Sex and Genetic Factors Involved in Alterations of Behavior and Brain Iron due to Diet-Induced Obesity

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Background

- Obesity has been linked to behavior issues\(^1\) and brain diseases\(^2\) with iron imbalance as a potential trigger for their development\(^4\).\(^5\).
- In our previous studies using a diet-induced obesity model in mice, we found an imbalance of iron in specific regions of the brain with potential connections to behavior modifications\(^6\).\(^7\).
- The influence of sex and genetics on brain iron homeostasis and behavior modifications has been reported in recent aging and obesity research, indicating that sex and genetics are key factors to consider when evaluating the impact of obesity on the brain\(^8\).\(^9\).

Objective

Investigate sex and genetic influences on the disturbance of brain iron and behavior due to diet-induced obesity in male and female mice with different genetic backgrounds. The mouse strains will include C57BL/6J (C57) and DBA/2J (DBA) strains.

Hypothesis

Based on our previous studies, we hypothesize that alterations caused by diet-induced obesity will be more pronounced in males than females, and more evident in the C57 strain compared to the DBA strain.

Methods

Diet Treatment

- Mice were randomly assigned a control low fat diet with 10% kcal fat/g or high fat diet with 60% kcal fat/g for a period of 16 weeks.
- A total of 72 mice in this study included male and female C57 (n=36) and DBA (n=36) strains.

Behavior

- Behavior tests were conducted during weeks 14 and 15 of the diet treatment.
  - Open Field – Locomotion & Anxiety
  - Novel Object Recognition – Memory
  - Nestlet Shredding – Compulsivity & Anxiety
  - Behavior analysis software - TopScan Lite Version 2.00, Clever Systems, Inc.

Brain Iron

- Iron was measured using graphite furnace atomic absorption spectroscopy.

Results

Behavior

- Open Field: Percent Center Time for C57 Mice
  - There was a diet by sex interaction for C57 mice only (p=0.019).
  - Opposite effects occurred for male and female C57 mice on a high fat (HF) diet.
  - Male C57 mice showed the most significant changes in behavior due to diet-induced obesity (p=0.034).

- Novel Object Recognition
  - Diet-induced obesity did not impact memory based on percent time exploring new object.

- Nestlet Shredding
  - There was a diet by sex interaction for C57 mice only (p=0.037).
  - Male C57 mice showed the most significant changes in behavior due to diet-induced obesity (p=0.008).

Brain Iron

- Striatum is a brain region involved in controlling motor activity.
- The effect of diet-induced obesity on striatum iron depends on sex for both strains. Overall diet by sex interaction: p=0.032. The diet effect on iron is more significant in females (p=0.026) than males (p=0.421).

Conclusions

- The impact of diet-induced obesity on anxiety is influenced by sex only in the C57 strain. Obese males spent more time in the center, while females spent more time near the walls in the open field test.
- There was no significant difference in novel object recognition, indicating that diet-induced obesity does not impact memory.
- The shedding behavior of male C57 mice was impacted the greatest by diet-induced obesity.
- Brain iron in the striatum increased in females fed a high fat diet but decreased in males.
- Contrasts between males and females revealed in this study highlight the need to consider sex as a biological factor in animal research.
- Strain differences observed due to diet-induced obesity are indicative of a gene-environment interaction that has substantial health implications.
- Future targeted therapies for obesity, behavior issues, and brain diseases may need to be specifically tailored to account for sex and genetics.

References


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