CHRD 2021: Abstract & Poster Submission Form

Submitter Name

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Research Category:

- ◉ Basic Science
- ○ Clinical
- ○ Community Health / Policy

What was your role in the project?

- ☑ Design
- ☑ Perform Experiments
- ☑ Analyze Data
- ☑ Write Abstract
- ☐

Presenter Status:

- ○ Undergraduate Students
- ○ Masters Student
- ◉ PhD Student
- ○ Post-Doctoral Fellows
- ○ Residents
- ○ Non-Trainee

Title

Does the HNF-1aG319S variant confer a metabolic advantage to a traditional First Nations lifestyle but promote youth-onset type 2 diabetes under modern dietary conditions?

Background

Genetic testing in Anishininew communities in central Canada led to the discovery of the HNF-1aG319S variant, which may contribute to youth-onset T2D. HNF-1a is a transcription factor that controls glucose and lipid regulation in the pancreas and liver; however, it is unclear how the G319S variant influences these pathways. Given the metabolic demand associated with traditional lifestyle practices in Northern Manitoba, the G319S variant may instead confer an advantage to prolonged fasting and/or very low carbohydrate intake.

Objective

In this study, we examine the impact of prolonged fasting on glucose and lipid metabolism on mice that express the G319S variant.

Methods

CRISPR-Cas9 was used to knock the G319S variant into mice. 3-month-old male and female mice with all 3 genotypes (GG, GS and SS) were divided into 2 groups: non-fasted (NF) and fasted for 24hr to assess blood glucose (BG) and ketones (BK). Livers were collected for gene expression, triglyceride and glycogen contents. Islets were isolated to assess insulin secretion capacity and insulin content.

Results

In female mice, the G319S variant promoted a trend towards increased blood ketones after fasting, evidenced by increased ketogenic gene expression, and increased liver triglycerides ($P<0.01$). In male mice, G319S variant led to decreased blood glucose ($P<0.0001$). Finally, insulin secretion is increased in G/S mice under low glucose conditions ($P<0.05$).

Conclusion

The G319S variant under fasting conditions appears to alter pancreas and liver metabolism to promote ketogenesis in female mice and decrease blood glucose in male mice. This data suggest that the G319S variant may confer a metabolic advantage during prolonged fasting and that a therapeutic fasting protocol may be an intervention to reduce blood glucose in T2D patients who carry this variant.

Authors

- For each author, please click "**[+] Add Item**" and provide the author's information

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