Cardiometabolic Disease Promotes Sex-Specific Cognitive Decline

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Introduction

Cardiometabolic disease (CMD), which describes coexisting conditions of obesity, insulin resistance, and elevated blood pressure (BP), is a leading global health concern. The detrimental effect of CMD on metabolic health is well-established and increasing evidence suggests a link between metabolic dysfunction and cognitive impairment, though the mechanisms are not well-understood. Previously, our lab observed that mice maintained on a high-fat diet (HFD; 60% kcal) exhibited significantly reduced glucose tolerance compared to those on a regular diet (RD), implicating metabolic dysfunction as a potential contributor to cognitive impairment in CMD.

Aim

Our aim is to investigate the link between chronic HFD consumption and associated cognitive impairment.

Hypothesis

We hypothesize that chronic HFD consumption impairs cognition in CMD mice, potentially in a sex-dependent manner, with males being more vulnerable than females who would experience a milder CMD-driven cognitive dysfunction.

Experimental Design

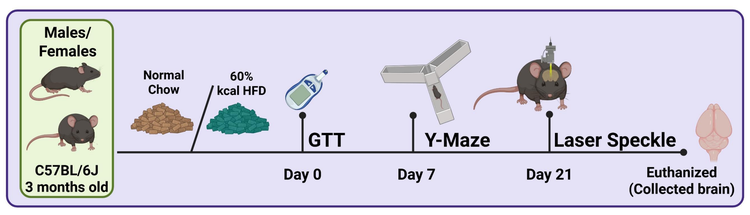


Figure 1: Male and female C57BL/6J mice (3 months old) were maintained on RD or HFD for the duration of the study (6 months). Glucose tolerance testing (GTT) was conducted on Day 0, followed by Y-maze behavioral assessment on Day 7 and laser speckle imaging on Day 21 to evaluate cerebral perfusion. Mice were euthanized afterward, and brains were collected for subsequent analyses.

Results

HFD Induced Glucose Intolerance Between Sexes

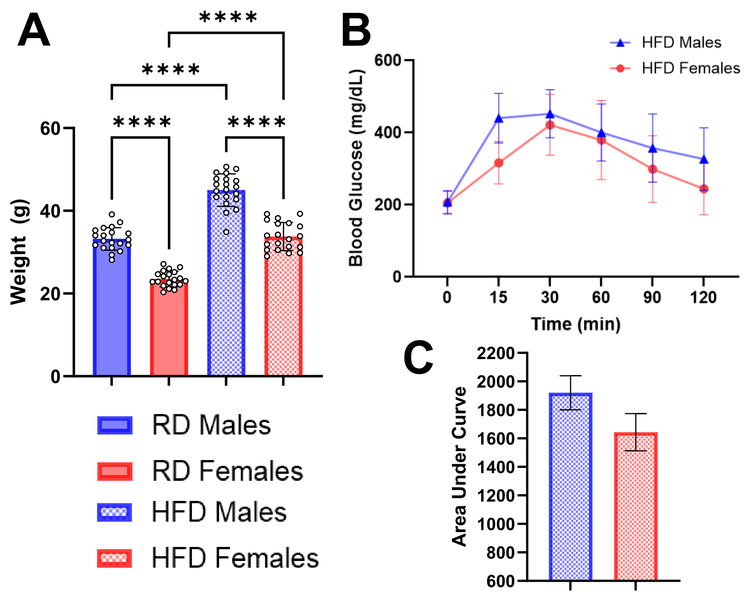


Figure 2: HFD induces greater glucose intolerance in male mice. (A) HFD-fed mice of both sexes showed a significant increase in body weight compared to RD-fed controls ($p < 0.0001$). **(B)** GTT revealed slower normalization of blood glucose levels in HFD-fed males compared to HFD-fed females ($p < 0.05$), indicating greater glucose intolerance in males. **(C)** AUC analysis supported this sex difference, with HFD males showing a higher AUC than HFD females. Data are mean ± SEM; one-way ANOVA with Tukey's multiple comparisons test.

HFD Induces Sex-Dependent Cognitive Impairment

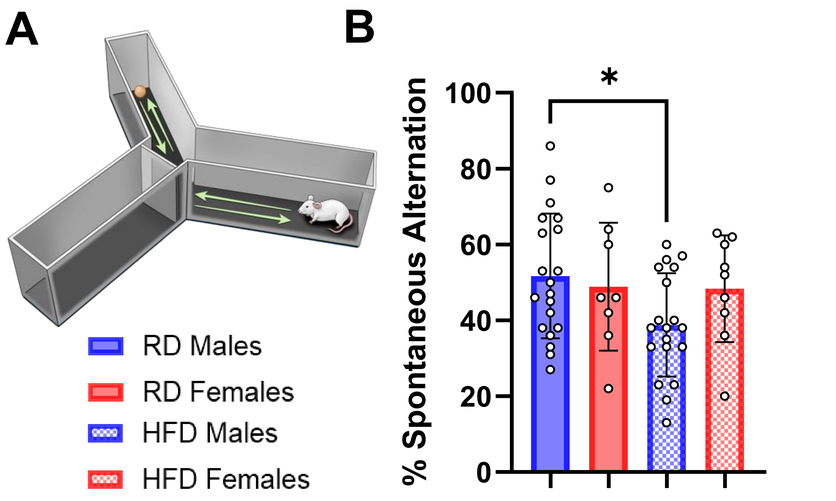
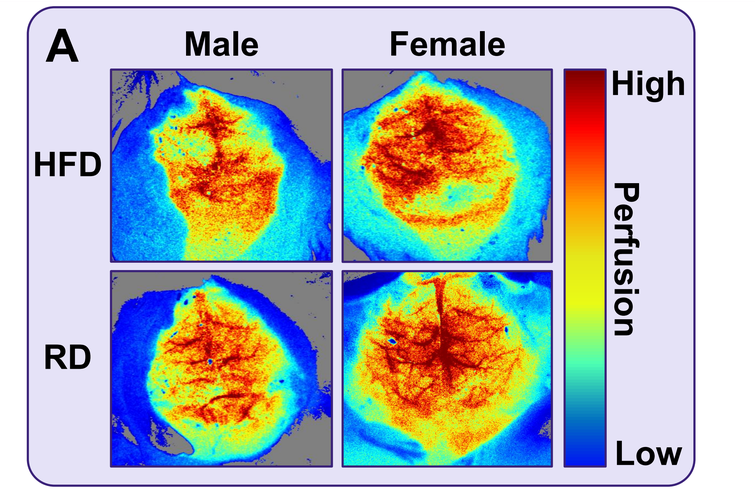


Figure 3: HFD induces cognitive impairment in male mice. (A) Y-maze task schematic used to assess spontaneous alternation behavior. **(B)** Quantification of spontaneous alternation behavior shows that HFD-fed male mice exhibited significantly lower alternation compared to RD-fed males ($p < 0.05$), indicating impaired cognitive flexibility. Data are expressed as mean ± SEM. Two-way ANOVA with Tukey's multiple comparisons post hoc test.

HFD Reduces Cerebral Perfusion



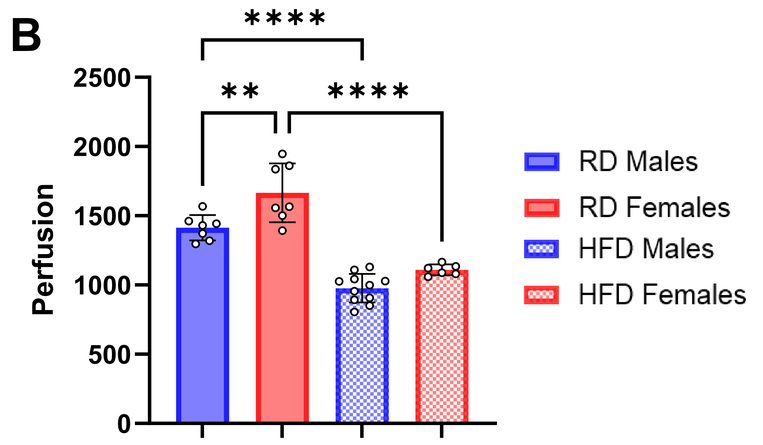


Figure 4: HFD exhibits reduced cerebral perfusion (A) Laser speckle contrast imaging heat maps showing cortical perfusion in male and female mice maintained on either regular diet (RD) or high-fat diet (HFD). **(B)** Quantification of cortical perfusion revealed significant differences between RD males and RD females ($p < 0.01$), RD males and HFD males ($p < 0.0001$), and RD females and HFD females ($p < 0.0001$). Data are mean ± SEM; two-way ANOVA with Tukey's post hoc test.

Conclusion

- Chronic HFD consumption promotes metabolic dysfunction and impairs cognitive function in a sex-dependent manner, with males displaying greater vulnerability than females.
- HFD-fed males exhibited greater glucose intolerance, reduced cerebral perfusion, and impaired cognitive performance compared to females.
- These findings suggest that males are more vulnerable to the detrimental cerebrovascular and cognitive effects of chronic HFD consumption, highlighting a potential link between metabolic dysregulation and cognitive decline in CMD.