



Mid Atlantic Regional Chapter of the American College of Sports Medicine

Annual Scientific Meeting, November 1st – 2nd, 2019
Conference Proceedings

International Journal of Exercise Science, Volume 9, Issue 8



Gut Microbiota Contribute to Exercise Capacity and Metabolic Profile in a Wildtype and Longevity Model Mouse

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The gut microbiota can be influenced by many factors including host genotype, diet and exercise training. Previously, we have shown host genotype and behavior (i.e. exercise) can influence the selection of individual species and strains of microbes in the mouse gut. **PURPOSE:** The purpose of this study was to examine the role of gut microbes and their impact on exercise tolerance, metabolic outcomes and short chain fatty acids (SCFA) profiles in two strains of mice, a wild type (WT, n=15) and disruption of adenylyl cyclase type 5 knock out (AC5KO, n=17), a well-established model of longevity, healthy aging and enhanced exercise capacity. **METHODS:** Mice (n=32) were randomly assigned to either sedentary (PRE) or exercise (POST) conditions. Exercise training consisted of forced treadmill running (FTR) at 60-70% of maximal running capacity 5 days/week for five weeks. Following training, a subset of animals (n=3, each) were given an oral antibiotic (ABX) treatment for one week to eliminate gut microbes. **RESULTS:** Exercise tolerance was reduced in WT-ABX (233.0 m vs. 524.1 m, p=0.0161) and AC5KO-ABX (248 m vs. 951 m, p<0.0001) mice compared to POST. WT-POST mice showed a significant reduction in glucose tolerance testing (GTT) area under the curve ([AUC]) (4,607,903.5±247,340.1 vs. 3,640,733.3±160,536.2 arbitrary units [AU], p=0.009) indicating enhanced glucose uptake compared to PRE. AC5KO-ABX mice displayed a significant reduction in GTT AUC (3,322,485.0±308,117.1 AU vs. 2,249,800.0±266,022.9 AU, p=0.01) which coincided with a significant decrease in insulin tolerance testing (ITT) area above the curve (269,197.5±42,952.5 vs. 560,307.5±48,065.4, p=0.006), demonstrating increased insulin sensitivity. SCFA profiles were altered in both WT-ABX and AC5KO-ABX mice from PRE to POST, with significant increases in acetic acid (24% vs. 87%, p=0.003) and (19% vs. 89%, p=0.031) which was associated with proportional decreases in butyric acid (58.3% vs. 1.9%, p=0.003) and (66.1% vs. 0.7, p=0.009), respectively. **CONCLUSION:** Our results suggest that depletion of the gut microbiome significantly reduces exercise tolerance, regardless of genotype; changes glucose and insulin sensitivity; and alters SCFA concentrations by reducing butyric acid in favor of acetic acid.