Characterization of FATZO Mice for Diabetes and Obesity Research

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INTRODUCTION

Obesity is a growing threat resulting in co-morbidities of diabetes and cardiovascular disease. Developing pharmacological treatments to fight this pandemic disease requires an understanding of disease progression and pathophysiology. Current preclinical animal models used in obesity and diabetes research have monogenic defects. However, a monogenic cause for obesity and diabetes is not at all common in humans. In that regard, having an animal model with a polygenic background and showing many signs of metabolic disease is essential for development of treatments targeting different stages of metabolic disease progression. In this study, we aimed to characterize a new mouse model, called FATZO, with and without a high fat containing diet.

METHODS

FATZO mice were developed by crossing *AKR/J* and *C57BL/6J* mice with selective breeding for obesity, insulin resistance, and hyperglycemia at PreClinOmics (Indianapolis, IN), now a CrownBio company. Eight to ten week old male FATZO mice with body weights ranging from 24 to 43g were randomized based on body weight and placed in low (29.4 ± 0.7g), middle (35.7 ± 0.7g), and high (38.9 ± 0.7g) weight groups. Mice selected for low, middle, and high body weight groups (n=8/group) were fed either Purina 5008 (16% fat-normal chow) or D12492 (60% fat diet). Body weight, food intake, and blood glucose were measured weekly, while insulin was measured every two weeks. An oral glucose tolerance test (OGTT) was performed after 8-weeks of the study to assess glucose disposal. Pancreas was collected at the end of the study for the determination of islet function. All data are represented as the group mean ± standard error of the mean (SEM) and statistical difference was expressed as $p<0.05$ using one-way ANOVA.

RESULTS

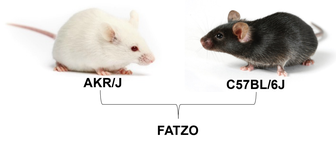

FIGURE 1: FATZO mice were developed by crossing AKR/J and C57/BL/6J mice with selective breeding for obesity, insulin resistance and hyperglycemia at PreClinOmics, now a Crown Bioscience Company.

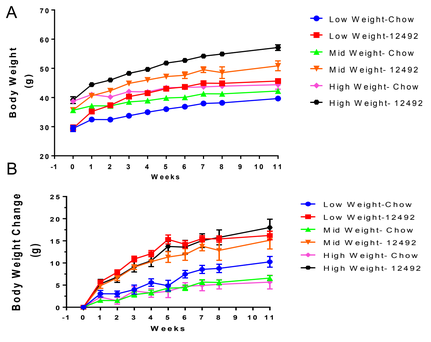

FIGURE 2: Body weight (A) and body weight change (B) of FATZO mice induced with a diet containing low and high fat content.

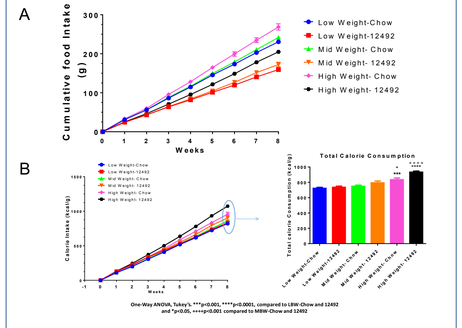

FIGURE 3: Cumulative food intake (A) and calorie intake (B) of FATZO mice with diet containing low- or high-fat content.

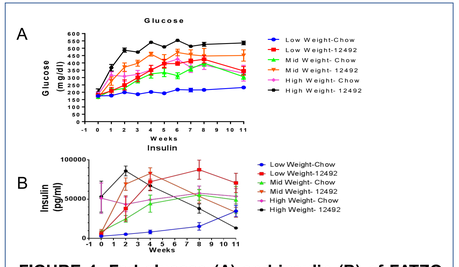

FIGURE 4: Fed glucose (A) and insulin (B) of FATZO mice demonstrate hyperglycemia and insulin resistance.

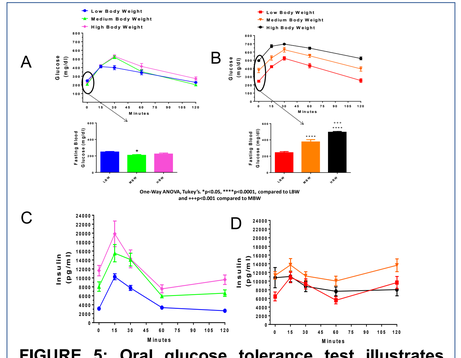

FIGURE 5: Oral glucose tolerance test illustrates fasted glucose levels are high in low fat-fed animals (A) and high-fat-fed animals (B). Fasted insulin levels in low fat-fed animals (C) demonstrate a rationale for faster disposal rate of glucose when compared to high-fat-fed animals (D).

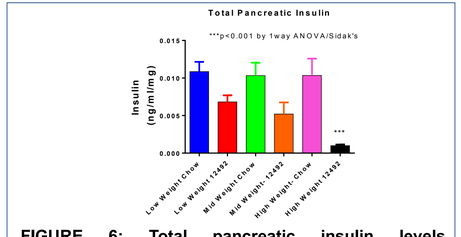

FIGURE 6: Total pancreatic insulin levels demonstrate loss of islet β cell function in high-fat-fed animals.

SUMMARY

Our results indicated that:

- Even with a low fat diet, FATZO mice demonstrated progressive signs of insulin resistance that was highly correlated with body weight.
- Consumption of a diet containing high fat was shown to enhance disease progression and also cause a detrimental loss of islet β cell function.

In conclusion, the FATZO mouse is a good animal model to study obesity-induced diabetes accompanied with insulin resistance leading to hyperglycemia and progressive loss of islet β cell function.