm plates until approximately 60% confluent. Cells were re-plated onto 6 well plates. After differentiating, deuterium oxide was applied 24 hours prior to harvest of the cells at a level of 4% and the cells underwent an exercise protocol. Bestatin was applied 2 hours prior to harvest, respectively. Cells were harvested 1 hour, 4, 8, 16 and 24 hours post exercise. Media containing deuterium oxide was reserved for analysis. Cells were washed with two applications of PBS. Plates were then placed on ice for 5 minutes. Cells were harvested and deposited into centrifuge vials. Samples were centrifuged at 150g for 5 minutes. PBS was removed from samples by decanting. Norris buffer was added to muscle cells and vortexed vigorously. Vials were spun at 14,000 G for 30 minutes to separate cytosolic and myofibrallar fractions. The supernatant (containing the cytosolic fraction) from the vial was decanted into another vial and saved for analysis. The historical harvest protocol was completed after the decanting of the cytosol. Vials that received the new protocol, with the purpose of isolating di/tripeptides, continued by adding 10% TCA to the cytosolic fraction to precipitate out

soluble proteins. The supernatant was collected in a different vial. This TCA wash step was repeated for a total of 3 washes. 2H-alanine and plasma enrichment was determined by GC-MS.

RESULTS: Preliminary data demonstrates the application of bestatin has no effect on myofibrillar FSR across the time points (P = 0.5257). The type of harvest protocol (historical vs. di/tri peptide) had no impact on myofibrillar FSR (P = 0.6293). **CONCLUSIONS:** Bestatin can be applied without interfering with protein synthesis rates in C2C12 cell culture. This can open up potential methodologies to investigate protein degradation in cell culture for future studies. The methods which are utilized by our lab to harvest muscle cells will not confound FSR calculations. Supported by Huffines Institute.

Skeletal muscle, exercise, inactivity, and signaling

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Board #43

Do Muscle- And Tendon- Derived Factors Contribute To Muscle Regeneration?

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PURPOSE: To address a rapid recovery from severe muscle damage is important to established exercise habit for elderly and to continue a hard training or meet a competition for athlete. A recent report that activated satellite cells interact with surrounding extracellular environment to facilitate tissue plasticity via exosomes containing miR-206 (Fly et al., 2017. *Cell Stem Cell*). Although cell-cell communication networks gradually have been unveiled, it still remains unclear. Moreover, tendon tissue has not been regarded as endocrine organ in spite of motor organ. In present study, we aimed to identify factors which characterized as activate, proliferate and/or differentiate of satellite cells or myoblasts from muscle and tendon cells, and to elucidate a newly muscle regeneration mechanism.

METHODS: The present study is consisted of two experiments. First, we verified that whether damaged myofiber-derived factors activate, proliferate and/or differentiate muscle satellite cells. Isolated myofiber from WT mice were divided into intact myofiber (Control condition and co-culture with damaged myofiber condition (Damaged condition). Activation of the satellite cells was observed by immunostaining fluorescence of Dapi, Pax7 and MyoD at 72 h after isolation from mice. Similarly, satellite cells were observed by Dapi, ki-67 and EdU to check the cell cycle. Secondly, we verified that whether tenocyte-derived factors regulate proliferation and differentiation of primary cultured myoblasts. We used a trance-well system which is co-culture with tenocytes and myoblasts to remove cell-cell contact during culture. The evaluation for proliferation and differentiation of the myoblasts were used by immunostaining fluorescence of Ki-67, EdU and myosin heavy chain, respectively.

RESULTS: In Damaged condition, the population of $Pax7^{+ve}MyoD^{+ve}$ (activated satellite cells) cells on a myofiber significantly increased compared with Control condition. Similarly, $Pax7^{+ve}Ki\text{-}67^{+ve}$ was also increased in Damaged condition than that in control condition, but not $Pax7^{+ve}EdU^{+ve}$. In second experiment, co-culture condition significantly increased in the number of Dapi, $Ki\text{-}67^{+ve}$ and EdU+ve cells compared with control condition. Furthermore, fusion index (ratio of $Dapi^{+ve}$ and MHC^{+ve} cells) was facilitated by co-culture condition.

CONCLUSIONS: Muscle (damaged)-derived factors contribute to activation of satellite cells. Tendon-derived factors facilitate differentiation of the myoblasts.

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Board #44

Effect of Aging and Lifelong Exercise on Basal and Exercise-Induced Inflammation in Females

Bridget Lester, Kaleen Lavin, Ryan Perkins, Bozena Jemiolo, Ulrika Raue, Scott Trappe, FACSM, Todd Trappe, FACSM. *Ball State University, Muncie, IN.*

Purpose: Muscle mass decline, frailty, and dependence are especially prevalent in females and may be accelerated by age-related inflammation. Habitual physical activity throughout the lifespan (lifelong exercise) may prevent muscle inflammation and the associated pathologies, but this is unexplored in the female population. **Methods:** This investigation assessed basal and acute exercise-induced inflammation in three female cohorts: young exercisers (YE, n = 10, 25 ± 1 y, VO_2max: 44 ± 2 mL/kg/min, quadriceps size: 59 ± 2 cm^2), old healthy non-exercisers (OH, n = 10, 75 ± 1 y, VO_2max: 18 ± 1 mL/kg/min, quadriceps size: 40 ± 1 cm^2), and lifelong exercisers with a 48 ± 2 y aerobic training history (LLE, n = 7, 72 ± 2 y, VO_2max: 26 ± 2 mL/kg/min, quadriceps size: 42 ± 2 cm^2). Resting serum IL-6, TNF-α, CRP, and IGF-1 were measured. Vastus lateralis muscle biopsies were obtained at rest (basal) and 4h after an acute exercise challenge (3 x 10 reps of knee extension, 70% 1RM) to assess gene expression of cytokines (IL-6, TNF-α, IL-1β, IL-10, IL-4, IL-1Ra, TGF-β), chemokines (IL-8, MCP-1), cyclooxygenase enzymes (COX-1, COX-2), prostaglandin E_2 synthases (mPGES-1, cPGES) and receptors (EP3-4), and macrophage markers (CD16b, CD163), as well as basal macrophage abundance ($CD68^+$ cells). **Results:** The aging cohorts (LLE and OH combined) demonstrated increased ($P \leq 0.05$) circulating CRP and muscle IL-6 and COX-1, and lifelong exercise led to reduced ($P \leq 0.05$) skeletal muscle IL-1β. Acute exercise increased ($P \leq 0.05$) expression of IL-6 in YE only, whereas the older cohorts combined had heightened expression of IL-8 and TNF-α after exercise. After exercise, LLE had higher IL-1β ($P \leq 0.05$ vs. OH) and MCP-1 ($P \leq 0.05$ vs. YE). Exercise increased IL-1Ra, COX-2, EP4, and CD16b across all three groups. **Conclusion:** Aging led to mild basal inflammation in circulation and skeletal muscle that was unaffected by lifelong exercise. This contrasts our findings in males that lifelong exercise confers anti-inflammatory benefits and protection against age-related inflammation. In females, the response to exercise was altered by aging and further exaggerated in LLE, suggesting that preparedness to handle a loading stress was not preserved by lifelong exercise, as it was in males. These sex differences warrant further investigation and may have implications for long-term muscle health and adaptability. Supported by NIH Grant R01-AG038576.

Skeletal muscle, exercise, inactivity, and signaling

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Board #45

Effect Of VitaminD Supplementation On Resistance Exercise-induced Intramuscular VitaminD And Muscle Protein Metabolism

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PURPOSE: Vitamin D has numerous physiological and biochemical functions, including mineral homeostasis and regulation of cell cycling, through its binding to vitamin D receptor(VDR). Furthermore, vitamin D deficiency is associated with muscle atrophy and dysfunction. Vitamin D supplementation has been shown to increase VDR expression and muscle fiber cross-sectional area in vitamin D-deficient elderly women. Further, VDR-knockout mice showed muscle atrophy and poor muscle function compared with wild type mice. We have previously shown that acute bout of resistance exercise(RE) increased VDR expression in rat skeletal muscle. However, the effect of short-term vitamin D supplementation on RE-induced VDR expression and mTORC1 signaling pathway have not been investigated.

METHODS: Male adult Sprague-Dawley(SD)rats were randomly assigned to either RE with high vitamin D intake(about 100IU/day; VD)or RE with control intake(about 25IU/day; CON)for 10 days. After the supplementation period, rats were subjected to RE by isometrically exercising right gastrocnemius muscle via percutaneous electrical stimulation and contralateral leg was used as non-exercised control. Rats were sacrificed 1 and 3 h after completion of RE, and muscle samples were removed.

RESULTS: Intramuscular VDR protein expression was significantly higher for VD(significant treatment effect; P<0.05). Additionally, CYP27B1, metabolic enzyme of vitamin D, increased significantly in both groups after RE(significant time effect; P<0.05). The phosphorylation level of p70S6K, increased significantly after exercise in both groups, but the phosphorylation level was attenuated at 1hr post-exercise in VD. RE-induced phosphorylation of ribosomal protein S6 increased significantly in both groups after RE(significant time effect; P<0.01), but there was no difference between groups

CONCLUSIONS: Intramuscular VDR expression increased with ingestion of high vitamin D intake for 10 days. However, acute RE-induced activation of mTORC1 signal was not modified with short-term supplementation.

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Board #46

Effects of Aging and Lifelong Exercise on Basal and Exercise-Induced Inflammation in Males

Andrew Jones, Kaleen Lavin, Ryan Perkins, Bozena Jemiolo, Ulrika Raue, Scott Trappe, FACSM, Todd Trappe, FACSM. *Ball State University, Muncie, IN.*

Purpose: Age-associated chronic basal inflammation compromises muscle mass and adaptability, but exercise training may exert an anti-inflammatory effect. **Methods:** This investigation assessed basal and exercise-induced inflammation in three male cohorts: young exercisers (YE, *n* = 10, 25 ± 1 y, VO_2max: 53 ± 3 mL/kg/min, quadriceps size: 78 ± 3 cm^2), old healthy non-exercisers (OH, *n* = 10, 75 ± 1y, VO_2max: 22 ± 1 mL/kg/min, quadriceps size: 56 ± 3 cm^2), and lifelong exercisers with a 52 ± 1 y aerobic training history (LLE, *n* = 21, 74 ± 1 y, VO_2max: 34 ± 1 mL/kg/min, quadriceps size: 67 ± 2 cm^2). Resting serum IL-6, TNF-α, CRP, and IGF-1 were measured. Vastus lateralis muscle biopsies were obtained at rest (basal) and 4h after an acute exercise challenge (3 x 10 reps of knee extension, 70% 1RM) to assess gene expression of cytokines (IL-6, TNF-α, IL-1β, IL-10, IL-4, IL-1Ra, TGF-β), chemokines (IL-8, MCP-1), cyclooxygenase enzymes (COX-1, COX-2), prostaglandin E2 synthases (mPGES-1, cPGES) and receptors (EP3-4), and macrophage markers (CD16b, CD163), as well as basal macrophage abundance ($CD68^+$ cells). **Results:** Circulating IL-6 was higher ($P \leq 0.05$) in OH than both YE and LLE. The older cohorts had higher ($P \leq 0.05$) basal COX-1, mPGES-1, and CD163 expression. However, LLE had higher basal IL-10 ($P \leq 0.05$ vs. YE), TNF-α, TGF-β, and EP4 ($P \leq 0.05$ vs. OH). Exercise increased expression of TNF-α, TGF-β, IL-8 ($P \leq 0.05$), and COX-1 ($P \leq 0.10$) in only OH. LLE had lower postexercise expression of IL-10 ($P \leq 0.10$), mPGES-1, and EP3 ($P \leq 0.05$) than YE. COX-2, EP4, CD16b, ($P \leq 0.05$) and CD163 ($P \leq 0.10$) increased after exercise across all groups. **Conclusion:** Aging led to a pro-inflammatory profile within blood and muscle. Lifelong exercise partially prevented this and generally preserved the acute inflammatory response to exercise. Lifelong exercise promotes an anti-inflammatory muscle environment, which may positively impact muscle health throughout aging. Supported by NIH Grant R01-AG038576.

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Presentation Number: 254

Board #47

Effects of Aging and Lifelong Exercise on the Innate Immune System in Skeletal Muscle of Females

Ryan Perkins, Kaleen Lavin, Ulrika Raue, Bozena Jemiolo, Scott Trappe, FACSM, Todd Trappe, FACSM. *Ball State University, Muncie, IN.*

Purpose: The purpose of this investigation was to assess the effects of aging and lifelong exercise on cellular components of the innate immune system in skeletal muscle of females. In addition, an aim focused on the effect of an acute resistance exercise (RE) challenge was explored. **Methods:** Three groups of females were studied: young exercisers (YE, n=10, 25±1 y, VO_2max: 44±2 mL/kg/min, quadriceps size: 59±2 cm^2), lifelong aerobic exercisers with a 48±2 y training history (LLE, n=7, 72±2 y, VO_2max: 26±2 mL/kg/min, quadriceps size: 42±2 cm^2), and old healthy non-exercisers (OH, n=10, 75±1 y, VO_2max: 18±1 mL/kg/min, quadriceps size: 40±1 cm^2). Vastus lateralis muscle biopsies were obtained in the basal state and 4 h after RE (3x10 reps of knee extension, 70% 1RM) to assess Toll-like receptor (TLR)1-10, TLR adaptor (Myd88 and TRIF), and NFκB pathway component (IκBα and IKKβ) mRNA expression. **Results:** Basal expression of TLR9 was 43% higher in OH than YE ($P<0.05$). LLE protected against the age-related increase in TLR9 expression as LLE was similar to YE ($P>0.05$) and 30% lower than OH ($P=0.07$). On average, exercise training (YE and LLE combined) reduced basal expression of TLRs by 26%. For all groups combined (main effect, $P \leq 0.05$), acute RE increased expression of TLR3 (50%), TLR4 (77%), TLR6 (63%), and Myd88 (19%). **Conclusion:** Aging females appear to be better protected from increased basal TLR expression in skeletal muscle than males. Furthermore, aerobic exercise training generally reduces TLR expression in females, whereas training does not affect TLRs in males. However, an acute resistance exercise challenge elicits a similar response in both females and males, generally increasing expression of TLRs and associated adaptors. The divergent findings in TLRs and downstream signaling components between females and males have implications for muscle mass and differences in infection susceptibility and preparedness between the sexes. Supported by NIH Grant R01-AG038576.

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Board #48

Effects of Aging and Lifelong Exercise on the Innate Immune System in Skeletal Muscle of Males

William Fountain, Ryan Perkins, Kaleen Lavin, Ulrika Raue, Bozena Jemiolo, Scott Trappe, FACSM, Todd Trappe, FACSM. *Ball State University, Muncie, IN.*

Purpose: The purpose of this investigation was to evaluate the effects of aging and lifelong exercise on skeletal muscle components of the innate immune system in males. Additionally, the effect of an acute resistance exercise (RE) challenge was explored. **Methods:** Three groups of males were studied: young exercisers (YE, n=10, 25±1 y, VO_2max: 53±3 mL/kg/min, quadriceps size: 78±3 cm^2), lifelong aerobic exercisers with a 52±1 y training history (LLE, n=21, 74±1 y, VO_2max: 34±1 mL/kg/min, quadriceps size: 67±2 cm^2), and old healthy non-exercisers (OH, n=10, 75±1 y, VO_2max: 22±1 mL/kg/min, quadriceps size: 56±3 cm^2). Vastus lateralis muscle biopsies were obtained in the basal state and 4h after RE (3x10 reps of knee extension, 70% 1RM) to assess Toll-like receptor (TLR)1-10, TLR adaptor (Myd88 and TRIF), and NFκB pathway component (IκBα and IKKβ) mRNA expression. **Results:** Basal TLR3, TLR6, and TLR7 tended to be higher ($P \leq 0.10$) with aging (LLE and OH combined). In general, exercise stimulated the expression of TLR1 and TLR8 ($P \leq 0.10$) and TLR3 and TLR4 ($P<0.05$), although TLR3 did not respond in OH. Both TLR-related adaptors also responded to the exercise bout; these were primarily (Myd88, main effect $P \leq 0.10$) or exclusively (TRIF, $P<0.05$) driven by the OH group. **Conclusion:** Aging appears to increase basal expression of some innate immune components (TLR3, TLR6, and TLR7) in human skeletal muscle, and lifelong aerobic exercise does not

affect this age-related increase. An exercise challenge stimulates the expression of several TLRs, while the TLR adaptor response appears to be dysregulated with aging and maintained with lifelong exercise. Partially preserved muscle mass, coupled with a notable immunity profile, suggests LLE are well-prepared for an immune challenge. Supported by NIH Grant R01-AG038576.

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Board #49

Effects of Deloading on Fiber Cross-Sectional Area After High Volume Resistance Training

Christopher Vann, Cody Haun, Shelby Osburn, Matthew Romero, Petey Mumford, Paul Roberson, Christopher B. Mobley, Michael Roberts. *Auburn University, Auburn, AL.*

Purpose: Deloading after a period of overloading training is widely accepted to be beneficial for reducing fatigue and allowing adaptations from exercise to occur. While this is widely practiced by those in the strength and conditioning field, there is limited research on responses of fiber cross-sectional area (fCSA) and changes in myonuclear quantity as a result of deloading after voluminous resistance training (RT) to further support this practice. **Methods:** Subjects (n=31) completed 7 weeks of voluminous RT starting at 10 sets of 10 repetitions per exercise at week 1 and ending at 32 sets of 10 repetitions per exercise at week 6 before being assigned to passive recovery (PR) or active recovery (AR) for week 7. PR (n = 15) ceased training while AR (n = 16) completed 5 sets of 10 per exercise over the span of week 7. Vastus Lateralis (VL) biopsies were taken before week 1, at the end of weeks 3 and 6, and again following the week 7. 7µm thick cross sections were fixed to slides and stained for fiber type and myonuclear count. **Results:** There were no significant differences observed between groups for total fCSA, Type II fCSA, Type I fCSA, nor total myonuclear quantity ($p > 0.05$). **Conclusion:** In relation to fCSA and myonuclear quantity, these data suggest that PR may be as effective as AR to facilitate recovery following successive voluminous training bouts however more research is needed to fully elucidate these effects.

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Presentation Number: 257

Board #50

Effects Of Extremely Voluminous Resistance Training On Blood Markers Of Immune Status

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Purpose: Although previous studies have reported immune responses to exercise, responses to extremely high-volume resistance training remain unclear. Therefore, we sought to explore immune responses to 6 weeks of extremely high-volume resistance training followed by a 1-week recovery period (deload). **Methods:** College-aged resistance-trained males trained 3d/wk (2 upper- and 2 lower-body exercises/d, 10 repetitions/set, 60% 1-RM). Over the 6-week training period, volume increased from 10 sets/exercise during week 1 to 32 sets/exercise during week 6. A deload occurred following the training intervention to conclude the training. Blood was collected before week 1 (T1), following week 3 (T2), following week 6 (T3), and following the deload (T4). Immune responses were characterized via a complete blood count (CBC). Data are presented as mean ± standard deviation. The alpha level was set at $p<0.05$. Blood markers were analyzed using a repeated measures ANOVA, and if statistical significance was identified then a Fisher's LSD post hoc test was performed. **Results:** Neutrophil counts were significantly higher at T1 compared to T2 ($p = 0.027$) and T3 ($p = 0.039$). Neutrophil counts were also significantly higher at T4 compared to T2 ($p = 0.008$). Lymphocyte counts were significantly lower at T2 compared to T1 ($p = 0.004$) and T4 ($p = 0.012$), but no other time points were significantly different. No significant changes were observed in white blood cell counts, monocyte counts, or the neutrophil to lymphocyte ratio (NLR) over time. **Conclusions:** The data shows a decrease in neutrophil and lymphocyte counts as a result of this training intervention, but no levels fell outside of the normal range. These changes are likely indicative of immune stress, and future studies will better assess if this led to downstream effects in skeletal muscle.

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Board #51

Evaluation, Description And Analysis Of Stabilometric Tests In Sedentary Elderly Women.

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Background: The postural balance is evidenced in the variations that the center of foot pressure (COP) of the elderly may suffer due to internal or external disturbances. The objective of this study was to determine and characterize the stabilometric behavior by means of the following variables: middle lateral pressure center (COP X), posterior antero pressure center (COP Y), pressure center distance (COP distance), mean velocity of movement (Vel Media), lumbar lateral flexion (LSF), left foot stability radius (r PI), right foot stability radius (r PD) and body stability radius (RC). Tests on a pressure walkway were analyzed, making measurements lasting 30 seconds under criteria of open eyes, closed eyes for bipodal and unipodal support tests.**Methods:** thirty healthy older adult women, between 60 and 80 years of age (66.83 ± 5.21 years), height (157 ± 0.06 m) and body weight (64.04 ± 9,59Kg) participated in this study. Older adult women were sedentary. The Helsinki declaration was followed and an informed consent was signed. To determine the variables of stabilometry in the orthostatic position, a multiple pressure platform (BTS P Walk) was used. Subjects were asked to adopt a bipedal position, with arms down and with eyes open and closed for 30 seconds on the platform. (Romberg test). After the above, the test was performed with left and right unipodal support with with eyes open and closed for 30 seconds. To test the null hypothesis, the Kolmogorov Smirnov test was used, a correlation coefficient (Pearson) and a linear regression were established. **Results:** Correlations found between stabilizing variables in orthostatic position with open eyes versus closed eyes. Bipodal lumbar lateral flexion (LSF) ($r = 0.73$, $p = 0.0001$). COP And unipodal right foot ($r = 0.52$, $p = 0.002$). COP and unipodal left foot ($r = 0.59$, $p = 0.0006$). COP distance unipodal left foot ($r = 0.57$, $p = 0.0009$). Average speed of the left foot movement. ($r = 0.59$, $p = 0.0009$). Lumbar lateral unipodal left foot (LSF) ($r = 0.66$, $p=0.0001$).**Conclusion:** The corporal conditions of a sedentary older adult person have variations on the lateral lumbar flexion (LSF) with the two feet supported, which is modified between the test of open and closed eyes in order to avoid the loss of stability, looking altered in greater proportion with closed eyes. This establishes within the sample of the study, a loss of balance with greater predominance towards later than before. The results indicate that the left unipodal COP distance presents a significant variation due to a constant movement compensating the imbalance generated by the support.

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Board #52

Fatigue-induced Changes In Intracellular Calcium Transients In Single Myofibers From Parvalbumin Conditional Knockout Mice

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Human skeletal muscle does not express the intracellular Ca^{2+} buffer parvalbumin (PV). However, fast-twitch fibers in mice, in which the intracellular Ca^{2+} responses during fatigue have been most extensively studied, express abundant intracellular PV. **PURPOSE:** To investigate the effect of a conditional ablation of PV expression in adult mice on skeletal muscle contractile and intracellular Ca^{2+} handling responses during fatiguing contractions. **METHODS:** B6(Cg)-Pvalb$^{tm1(cre/ERT2)Zjh}$/J (Pv-CreER$^{+/+}$) mice (17 weeks old) and control littermates (Pv-CreER$^{-/-}$) were treated for 5 days with tamoxifen (Tam, i.p.) and euthanized 3 weeks after the first injection. Extensor digitorum longus (EDL) and soleus (for intact muscle contractility), and single myofibers from flexor digitorum brevis (FDB) were tested for contractility at different frequencies of stimulation and fatigue resistance by repetitive contractions. Single myofibers were microinjected with FURA-2 to measure the intracellular Ca^{2+} concentrations ($[Ca^{2+}]c$) during contractions. EDL and soleus were homogenized to detect the amount of contractile and metabolic proteins. **RESULTS:** PV in EDL was abolished only in the Pv-CreER$^{+/+}$ mice after treatment with Tam. There was no change in EDL mass and cross-sectional area between mouse strains. Tam-treated Pv-CreER$^{+/+}$ showed a left-shift in the force-frequency (FF) curve as well as a slowed relaxation compared to Pv-CreER$^{-/-}$ mice. No differences in morphology or contractility were detected in soleus muscles. There were no differences in DHPR, SERCA 1, GAPDH, or Mitoprofile between mouse strains in the EDL. Time to fatigue was not different between mice in EDL or soleus muscles, but the relaxation time during fatiguing contractions in EDL muscles was higher in Pv-CreER$^{+/+}$ mice. In single myofibers, the left-shift in the FF curve in Pv-CreER$^{+/+}$ myofibers was accompanied by higher $[Ca^{2+}]c$ at all frequencies of stimulation, but myofilament Ca^{2+} sensitivity was not altered. During fatigue, $[Ca^{2+}]c$ during contractions was higher in Pv-CreER$^{+/+}$ and showed a prominent decrease in myofilament Ca^{2+} sensitivity during fatiguing contractions compared to Pv-CreER$^{-/-}$. Ca^{2+}-derived tension was not altered by fatiguing contractions in both mouse strains, which suggests that the slowing in relaxation in Pv-CreER$^{+/+}$ was not due to a slowing in Ca^{2+}-uptake into the sarcoplasmic reticulum in PV KO mice. **CONCLUSION:** The ablation of PV in adult mice increased Ca^{2+} for contractions due to diminished Ca^{2+} buffering but did not increase time to fatigue, suggesting that kinetics of intracellular Ca^{2+} handling do not solely limit fatigue resistance. **FUNDING:** NIAMS AR069577

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Presentation Number: 260

Board #53

Hydrogen Sulfide Prevents Mechanical Ventilation-induced Diaphragm Atrophy and Dysfunction

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PURPOSE: Mechanical ventilation (MV) is a life-saving intervention for critically ill patients. Unfortunately, an unintended consequence of prolonged MV is the rapid development of diaphragmatic weakness due to both diaphragm atrophy and contractile dysfunction (known as ventilator-induced diaphragm dysfunction (VIDD)). This MV-induced diaphragmatic weakness is a major risk factor for problems in weaning patients from the ventilator; the failure to wean results in prolonged hospitalization and increased mortality and morbidity. Therefore, developing a therapy to prevent VIDD is important. Our previous work indicates that protection of diaphragmatic mitochondria can guard against VIDD. In this regard, hydrogen sulfide (H2S) has been shown to prevent diaphragm weakness during sepsis and protect the heart against ischemia-reperfusion injury through preservation of mitochondrial function. Given that mitochondrial dysfunction has been demonstrated to play a required role in the development of VIDD, the current study tested the hypothesis that H_2S preconditioning will protect the diaphragm against VIDD. **METHODS:** Adult female Sprague-Dawley rats were randomly assigned to one of four experimental groups: 1) 12 h spontaneous breathing (SB), animals injected with saline (SB-SALINE); 2) 12 h SB, animals injected with 50uM/kg body weight of Na_2S as a H_2S donor (SB-H_2S); 3) 12 h of MV, animals injected with saline (MV-SALINE); 4) 12 h of MV, animals injected with 50uM/kg body weight of Na_2S (MV-H_2S). At the completion of the experimental treatments, diaphragmatic contractile properties and fiber cross sectional areas were determined. Further, mitochondrial function (i.e., state 3/state 4 respiration) was evaluated in mitochondria isolated from diaphragm fibers. **RESULTS:** Compared to both SB-SALINE and SB-H_2S, 12 h of MV resulted in significant diaphragm atrophy and contractile dysfunction (i.e., VIDD). Importantly, treatment with Na_2S prior to MV protected the diaphragm against VIDD. Further, 12 h of MV resulted in increased mitochondrial uncoupling as evidenced by a significant decrease in the mitochondrial respiratory control ratio (RCR) in mitochondria isolated from the diaphragm of MV-SALINE animals. Importantly treatment with H_2S protected diaphragmatic mitochondria against MV-induced uncoupling. **CONCLUSION:** Our findings support the hypothesis that H_2S preconditioning protects the diaphragm against VIDD. *This work was supported by JSPS KAKENHI Grant Number 15KK0131 and NIH R01, R01AR064189*

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Board #54

IL-6 Regulation of Skeletal Muscle Fatigue and Oxidative Metabolism Through gp130 Signaling

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PURPOSE: Perceived fatigue and disrupted metabolic homeostasis occurs with many chronic diseases and contributes to reduced life quality and poor prognosis. The difficulty in determining if fatigue has central, peripheral, or musculoskeletal origins has served as a significant barrier to understanding fatigue's etiology. Skeletal muscle fatigability, or the ability to sustain force over time, requires adequate ATP production by mitochondrial respiration, glycolytic pathways, and the clearance of metabolic biproducts. Interleukin 6 (IL-6) and associated gp130 signaling regulates skeletal muscle mass and metabolism in physiological and pathological conditions. Elevated circulating IL-6 and associative muscle gp130 signaling have been linked to exercised-induced fatty-acid oxidation and glucose metabolism as well as cancer-induced skeletal muscle metabolic dysfunction. Whether IL-6 and muscle gp130 signaling is sufficient to induce muscle weakness and fatigue has not been described. We determined if chronically elevated IL-6 can regulate skeletal muscle fatigability, force production, and muscle oxidative metabolism directly through activation of muscle gp130 signaling.

METHODS: An IL-6 overexpression plasmid was electroporated into the quadriceps of male wildtype (WT) and skeletal muscle gp130 knockout (KO) mice to elevate circulating IL-6. Tibialis anterior (TA) functional properties were assessed *in situ* after 14 days of elevated IL-6.

RESULTS: IL-6 overexpression (~119 ± 12 pg/mL) had no effect on body weight, muscle mass, force, or fiber-type in either WT or KO mice. Submaximal contraction-induced muscle fatigability was increased (20%, $p=0.015$) by IL-6 in WT mice but had no effect in the KO mice. Furthermore, maximal contraction-induced muscle fatigability was increased (10%, $p<0.001$) by IL-6 in both WT and KO mice. IL-6 decreased TA mitochondrial protein complexes I, II, and IV, TA respiratory control ratio (35%, $p<0.01$), and EDL COX activity (42%, $p<0.001$).

CONCLUSIONS: These results demonstrate that chronically elevated IL-6 is sufficient to increase submaximal contraction-induced skeletal muscle fatigue and disrupted muscle oxidative metabolism through muscle gp130 signaling. Interestingly, these disruptions occur independent of body weight, skeletal muscle mass, strength, and fiber-type changes.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 262

Board #55

Long-Term Swim Exercise in *C. elegans* Promotes Systemic Health Benefits

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Purpose: Physical exercise is the most efficient and accessible intervention that can promote healthy aging in humans. In fact, exercise has been reported to prevent, or mitigate consequences of, a wide range of conditions such as diabetes, cancer, sarcopenia, cardiovascular disease, and neurodegenerative diseases. However, the molecular mechanisms by which exercise can confer systemic health benefits remain poorly understood. We have shown recently that single swim sessions in the microscopic roundworm *C. elegans* induce key features of mammalian exercise.

Methods: We developed a long-term exercise regimen for *C. elegans* based on multiple daily 90 min swim sessions over the first four days of adulthood. Both control and exercised *C. elegans* were assayed on days 5, 8, and 11 for locomotion activity, muscle gene expression, mitochondrial morphology and function, and neuronal function.

Results: This long-term training leads to clear exercise adaptations at the body wall muscle level, namely, increased crawling maximum velocity, upregulation of muscle structural gene expression, and improved maintenance of the muscle mitochondrial network during aging. Moreover, mitochondrial function in the whole animal is more energetically efficient after long-term exercise as assessed by multiple parameters of oxygen consumption. At the neuronal level, mitochondria in touch neurons of exercised animals exhibit a lower matrix oxidation level and an increased turnover rate, both indicators of mitochondrial health. Furthermore, swim exercise delays the functional decline of touch neurons in a *C. elegans* model of Huntington's disease (polyglutamine aggregation model).

Conclusions: Our results show that swim exercise promotes physiological changes in multiple tissues of *C. elegans* and open the door to the genetic dissection of systemic health benefits in this novel exercise model.

Supported by NIH R01AG051995 and by Postdoctoral Fellowships from Life Sciences Research Foundation (sponsored by Simons Foundation) and American Heart Association to RL.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 263

Board #56

Nitric Oxide Donor Treatment Following Muscle Contusion Injury In Rats: HGF, Satellite Cells And Myogenesis

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PURPOSE: Satellite cells (SC) respond to various cues in injured muscle such as hepatocyte growth factor (HGF) and participate in regeneration by proliferating and differentiating. Myogenesis during differentiation is accompanied by embryonic myosin heavy chain (eMHC) synthesis. Nitric oxide (NO) is an endogenous bioactive molecule with multiple roles. The aim of this study was to assess if NO may be pro-myogenic after muscle trauma.

METHODS: The *gastrocnemius* of adult male rats were contusion injured (drop-mass) followed by one of four treatments: placebo, NO-donor, NO-inhibitor or combination (Comb). Treatments were administered in jelly immediately and one day post-injury and in un-injured controls. Rats were sacrificed at 5 (D5) and 21 (D21) days after intervention (n=6/group; total n=78). Mean fluorescence intensity (MFI) of HGF staining was quantified with fluorescence microscopy. Satellite cells were identified in cross-sections with Pax7 antibody staining. eMHC protein levels were quantified using Western blotting. eMHC antibodies were used to identify new and regenerating myofibers using immunohistochemistry. Cross-sectional areas (CSA) were determined.

RESULTS: HGF was significantly increased on D5 post-injury in all groups and returned to near uninjured values at D21 post-injury. NO-donor HGF (6.1 ±1.5 MFI) was higher than NO-inhibitor (3.6 ±1.7 $p<0.001$), placebo (4.6 ±1.2 $p<0.01$) and Comb (4.7 ±1.7 $p<0.05$) groups. Post-injury SC number per field of view was higher than baseline on D5 (all groups: 69.2 ±24.9 $p<0.001$) but returned to near baseline on D21 (10.4 ±7.1). In the injured area on D5, SC number was highest in placebo (82.6 ±32.2), significantly greater than both NO-donor (59.2 ±18.9 $p<0.01$) and Comb treated groups (58.4 ±20.8 $p<0.01$). NO-inhibitor treatment (76.4 ±22.1) resulted in significantly greater SC number than either NO-donor ($p<0.05$) or Comb ($p<0.01$). But, on D21 post-injury, SC number did not return to baseline *only* after NO-inhibitor (18.4 ±8.7), with NO-donor treatment showing the lowest number of SCs (5.0 ±0.9 $p=0.09$). NO-donor significantly increased eMHC protein levels (5.29 ±2.64 AU versus placebo: 0.65 ±0.64; NO-inhibitor: 0.58 ±0.51; Comb: 0.45 ±0.9 AU; $p<0.001$) and new fiber CSA (501 ±34 um^2) versus other treatments (PI: 421 ±27 $p<0.01$; NO-inhibitor: 240 ±38 p&lt0.001; Comb: 313 ±36 um^2; $p<0.001$).

CONCLUSIONS: NO-donor improved HGF and myogenesis. An apparent disconnect between eMHC protein and fiber CSA improvement and less SCs on D5 post-injury may be explained by NO-donor promoting differentiation, an interpretation that must be tested in vitro.
Funded by the South African National Research Foundation.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 264

Board #57

Physical Activity's Role in Diurnal Skeletal Muscle mTORC1 Signaling in Tumor-Bearing Mice

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Mechanistic target of rapamycin complex 1 (mTORC1) signaling axis is central to daily anabolic fluctuations regulated by activity and food. Inability to stimulate muscle protein synthesis in response to anabolic stimuli is thought to contribute to cancer-induced muscle mass loss. $Apc^{Min/+}$ (MIN) mouse, an established preclinical cancer cachexia model, has suppressed basal skeletal muscle mTORC1 signaling and occurs without reductions in overall food intake. While MIN mice exhibit increased fatigue and reduced volitional activity before cachexia development, the cancer environment's regulation of physical activity induced mTORC1 signaling has not been established. **Purpose:** We investigated the role of physical activity on diurnal skeletal muscle mTORC1 signaling in the MIN mouse. **Methods:** Male C57BL/6 (B6) and MIN had access to wheels (B6 N=17, MIN=19) or cage controls (Free Living (FL)) (B6 N=24, MIN N=22) for 2wk. Body weight, food intake, and physical activity were monitored for 4 consecutive days following the light (SEDINTARY [SED]) and dark cycles (ACTIVE [ACT]). Mice were sacrificed following SED or ACT. Gastrocnemius muscle was used for analysis; significance set at $p\leq0.05$. **Results:** FL and wheel B6 mice showed significant differences in physical activity and food intake between SED and ACT, which was disrupted by cancer environment. MIN-FL cage activity reduced 50% ($p=0.002$) and wheel distance reduced 64% ($p=0.01$) during ACT compared to B6. Wheel activity increased B6 protein synthesis during ACT compared to FL-B6 ($p=0.02$) but did not alter MIN-ACT muscle protein synthesis ($p=0.83$). FL-B6 muscle 4EBP1 activation, a mTORC1 target, was induced during ACT compared to SED

(p=0.003); wheel activity trended (p=0.06) to increase 4EBP1. FL-MIN had suppressed 4EBP1 during ACT compared to SED (p=0.05), and wheel activity did not alter this response. Interestingly, time spent on the wheel correlated to 4EBP1 activation (R^2=0.49; p=0.04). **CONCLUSION:** Cancer can disrupt daily muscle anabolic fluctuations in mice. This suppressed anabolism may be driven by reduced physical activity and an attenuation in exercise-induced mechanical signaling. Future studies are warranted to investigate if targeting physical activity induced mechanisms can improve skeletal muscle anabolic flux in the cancer environment. Supported by NCI R01-CA121249

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 265

Board #58

Precision High Intensity Training through Epigenetics (PHITE): A Molecular Approach to Preparing the Modern Warfighter

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PURPOSE: The military relies on physical training for warfighter readiness. High-intensity training modalities have increased in popularity among military populations because of perceptions that they achieve higher levels of physical performance more quickly and with shorter training sessions. The purpose of this single blind, randomized trial is to phenotype the exercise dose-response to moderate vs. high intensity combined training in 18-27 y untrained females and males (n=150) who typify Marine and Navy recruits, and to reveal molecular cues that may be key determinants of individual responsiveness. For the latter, each participant completes two acute exercise response bouts (pre- and post-training) with serial biospecimen collections (blood: pre-exercise, immediate post, 3 h post, 24 h post; muscle: pre-exercise, 3 h post, 24 h post). Additional biospecimens are collected after 4 wk of detraining. **METHODS:** The PHITE trial is currently in year 2 of 5. Participants are randomized to 12 weeks of traditional, moderate-intensity endurance (ET) and resistance training (RT) (MOD) or high-intensity interval training (HIIT) integrated with high-intensity RT (HI). For MOD, ET consists of 3 d/wk continuous exercise at 70% HRR (2 d cycle ergometry; 1 d treadmill), and RT is whole-body progressive RT 2 d/wk at moderate intensity (12RM) (10 movements x 12RM x 3 sets each). In lieu of moderate ET, HI consists of HIIT (30 s work: 30 s rest x 10 rounds of maximum intensity, explosive movements; box jumps, burpees, kettlebell swings, battle ropes, split squats, dips, medicine ball throws, cycle sprints). HI RT involves the same 10 movements as MOD, but at higher intensity (8RM) and faster pace (supersets). In vivo phenotyping outcomes: VO2peak, 1RM strength, anaerobic power, vertical jump, DXA body composition, circulating cytokine and anabolic hormone profiles. Muscle tissue phenotyping outcomes: myofiber type distribution and cross-sectional area, Pax7+ satellite cell density, capillary supply, mitochondrial function and biogenesis; ribosome biogenesis. Acute molecular response signatures: miRNA-seq on serum exosomes and muscle, muscle transcriptomics, methylomics, histone modifications and chromatin remodeling, exercise-induced mRNA splice variation, targeted protein metabolism proteomics. Genotyping: Finally, whole-genome sequencing at baseline will explore genotype linkages to performance adaptation potential. **CONCLUSIONS:** Preliminary results will be presented based on our a priori planned interim analysis of the first 20% of the cohort, to be analyzed in July-August 2018.

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Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 266

Board #59

Recovery from Extreme and Severe Intensity Exercise

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Our lab has recently collected data suggesting that central and peripheral measurements of fatigue, as measured by potentiated twitch force (Q_{tw}) and maximal voluntary contraction (MVC) returned to baseline values following extreme exercise, whereas Q_{tw} and MVC remained less than baseline values following severe exercise. However, a limitation to this protocol was that the last 3 of 6 measurements averaged to represent the exhausted muscle were taken at least 2 min following exercise. **PURPOSE:** The purpose of this study was to test the hypothesis that Qtw and MVC immediately following task failure of extreme intensity exercise would be significantly lower than those measured ~2 min into recovery. **METHODS:** Four subjects (3 men, 1 woman, age 24 ± 4 yrs, 74.5 ± 17.4 kg; 173 ± 5 cm) performed 2 intermittent isometric knee extension tests to exhaustion at 40% and 70% MVC in random order. Repetitions were performed at a 60% duty cycle (3s on, 2s off). Exercise intensities were chosen to elicit time to task failure (Tlim) in < 2min (extreme intensity) and 2-15 min (severe intensity). Task failure was defined as the inability to maintain target force. Neuromuscular measurements were made every 30s prior to and immediately following exercise. Qtw and MVC were compared pre- and post-exercise and between intensity. Furthermore, individual Qtw and MVC were compared over time during recovery following extreme and severe exercise. **RESULTS:** Qtw and MVC significantly decreased following severe and extreme exercise ($p<0.005$). Post exercise Qtw was not different between severe and extreme exercise ($p>0.05$). However, MVC was significantly greater (p=0.001) following extreme exercise, suggesting that MVC was able to recover faster following extreme exercise. Each individual MVC following extreme exercise was significantly greater ($p<0.05$) compared to its associated MVC following severe exercise. Individual Q_{tw} were not different between exercise intensities until the fifth and sixth measurement ($p<0.05$). Further, in recovery following extreme exercise, there were no differences among Q_{tw} until the fourth measurement, taken 2 minutes following exercise. **CONCLUSIONS:** The current data lend evidence that the mechanisms of fatigue developed during extreme exercise are able to recover in a shorter amount of time than those of severe exercise, as evidenced by Qtw and MVC being greater following extreme exercise compared to severe exercise. Importantly, these data suggest that the measurements typically used to represent the condition of the muscle are taken too far post-exercise such that much of the recovery of the muscle has already occurred, especially following extreme exercise.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 267

Board #60

Sex-Differences In Bench Press Muscle Activation With Pre-Exhaustion Of Triceps Brachii

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Purpose Pre-exhaustion is a resistance training method which activates a stronger single-joint muscle to momentary exhaustion directly before a multi-joint exercise including the pre-exhausted muscle. This results in greater recruitment of muscles in the multi-joint exercise to further increase muscle strength. The pre-exhaustion method in bench press has mainly been studied in men and it is uncertain if sex-differences exists. Men are stronger than women in absolute strength, especially in the upper body but if this holds true for upper body relative strength is debated. The purpose was to investigate muscle activity by surface electromyography (EMG) between women and men in bench press with and without pre-exhaustion of triceps brachii (TB) and to compare relative

strength in 10RM bench press between the sexes. **Methods** 15 women and 15 men in their 20s with weight lifting experience were recruited to the study. During the first session body composition and 10 repetition maximum (10RM) bench press were determined Participants performed both protocol A and B in a cross-over design on separate days. Protocol A began with 10 RM bench press, five minutes recovery, pre-exhaustion exercise (triceps extensions to failure) immediately followed by a second round of bench press with the same 10RM load as before pre-exhaustion. Protocol B started with triceps extensions to failure immediately before bench press at their before established 10RM, five minutes of recovery then they performed 10RM bench press again. IN both protocols, EMG electrodes were attached to TB), pectoralis major (PM) and deltoideus anterior (DA). EMG values were normalized to maximum voluntary isometric contraction (MVIC) and expressed as % MVIC. **Results** Bench press only EMG activity in %MVIC was similar between women and men, but analysis of variance (TB interaction p=0.02) showed that women had higher %MVIC in TB after pre-exhaustion whereas muscle activity decreased in men compared to bench press without pre-exhaustion. Yet, the number of repetitions completed in bench press after pre-exhaustion of TB were the same (women 4.3 ± 2.6 vs men 3.8 ± 2.2; p=0.55). As expected, in 10RM weight men (64.0 ± 7.1 kg) were stronger than women (37.1 ± 6.5 kg; p<0.01), however when related to fat free mass no difference was evident in relative strength between women and men. **Conclusion** Men and women have similar muscle activation patterns during a 10RM bench press, but TB pre-exhaustion followed by a bench press appears to have a greater effect on TB activation in women compared to men. Absolute strength was greater in men, but normalized to fat free mass women and men had similar upper body relative strength.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 268

Board #61

Skeletal Muscle Fiber Type and Morphology in a Middle-aged Elite Male Powerlifter using Anabolic Steroids

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Purpose: Powerlifting (a strength sport consisting of maximal squats, bench press, and deadlifts) regularly exposes athletes to extreme stimuli such as chronic heavy resistance training (HRT) combined with anabolic-androgenic steroid (AAS) use. However, little is known about the myocellular adaptations that occur from long-term HRT and AAS use, especially into middle-age. We were presented with the unique opportunity to study muscle from an elite-level powerlifter (EPL; age 40 y) with ≥30 y of HRT experience, ≥10 y of AAS experimentation, and ≥4 y of consistent AAS use. The purpose of this case study was to 1) identify the myosin heavy chain (MHC) fiber type and quantify muscle fiber morphology (size and myonuclear content) in EPL and 2) compare these data with values in the literature. **Methods:** EPL (ht: 180.3 cm, wt: 118.0 kg, max squat: 493 kg) underwent a resting *vastus lateralis* (VL) muscle biopsy. A total of 250 single fibers were analyzed for MHC content via SDS-PAGE. A subset of fibers (*n*=50) underwent fiber type-specific (MHC I & IIa) imaging analysis using laser scanning confocal microscopy (LSCM) to identify cell size (cross sectional area, CSA) and myonuclear domain size (MND). These fibers (>2 mm in length) were clipped into two portions (~1/3 for SDS-PAGE fiber typing, ~2/3 for LSCM). The larger fiber segments were mounted on microscope slides, stained with Phalloidin (w/Alexa Fluor 568; labels actin) and DAPI (labels myonuclei), imaged in three-dimensions via LSCM, and analyzed with customized software. **Results:** EPL's MHC fiber type was 9% MHC I, 12% MHC I/IIa, 79% MHC IIa, and 0% other MHC isoforms. LSCM imaging analysis of EPL's MHC IIa fibers revealed a mean CSA of 4,218 ± 933 μm^2 and MND of 12,548 ± 3,181 μm^3. **Conclusions:** EPL's 79% fast-twitch (MHC IIa) fiber content was amongst the highest reported in the literature (typical *VL* MHC IIa distribution in healthy men: ≤ 35%). While EPL's fiber MHC IIa CSA was comparable to values in previous literature, his mean MND was much smaller than has been reported (typical *VL* MND in healthy men: ~25,000-36,000 μm^3), suggesting EPL muscle contained ≥2x more myonuclei (per volume) compared to untrained men (implying a greater capacity for growth and repair signals). These findings showcase the unique myocellular structure of an individual who's whole muscle function approaches the "ceiling" of human performance [i.e., PRT max squat >4x body weight (>1,000 lbs)]. Future research should continue investigating the muscle of elite strength athletes to elucidate the performance effects and health implications of chronic PRT and AAS use into middle-age and across the lifespan. Funded by SFSU-ORSP Small Grant (ST672) to JRB.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 269

Board #62

Skeletal Muscle Transcriptome Response to Acute Interval and Continuous Exercise in Older Adults

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Exercise represents a powerful strategy to preserve skeletal muscle function with advancing age. However, less understood are the molecular mechanisms that may be targeted by different exercise strategies and intensities. **PURPOSE:** Identify the unique transcriptional response of skeletal muscle in older adults after acute high intensity interval (HIIE) and moderate intensity continuous (MOD) cycling exercise. **METHODS:** In a counter-balanced, cross over design, eight older adults (5M, 3F; 67±2yr; BMI: 26.0±1.8kg·m^{-2}) completed a bout of HIIE (ten, 1-min intervals, 85-95% heart rate max, 1-min rest between intervals) and MOD cycling (30-min, 65-70% VO_{2peak}), separated by ~1 week. Muscle biopsies (*vastus lateralis*) were obtained before exercise and at 4h after each exercise bout. Whole transcriptome next-generation sequencing was performed on cDNA synthesized from skeletal muscle RNA. Sequencing data were analyzed using HTSeq and differential gene expression from preexercise was identified using DESeq2. **RESULTS:** Relative to preexercise, HIIE resulted in ~350% more differentially expressed genes compared to MOD. Specifically, HIIE increased expression of 213 genes and decreased expression of 46 genes, whereas MOD increased expression of 53 genes and decreased expression of 18 genes. While 24 genes were responsive to both HIIE and MOD, we identified 231 genes that were only responsive to acute HIIE and 47 genes that were only responsive to acute MOD. Several of the top differentially expressed genes uniquely responsive to HIIE included genes involved in muscle growth. **CONCLUSION:** These data highlight mutual and unique transcriptome responses of aging skeletal muscle to acute HIIE and MOD. These findings also further highlight that different forms of exercise stimulate unique molecular activity in skeletal muscle, and in particular, acute HIIE appears to elicit greater transcriptional activity compared to MOD, at least in the immediate hours post exercise. Supported by a JumpStart grant, College of Health Solutions, ASU.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 270

Board #63

The Effect Of Resistance Exercise On Akt-mtorc1 Signaling Pathway After A Prolonged Fasting.

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PURPOSE: It is well known that resistance exercise (RE) activates Akt mTORC1 signaling pathway and increases muscle protein synthesis. In mammals, starvation such as fasting or severe food restriction induces AMPK activation. It has been reported that activation of AMPK attenuates mTORC1 activation. However, it is not clear whether the responses of Akt-mTORC1 signaling proteins by RE after a prolonged fasting are also suppressed. The purpose of this study was to investing the effect of acute bout of RE on Akt-mTORC1 signaling pathway during prolonged fasting in rat skeletal muscle. **METHODS:** Male Sprague-Dawley rats were divided into two groups: overnight fasted group (C) and 72 h fasting group (F). RE was conducted by percutaneous electrical stimulation in right gastrocnemius muscle. Muscle samples were taken at rest, immediately after and 3 h after resistance exercise. Western blotting analysis was used to measure phosphorylation status of signaling proteins associated with Akt-mTORC1 signal.

RESULTS: Phosphorylation of AMPK (Thr172) was significantly increased in F group compared with C group at rest. In C group, phosphorylation of Akt (Thr308andSer473) was significantly increased immediately after RE; however in F group, there was no significant change after RE. Phosphorylation of mTOR (Ser2448) was significantly increased immediately after RE in C group; however, there was no significant difference in phosphorylation of mTOR (Ser2448) in F group after RE. Phosphorylation of p70S6K (Thr389) and rpS6 (Ser240/244) was significantly increased 3 h after RE in both groups, but the magnitude of phosphorylation was significantly attenuated in F group as compared with C group.

CONCLUSIONS: These data indicated that a prolonged fasting attenuates acute RE- induced activation of Akt-mTORC1 signaling pathway.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 271

Board #64

The Influence of Chronic Resistance Training on Muscle Hypertrophy in Type 2 Diabetes Mellitus Rat Skeletal Muscle.

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PURPOSE: Type 2 diabetes mellitus (T2DM) is induced by whole body glucose intolerance. Skeletal muscle is essential for whole body glucose homeostasis. Resistance training (RT) is well known as one of the procedures for increasing skeletal muscle mass. Previous studies reported that overload-induced muscle hypertrophy is impaired in T2DM. However, it remains unclear whether RT-mediated muscle hypertrophy is blunted in T2DM. Thus, in present study, we evaluated whether RT-mediated muscle hypertrophy is impaired in T2DM.

METHODS: Otsuka Long-Evans Tokushima Fatty (OLETF; T2DM model rat) and Long Evans Tokushima Otsuka (LETO; healthy control rat) aged twenty-week were used as T2DM model and control, respectively. Both groups performed 18-bouts of RT (3-times/week, total 6-week) by percutaneous electrical stimulation on unilateral triceps surae.

RESULTS: Main effect of group and RT were observed in myofiber size. T2DM group showed significantly lower fiber size than control group, but percent increase in muscle mass by RT did not differ between groups. Main effect of group was significant in mTORC1 activity (phosphorylation of p70S6K and 4E-BP1). T2DM group showed significantly lower basal mTORC1 activity as compared with control. RT significantly increased apoptotic effector, caspase 3 expression in both groups. Pax7, a satellite cell specific protein expression, significantly was lower in both RT and control leg of T2DM muscle.

CONCLUSIONS: Present results indicated that protein expressions including those in mTORC1 pathway were blunted, but RT-induced muscle hypertrophy was not impaired in T2DM rat skeletal muscle.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 272

Board #65

Transcutaneous Carbon Dioxide Attenuates Muscle Loss In Rats With Type 2 Diabetes

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PURPOSE: Diabetes leads to glycation of proteins, and decrease of protein synthesis and increase of protein degradation in skeletal muscle. Transcutaneous application of carbon dioxide (CO2) can increase blood flow, a phenomenon known as the Bohr effect. Recently, it has been reported the transcutaneous CO2 treatment leads to an increase of muscle mass in normal rats. Therefore, the aim of the present study was to investigate the effects of transcutaneous CO2 treatment on diabetic muscle atrophy.

METHODS: Male Goto-Kakizaki (GK) rats were divided into control (GK) and CO2 treatment (CO2) groups and Male Wistar rats used as a nondiabetic control (Ctrl). The hair on the lower limbs was shaved and the hydrogel (CO2GEL) was applied. The hydrogel can increase the absorption of CO2 from skin. The CO2 adaptor was attached to the limbs and sealed, and CO2 gas was administered into the adaptor for 30 min. The CO2 treatment was performed everyday for 8 weeks.

RESULTS: The body weight, epididymal and retroperitoneal fat were lower in the CO2 treatment group than in the GK group. In addition, the level of fasting blood glucose in the CO2 treatment group was significantly decreased compared with the GK group. Furthermore, the muscle (EDL, gastrocnemius, plantaris, tibialis anterior) weights of lower limbs in the CO2 treatment group were higher than those in the GK group.

CONCLUSIONS: These results indicate that the transcutaneous CO2 treatment may have a therapeutic potential for diabetic muscle atrophy and fat mass.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 273

Board #66

Variability of Fat Deposition in Human Quadriceps Muscle in Vivo

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Obesity is a growing public health problem. Poor muscle function in overweight and obese individuals may limit the efficacy of activity-based interventions designed to improve health outcomes in this population. Visual inspection of serial anatomical MRI slices of human muscle generally suggests consistent, incremental changes in fat-free muscle cross-sectional area from one slice to the next, whereas fat deposition appears to show a disordered pattern of distribution. The extent to which this disordered pattern of fat deposition within muscle may affect its function is not clear. **Purpose:** To evaluate the spatial distribution of adipose tissue in the human quadriceps muscles. **Methods:** The right leg of 9 healthy young (30±5yrs, mean±SD; 3 men) adults with body-mass indices ranging from 18.7-32.4 $kg \cdot m^{-2}$ were evaluated using a 6-point Dixon MRI technique in a 70-cm bore, 3.0T magnetic resonance system. Ten consecutive 6-mm axial slices centered at the largest cross-sectional area of the quadriceps muscles were analyzed for muscle and fat volumes (cm^3) as well as fat fractions (%). The coefficient of variation (CoV; SD/mean) across the 10 slices were also determined for muscle and fat. Differences in the CoV for muscle and fat were evaluated using a paired t-test, and the association between fat fraction and fat CoV was determined with linear regression. **Results:** Muscle volume in the 60mm region of interest averaged 340±77cm^3 (range: 238-496 cm^3), fat volume was 31±9 cm^3 (21-49 cm^3) and fat fraction was 8.4±0.6% (6.0-10.6%). The interslice CoV for muscle volume (0.32±0.23) was lower than the CoV for fat volume (0.76±0.29, p=0.001), suggesting greater slice-to-slice variability in fat than in muscle. There was no association between fat CoV and fat fraction, r^2=0.05. **Conclusions:** The observation that the CoV for fat volume was greater than that of muscle suggests that the slice-to-slice distribution of fat is less ordered than that of muscle. This relationship also held true regardless of the amount of intramuscular fat, as reflected by the lack of association between fat fraction and CoV for fat. The extent to which this disordered pattern of fat distribution may alter muscle function in humans is not known, but warrants investigation. Supported by University of Massachusetts Amherst *Institute for Applied Life Sciences* Pilot Grant.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 274

Board #67

Wheel Running Decreases LINE-1 Gene Expression in Rodent Skeletal Muscle

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PURPOSE: Transposable elements or "jumping genes" are genetic elements that make up approximately half of the mammalian genome. A portion of these transposable elements, specifically the retrotransposon LINE-1, has the ability to move within the genome of a host via a "copy and paste" mechanism termed retrotransposition. Retrotransposition has shown to be advantageous in certain context, namely by introducing regulatory elements as well as adding genetic diversity both between and within species. These occurrences, although advantageous evolutionarily, have the ability to cause damage or harm to the host. Indeed, LINE-1 insertions have been the subject of intense investigation with respect to cancer causing mutations and genome instability. Moreover, LINE-1 has been implicated in a number of other diseases such as specific cases of Duchenne's muscular dystrophy, among others. Recently, research has revealed that LINE-1 is increased at both the RNA and DNA level in aged tissue and is attenuated with caloric restriction. This observation hints at the fact that LINE-1 gene regulation is affected by environmental factors. With the current study, we sought to investigate if LINE-1 gene expression would be similarly altered with high voluntary wheel running in the rat. **Methods:** Rats selectively bred for high voluntary wheel running and their sedentary age-match controls (n=11 per group) were compared for LINE-1 gene expression as well as endogenous inhibitors of LINE-1 activity. Skeletal muscle was harvested 27 weeks post-weaning in both groups. Due to the rich evolutionary history of LINE-1, multiple families exist within the LINE-1 gene family. For this reason, a qPCR primer set was designed for the youngest and most active form of LINE-1 along with a primer set that encompassed older LINE-1 elements, termed L1.3 and L1.tot, respectively. **Results:** L1.3 gDNA was not significantly different between groups (p=0.52). Similarly, no group differences were found for L1.tot gDNA (p=0.27). LINE-1 mRNA, however, was different between the running and sedentary groups. Both L1.3 and L1.tot showed a significant decrease in the running rodents when compared to their sedentary controls (p=0.03 and p=0.02, respectively). Negative regulators of LINE-1, PIWIL2 and TREX1, showed no significant difference between the two groups (p=0.92 and p=0.73, respectively). **Conclusions:** The data herein provide evidence that the retrotransposon LINE-1 can be regulated by exercise. Given that there are now multiple studies suggesting exercise affects LINE-1 expression, one can speculate that exercise may serve a larger role than expected in genome regulation.

Skeletal muscle, exercise, inactivity, and signaling

Presentation Number: 275

Board #68

Whole Muscle Size, Function, and Adiposity with Lifelong Exercise

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Purpose: This investigation examined the influence of lifelong aerobic exercise on skeletal muscle function, size, and adiposity. **Methods:** Young exercisers (YE; *n*=20, 10F, 25±1y), lifelong exercisers (LLE; *n*=28, 7F, 74±2y), and age-matched non-exercisers (OH; *n*=20, 10F, 75±1y) were studied. On average, LLE exercised 5d/wk for 7h/wk over the past 52±1y. The men were subdivided by exercise intensity into performance (LLE-P, *n*=14) and fitness (LLE-F, *n*=7). **Results:** Aging resulted in a decline in isotonic (1-repetition maximum) and isometric (Po) strength, speed (Vmax; males only), and power, as well as quadriceps and triceps surae (females only) muscle size (P<0.05). In females, LLE had no influence on muscle function, size, or function normalized to size. In males, LLE attenuated the decline in quadriceps muscle size and Po, where LLE was 20% and 24% greater than OH (P<0.05), respectively. LLE did not influence other aspects of muscle function and training intensity did not influence muscle function or size. In both sexes, aging increased thigh and calf intermuscular adipose tissue (IMAT) content by ~60% (P<0.05) and LLE reduced thigh IMAT by ~30% (P<0.05) with no influence on calf IMAT. In males, training intensity reduced thigh and calf IMAT by ~32% (LLE-P<LLE-F) (P<0.05). **Conclusion:** Lifelong aerobic exercise reduces age-related muscle mass loss in males and adipose tissue infiltration into muscle in both females and males. Training intensity over the lifespan does not appear to influence muscle mass or function, but higher intensity exercise does provide a greater protection against adipose tissue infiltration into muscle. Supported by NIH grant R01 AG038576

Hot topics in exercise physiology

Presentation Number: 276

Board #69

Translational Science at ACSM: Does the Science of Integrative Physiology Fit within ACSM's Newest Journal?

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Translational research covers a broad spectrum of science, from basic to implementation and policy change. Increasingly, scientists, clinicians, public health professionals, and funding agencies are recognizing the importance of scientific investigations that bridge traditional gaps between basic, clinical, community, and policy research. The American College of Sports Medicine (ACSM) recognizes the importance of this work and, in 2016, launched the Translational Journal of the American College of Sports Medicine (TJACSM). **PURPOSE:** We aim to inform attendees about the mission, vision, and scope of TJACSM. Further, we hope to clarify the types of research that TJACSM seeks to publish, to feature the most successful published articles to date, and to elucidate how the integrative physiology of exercise, as a content area, fits within the scope of this journal. **METHODS:** Utilizing the journal's webpage and the publisher's (Wolters Kluwer Health) annual reports, we identified information related to the journal's scope, availability and reach, and the number of reads and views of top articles. **RESULTS:** ACSM electronically publishes 24 issues of TJACSM per year and it is currently available in 2,154 institutions. The journal site had 22,879 visits during 2017 and approximately 48% of the journal's reach is outside the United States. Top viewed articles have covered topics such as the translational gap between the laboratory and playing field, the potential impact of sitting on mortality, exercise and breast cancer, and the association between aerobic fitness and academic achievement among elementary school youth. **CONCLUSION:** There is a desire to grow this journal to include all aspects of the translational science spectrum in exercise science, sports performance, and sports medicine. The integrative physiology of exercise, as an example, represents a content area that is currently under-represented in this journal but fits well within the scope of TJACSM. In addition, as an on-line journal, it provides a great deal of flexibility to respond to creative proposals. For example, scientific findings presented at this conference could be considered for a themed issue or a linked volume. Presenters are encouraged to discuss their research and ideas for innovative papers with TJACSM representatives to determine whether their work is appropriate for submission to TJACSM.

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