CHRD 2022: Abstract & Poster Submission Form

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Presenter Status

- ○ Undergraduate Students
- ○ Masters Student
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- ○ Non-Trainee

Research Category

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

Role in the project

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

Title

Investigating the effect of the HNF-1a G319S variant on liver and pancreas function under different physiological states

Background

Genetic testing in Anishininew communities in Canada led to the discovery of a variant in the HNF-1a gene (G319S), which strongly associates with youth-onset type 2 diabetes (T2D). HNF-1a regulates the expression of key genes in both the liver and pancreas. Genetic variants are relatively stable, and T2D only began to emerge in Indigenous communities recently. Given the metabolic demand associated with traditional lifestyle practices in central Canada, we hypothesize that the G319S variant may have conferred advantages to prolonged fasting.

Objective

To investigate the impact of prolonged fasting in G319S expressing mice compared to control mice

Methods

CRISPR/Cas9 were used to knock in the G319S variant in C57BL/6 mice, yielding wildtype (G/G), heterozygous (G/S), and homozygous (S/S) mice. At 3 months, mice were sacrificed either under ad libitum condition or after 24 hours fasting, and liver collected gene expression and triglyceride content assessments. Islets were isolated to assess insulin secretion capacity and pancreatic sections were used to asses structure and ultrastructural changes by microscopy.

Results

Liver triglycerides were significantly reduced in G/S mice compared to wildtype G/G (p=0.0397). Additionally, G/S mice showed decreased expression of insulin regulated genes. After a prolonged fast, blood glucose was lower in G/S (P=<0.0001) and S/S (P=0.0385) mice compared to G/G, which was accompanied by a trend towards increased blood ketones. Electron microscopy revealed an increased percentage of immature insulin granules in male S/S compared to G/G (p=0.0157).

Conclusion

The G319S variant alters fatty acid and glucose metabolism in the liver as there is a shift toward ketogenesis and a propensity toward insulin depletion in the islets, which may indicate that the G319S variant provides a metabolic advantage during extended periods of fasting.

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Authors

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