CHRD 2022: Abstract & Poster Submission Form

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

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

Role in the project
- ☑ Design
- ☑ Perform Experiments
- ☑ Analyze Data
- ☑ Write Abstract
- ☐

Title
A short-term high-fat, low-carbohydrate diet mitigates glucose intolerance and impaired insulin secretion in mice expressing the HNF-1αG319S variant

Background

40% of First Nations youth with type 2 diabetes (T2D) in Manitoba carry a variant in the HNF-1α gene (HNF-1αG319S). The G319S variant is thought to drive pancreatic β-cell dysfunction; however, youth-onset T2D is a relatively recent phenomenon. We hypothesize the G319S variant impairs insulin secretion when exposed to dietary carbohydrate stress but is protective when consuming traditional off-the-land foods that are rich in fat and protein.

Objective

In the context of colonial impacts on traditional food systems, we aim to define how the HNF-1αG319S variant interacts with diet to influence whole-body metabolism and nutrient-induced insulin secretion in a novel mouse model.

Methods

CRISPR/Cas9 was used to knock-in the G>A.955 substitution into C57/BL6 mice. Mice were weaned onto (1) a high-fat, low-carbohydrate (HFLC) diet reflecting off-the-land foods, or (2) a high-fat, high-carbohydrate (HFHC) diet reflecting present-day dietary patterns. Glucose and pyruvate tolerance were assessed prior to isolation of pancreatic islets to measure glucose-stimulated insulin secretion (GSIS), gene expression, or respiration.

Results

A HFHC diet induced glucose intolerance, fasting hyperinsulinemia, unrestrained endogenous glucose production, and attenuated GSIS in G319S-expressing female mice between 3- and 6-months-of-age, pointing to dysregulated glucose homeostasis. Conversely, the HFLC diet prevented glucose intolerance in G319S-expressing female mice via the suppression of endogenous glucose production. In isolated islets, fatty acid oxidation was increased 2-fold, and gene expression changes supported a metabolic switch toward fat oxidation that normalized insulin secretion.

Conclusion

In support of our hypothesis, a HFHC diet accelerated metabolic dysfunction in G319S-expressing mice. This was most prominent in females, consistent with the female predominance of youth-onset T2D. Conversely, aligning dietary fat with the observed shift in metabolism using a short-term HFLC diet prevented metabolic dysfunction in G319S carriers. These mechanistic and metabolic observations lend support to the previously established role of traditional foods in protecting against T2D within First Nations communities.

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