Mechanism of gut microbiome-induced obesity in the BTBR mouse strain

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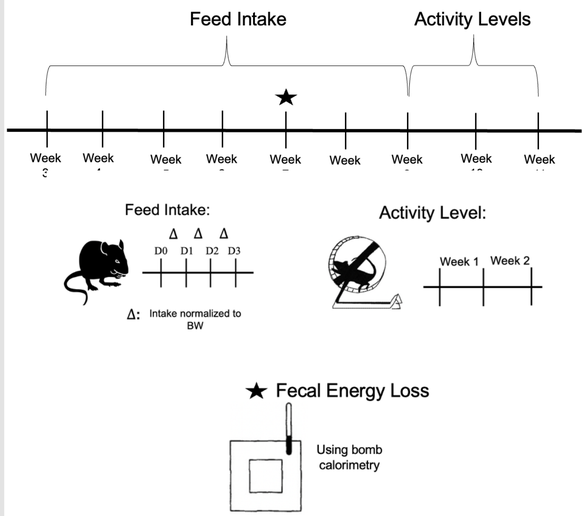
MMRRC Mutant Mouse Resource & Research Centers supported by NIH

Background

- Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder, frequently associated with obesity
- There is a correlation between gut microbiome (GM) and severity of ASD characteristics
- The BTBR mouse strain demonstrates behavioral features of ASD and obesity, providing a model to analyze contributing factors and mechanisms
- CD1 mice colonized with a low richness microbiome (GM_{Low}) demonstrate lower activity levels, and greater feed intake, birth weight, and body weight (BW), compared to mice with a high richness microbiome (GM_{High}) mice, with no difference in fecal energy loss
- In contrast, BTBR mice colonized with GM_{Low} are born lighter than those with GM_{High}, then show disproportionate weight gain in the post-natal period and heavier weaning weights
- We sought to determine the post-natal mechanisms by which the BTBR GM_{Low} mice are out-gaining the GM_{High} mice by investigating feed intake, activity levels, and fecal energy loss

Methods



- n = 6-8/sex/GM
- Jackson and Envigo laboratory BTBR mice, GM_{Low} and GM_{High} respectively

Results

Gut Microbiome Colonization Influence on Weight Gain

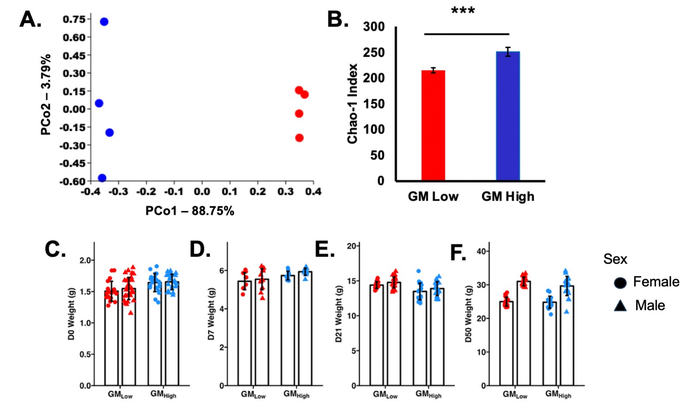


Figure 1. Two distinct gut microbiome populations established in BTBR mouse strain influence weight gain. BTBR mice from Jackson and Envigo Laboratories, colonized with low and high richness GMs respectively, were inbred for three generations at the MU Mutant Mouse Resource and Research Center prior to experimentation. PCoA (A) and Chao- 1 (B) bar graph depicting two distinct GM compositions. Bar graphs showing body weight (BW) of female and male mice colonized with GM_{Low} and GM_{High} at day 0 (C), day 7 (D), day 21 (E), and day 50 (F).
*** : $p < 0.001$

GM_{High} Associated with Greater Activity

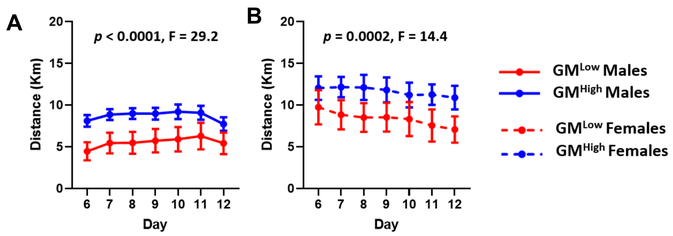


Figure 3. Previous CD1 model showed significant microbiome-dependent differences in activity levels. Line plots showing the distance (km) traveled by males (A) and females (B) colonized with low and high richness GM. We will be repeating this with BTBR mice, using a Bluetooth running wheel to detect the total distance traveled for each individually housed mouse. Based on previous CD1 results, we expect that the GM_{Low} BTBR mice will be less active than the GM_{High} mice

Microbiome Does Not Affect Food Intake

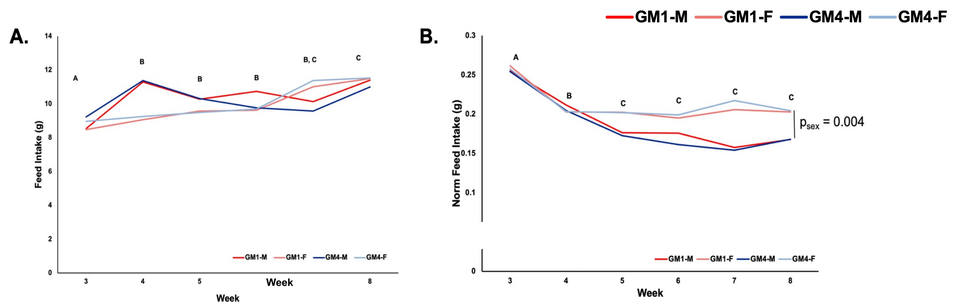


Figure 2. Feed intake levels in BTBR mice. Line plot of overall feed intake (A) $F_{GM} = 0.002$, $p_{GM} = 0.969$, $F_{Sex} = 2.96$, $p_{Sex} = 0.089$, $F_{Week} = 47$, $p_{Week} = 1.22\times10^{-9}$. Line plot of average normalized feed intake (B) $F_{GM} = 0.049$, $p_{GM} = 0.826$, $F_{Week} = 75.13$, $p_{Week} = 3.3\times10^{-13}$, $F_{Sex} = 26.56$, $p_{Sex} = 1.73X10^{-6}$. Differing letters indicate significance.

Fecal Energy Loss

Figure 4. Fecal energy loss measured using bomb calorimetry previously showed no difference in fecal energy loss. Fecal samples from the GM_{Low} and GM_{High} mice undergo bomb calorimetry to determine the caloric content of feces. Based on CD1 results, we expect that the BTBR fecal energy loss will likewise be insignificant between the two distinct microbiome populations. (Cheatam, et al., PMC9961083)

Conclusions

- We observed no difference in feed intake, therefore we expect the GM_{Low} mice to have much lower activity levels, while showing no difference in fecal energy loss when compared to GM_{High}
- If the expected outcomes prove true, this suggests that the gut microbiome-associated effect on weight gain is a result of an influence on energy expenditure regulation, and provides a potential basis for the development of obesity and other metabolic conditions
- Future research can be done to investigate the host mechanisms by which the GM mediates these effects, by examining differences in expression of genes controlling energy balance
- If the expected outcomes are incorrect, additional research is needed to determine the alternative mechanisms of weight gain leading to this discrepancy

Acknowledgements

- MU Metagenomics Center
- Drs. Kevin Gustafson and Christa Cheatham for previous project data
- Rebecca Dorfmeyer assistance with DNA extraction