The role of sex and age in the development of obesity in MuRF1 KO mice

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Introduction

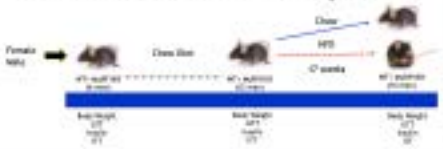
Diet-induced obesity is associated with body weight gain, glucose intolerance, and insulin resistance. Previous studies have shown that C57BL6 female mice are more resistant to developing obesity and glucose intolerance even on a high-fat diet, when compared with adult male mice (1,2). In the current study, we examined the impact of age and sex on the development of glucose intolerance and insulin resistance following 17 weeks on a HFD.

Objective

Based on our preliminary results, we hypothesized that female MuRF1 KO mice would be more resistant to the development of glucose intolerance and insulin resistance when subjected to a high lipid diet, regardless of age.

Study Design

- 152 female and male mice at 6, 12, and 16 months of age were used in this study.
- At the beginning of the protocol (6 months of age), mice were fasted for 6h then glucose tolerance test (GTT) was performed. One week later, insulin tolerance test (ITT) was performed across the groups. During this period of the protocol, all animals were submitted to a standard diet (Chow - Envigo 7013 NIH-31 Modified).
- At 12 months, mice were fasted for 6h then glucose tolerance test (GTT) was performed. One week later, insulin tolerance test (ITT) was performed across the groups. Mice were maintained on their respective diet for 17 weeks. At 12 months of age, mice were subjected to 2 different diets: Chow, or 45% High Fat Diet (HFD; RD D12451).
- At 17 weeks of treatment (Chow or HFD), mice were fasted for 6h then glucose tolerance test (GTT) was performed. One week later, insulin tolerance test (ITT) was performed across the groups.
- Body weights were measured at 6, 12 months and at the end of 17 weeks of treatment with their respective diets.



Results

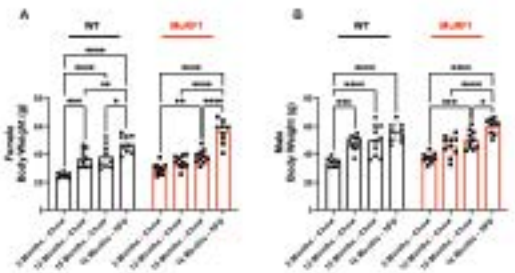


Figure 1: Age is a factor that already increases body weight regardless of diet or genotype. However, the HFD exacerbates the weight gain in female mice (A). However, in males, the HFD only exacerbated weight gain in the MuRF1-KO group not in the WT group (B). Values are means ± SD, $P < 0.05$. * significant difference. n = 8-10 mice per group.

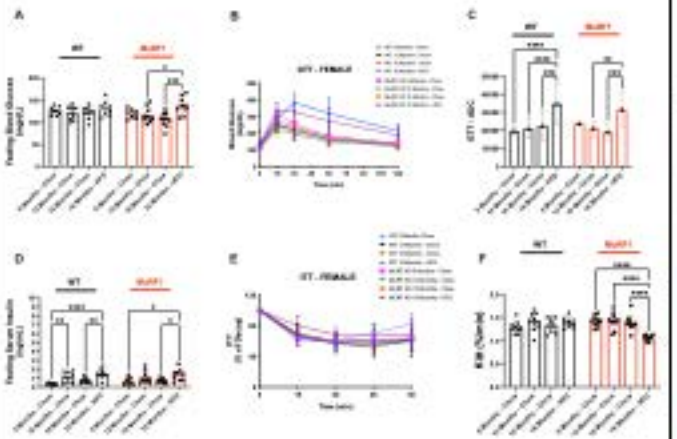


Figure 2: In females, long-term 45% high-fat diet, promote glucose intolerance and insulin resistance after 16 and 17 weeks of diet, respectively. A), Fasting blood glucose, B) Glucose tolerance test (GTT) performed after 6, 12, and 16 months on each diet C), GTT area under the curve, D) fasting serum insulin, E) insulin tolerance test (ITT) performed after 6, 12, and 16 months, and F) HOMA-IR, Homeostatic Model Assessment of Insulin Resistance. Values are means ± SD, * significant difference. n = 8-10 mice per group.

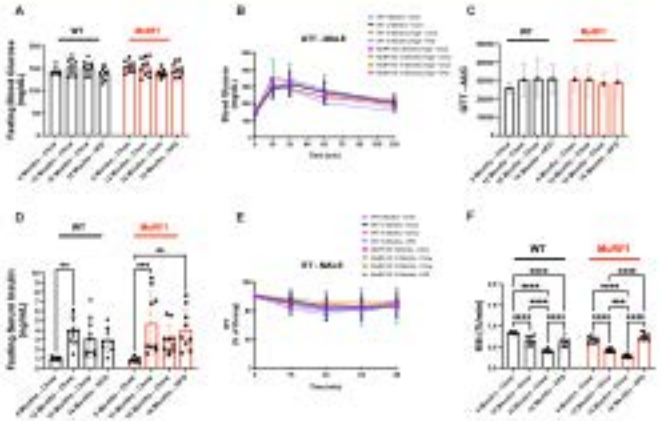


Figure 3: In males, long-term 45% high-fat diet, does not promote glucose intolerance in male mice independently of age or genotype. With advancing age, a lower response in Kitt test is observed, regardless of diet and genotype. Interestingly, the high-fat diet group normalized this response in the MuRF1 KO male mice. A), Fasting blood glucose, B) Glucose tolerance test (GTT) performed after 6, 12, and 16 months on each diet C), GTT area under the curve, D) fasting serum insulin, E) insulin tolerance test (ITT) performed after 6, 12, and 16 months, and F) HOMA-IR, Homeostatic Model Assessment of Insulin Resistance. Values are means ± SD, * significant difference. n = 8-10 mice per group.

SUMMARY

- After 17 weeks, the HFD induced a significant increase in the body weight of WT Female, but not WT male mice.
- In contrast, in females both WT and MuRF1KO mice showed a significant increase in body weight.
- Interesting, both WT and MuRF1KO became glucose intolerant and insulin resistant after 17 weeks on a HFD.
- Male WT and MuRF1KO mice were glucose intolerant and insulin resistant in both diets (Chow and HFD).

CONCLUSION

- These results differ from our previous study, which was performed in young adult mice, and revealed that with aging female mice become more similar to male mice, developing glucose intolerance and insulin resistance to a HFD.
- Interesting, at 12 months of age, male mice are insulin resistant even on a chow diet, and show little response to a HFD.
- The mechanisms underlying the sex and age interactions are unknown and require further study.

References

1 – Ingvorsen, C *et al.* The role of sex and body weight on the metabolic effects of high-fat diet in C57BL/6N mice. Nutr Diabetes. 2017 Apr 10;7(4):e261. doi: 10.1038/nutd.2017.6. 2 – Kalyani, RR. Sexual dimorphism in biomedical research: a call to analysis by sex. Trans R Soc Trop Med Hyg. 2014 Jul;108(7):385-7. doi: 10.1093/trstmh/tru079.

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