CHRD 2021: Abstract & Poster Submission Form

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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

The HNF-1αG319S variant shifts β-cell metabolism towards fat oxidation in MIN6 β-cells and mouse islets

Background

40% of Indigenous youth with type 2 diabetes (T2D) in Manitoba harbour a variant in the HNF-1α gene. The G319S variant is thought to drive pancreatic β-cell dysfunction; however, youth-onset T2D is a relatively recent phenomenon.

Objective

We hypothesize the G319S variant impairs β-cell insulin secretion when exposed to dietary carbohydrate stress, but is protective in the context of traditional foods rich in fat and protein.

Methods

CRISPR/Cas9 was used to knock-in the G>A.955 substitution into MIN6 β-cells (G319S-MIN6) and C57/BL6 mice (male and female). Mice were weaned onto (1) standard chow, (2) a “traditional” high-fat, low-carbohydrate (HFLC) diet, or (3) a “present-day” high-fat, high-carbohydrate (HFHC) diet for 12 or 24 weeks. β-cell function was assessed by glucose-stimulated insulin secretion (GSIS) and oxygen consumption rates for glucose or palmitate metabolism.

Results

In the absence of dietary manipulation, a consistent reduction (>2.8-fold) in basal insulin secretion was observed in G319S-MIN6 and islets from G319S-expressing male mice. The suppression of basal insulin may be driven by increased fatty-acid β-oxidation (1.5-fold), which also protects G319S-MIN6 from palmitate-induced impairments in GSIS. Given this propensity for fatty-acid metabolism, G319S-expressing mice retained both glucose tolerance and GSIS when fed a HFLC diet that otherwise impaired wildtype mice at 12-weeks-of-age. Conversely, a HFHC diet elevated weight gain and impaired GSIS in G319-expressing mice at 24 weeks-of-age.

Conclusion

The G319S variant appears to shift β-cell metabolism towards fat oxidation which may suppress plasma insulin and reduce systemic glucose utilization. To align nutritional intake with this metabolic shift, the consumption of a HFLC diet appears to normalize insulin secretion and glucose tolerance in G319S carriers, although studies to assess long-term effects are underway. Conversely, the HFHC diet worsens metabolic outcomes across genotypes. These studies may inform future nutritional interventions for children with T2D, while ultimately supporting community efforts to access traditional foods.

Authors

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