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**"High-fat diet induces sex-specific cognitive dysfunction in mice."**

BACKGROUND: 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. Given this connection, we aim to investigate the link between chronic HFD consumption and associated cognitive impairment. 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 phenotype.

METHODS: Three-month-old male and female C57BL/6J mice were fed a 60% kcal HFD for six months to induce the CMD phenotype, while RD groups received standard chow. To assess metabolic parameters, body weights were recorded weekly, and a glucose tolerance test (GTT) was performed for both groups. Cognitive performance was assessed using the Y-maze task (working memory), and cerebral perfusion was evaluated using laser speckle contrast imaging.

RESULTS: All mice fed HFD developed significantly greater body weight compared to RD-fed mice by the start of experiments with males displaying greater weight than females (>35 g for males and >30 g for females). In addition, GTT data showed that HFD-fed mice had significantly reduced glucose tolerance compared to RD mice. Results of the Y-maze task revealed that HFD-fed males exhibited significantly reduced percent spontaneous alternation ($p < 0.05$) and correct alternation ($p < 0.05$) compared to RD-fed males. Additionally, total arm entries did not significantly differ between the two male groups, suggesting preserved locomotor function. In contrast, HFD-fed females performed similarly to RD-fed females in the Y-maze task, though they displayed increased total arm entries ($p < 0.05$). Comparisons between sexes revealed that HFD-fed males exhibited significantly lower correct alternation ($p < 0.05$) and a reduced spontaneous alternation relative to HFD-fed females, though not significant ($p = 0.0985$). Laser speckle imaging showed significantly reduced cerebral perfusion in HFD mice compared to RD mice, with a more profound effect seen in males compared to females in both diet groups ($p < 0.05$).

CONCLUSION: Chronic HFD consumption promotes metabolic dysfunction and impairs cognitive function in a sex-dependent manner, with males displaying greater vulnerability than females, possibly due to the development of more severe CMD. Reduced cerebral perfusion may be a major contributor to these sex-specific cognitive deficits. Ongoing metabolic and cognitive studies will further define the mechanisms underlying CMD-induced cognitive dysfunction.