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Gut Microbiota Removal Eliminates Enhanced Exercise Capacity Mediated by Skeletal Muscle Metabolome and Mitochondrial Proteins

Candace R. Longoria[1], Daniel D. DeSio[1], Xiaoyang Su[1], Eric Chiles[1], John J. Guers[2], Jie Zhang[1], Dorothy E. Vatner[1], Stephen F. Vatner[1], Sara C. Campbell, FACSM[1]. Rutgers, The State University of New Jersey, New Brunswick, New Jersey[1]. Rider University, Lawrence Township, New Jersey[2]

The Regulator of G Protein Signaling 14 knockout (RGS14 KO) mouse is a model for healthful aging and has unique brown adipose tissue and skeletal muscle mechanisms mediating its phenotype of improved exercise performance i.e., a 51 ± 8% increase in running distance (meters/min) and a 44 ± 7% increase in work to exhaustion compared to wild type (WT) mice. We also found that eliminating the RGS14 KO microbiota with antibiotic treatment (ABX) abolished the enhanced exercise capacity (EXC) in the RGS14 KO mice. **PURPOSE:** The goal of this investigation was to determine if the distinct gut microbiota and skeletal muscle (SKM) metabolism in the RGS14 KO mice mediate its enhanced EXC. Accordingly, we examined 1) EXC and tissue (quadriceps) metabolomes of RGS14 KO mice before and following ABX, and 2) SKM for markers linked to exercise performance before and after ABX. **METHODS:** Thirty-eight mice (n=14 RGS14 KO, n=10 WT, n=8 RGS14 KO+ABX, n=6 WT+ABX) were used to examine EXC, identify predominant metabolites in SKM and analyze the expression/activity of proteins linked to EXC, e.g., nitrate/nitrite (NO), citrate synthase (CS), complex IV, AMP-activated protein kinase (AMPK), and sirtuin-3 (SIRT3) before and following ABX. Student's T-test was used to compare two groups and ANOVA was used for multiple group statistical comparisons. **RESULTS:** We found that ABX eliminated the enhanced running distance and work to exhaustion in the RGS14 KO mice. Significant baseline SKM metabolite pathways included purine ($p<0.001$) and phenylalanine ($p<0.01$) metabolism, branched-chain amino acid (BCAA) metabolism ($p<0.01$) and pentose phosphate pathway ($p<0.05$). No significant SKM metabolite pathways were detected after ABX. Mitochondrial protein analysis showed that RGS14 KO had significantly higher NO, CS, AMPK and SIRT3 (77%, 77%, 20% and 265% respectively) relative to WT before ABX. After ABX, the significant decreases in these proteins were augmented in RGS14 KO mice compared to WT, such that the greater levels in RGS14 KO vs WT were no longer observed. **CONCLUSION:** Our findings demonstrate that RGS14 KO SKM responds to changes in resident microbiota that are beneficial to EXC and, upon removal of the microbiota with ABX, the enhanced EXC in RGS14 KO compared to WT was no longer observed. **SIGNIFICANCE:** These findings support the multi-axis communication of the gut microbiota with host muscle and EXC via metabolites and mitochondrial proteins. Additionally, our research contributes to the fast-growing field demonstrating that the alterations to the gut microbiota can affect exercise performance. Future work will translate these findings from the RGS14 KO mouse into human athletes.

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