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Resident Gut Microbiota Mediates Exercise Capacity and Tissue Metabolomes in Mice

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The Regulator of G Protein Signaling 14 knockout (RGS14 KO) mouse has a unique brown adipose tissue (BAT) mechanism mediating its phenotype of improved exercise performance. RGS14 KO mice showed a 51 ± 8% increase in running distance and a 44 ± 7% increase in work to exhaustion compared to wild type (WT). Three days after BAT transplantation from RGS14 KO mice to WT mice, RGS14 KO BAT donors lost their enhanced exercise capacity (EXC), whereas WT BAT recipients gained this EXC. We also found that RGS14 KO mice harbor a distinct gut microbiota and BAT metabolome, suggesting a gut-BAT-muscle axis that may regulate EXC. **PURPOSE:** 1) Examine EXC and tissue (BAT, quadriceps) metabolomes of RGS14 KO mice upon antibiotic treatment (ABX) and 2) begin establishing a gut-BAT-muscle axis that may regulate EXC. **METHODS:** Eight mice (n=4 RGS14 KO, n=4 WT) were used to examine EXC and identify predominant metabolites following ABX. Metabolomics used ultra-high performance liquid chromatography and mass spectrometry to evaluate untargeted metabolites in fecal, quadriceps, and BAT samples. T-test was used to compare EXC before and after ABX. Two-tailed t-tests were used to compare WT and RGS14 KO metabolite means ($p<0.05$). MetaboAnalyst 5.0 was used to identify significant metabolite pathways and generate pathway plots. **RESULTS:** RGS14 KO running distance fell by 35 ± 7%, and work to exhaustion fell by 41 ± 7%, showing RGS14 KO mice lost their enhanced EXC after ABX. Significant baseline BAT metabolite pathways included starch and sucrose metabolism ($p=0.004$); no significant BAT pathways were detected after ABX. Further, significant baseline quadriceps metabolite pathways included pentose and glucuronate interconversion ($p=0.024$) and the pentose phosphate pathway ($p=0.029$). Of the 6 significant metabolite pathways in quadriceps after ABX, none included baseline pathways. **CONCLUSIONS:** RGS14 KO BAT responds to changes in resident microbiota that are beneficial to EXC and upon removal with ABX EXC declines. Ablation of the gut microbiota alters metabolite pathways in RGS14 KO compared to baseline suggesting the absence of the resident microbiota changes metabolism. These data support the importance of the gut microbiota in tissue-specific metabolite production and how the gut microbiota may influence BAT and muscle function.