Glucagon-like Peptide-1 Promotes Beta Cell Proliferation and Improves Glycemic Control in a Murine Model of Neonatal Diabetes

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Abstract

Glucagon-like peptide-1 (GLP-1) has been shown to potentiate insulin secretion, promote beta cell proliferation, and reduce apoptosis. To test the hypothesis that GLP-1 would preserve beta cell function and improve glycemic control in a murine model of neonatal diabetes, we examined the effects of a GLP-1 agonist (exendin-4) on Akita mice, which are characterized by severe and progressive hyperglycemia. Upon weaning, wild type and Akita littermates were given daily intraperitoneal injections of exendin-4 or PBS for a four-week period. Random blood glucose (BG) was measured twice per week, and fasting BG, plasma insulin, and plasma glucagon were measured at the end of the treatment period following a six-hour fast. In pancreatic cryosections, beta cell proliferation was assessed by Ki67 labeling and apoptosis by TUNEL staining. Prior to treatment, there was no significant difference in BG between mice assigned to receive control vs. GLP-1. Three to four days after initiation of treatment, BG further increased in the control group but was reduced in GLP-1 treated mice. After four weeks of treatment, the random and fasting BG were lower in the GLP-1 treated group. GLP-1 treated mice had higher fasting plasma insulin (corrected for glucose) than the control group, but fasting glucagon levels were similar. Beta cell proliferation, but not apoptosis, was greater in the GLP-1 treated group. The abnormal islet morphology that characterizes the Akita mouse was not improved by GLP-1 treatment. The initial group. The abnormal islet morphology that characterizes the Akita mouse was not improved by GLP-1 treatment. The initial

Hypothesis

- GLP-1 will preserve beta cell mass in Akita mice via promoting beta cell proliferation and inhibiting beta cell apoptosis.

Methods

- Experimental groups:
  - WT PBS (Control)
  - WT GLP-1 Injections
  - WT GLP-1 Pump
  - Akita PBS (Control)
  - Akita GLP-1 Injections
  - Akita GLP-1 Pump

- Variables measured during the treatment period:
  - Body weight
  - Random and fasting blood glucose
  - Fasting plasma insulin and glucagon
  - Immunohistochemical staining on cryosections:
    - Insulin & Glucagon (beta:alpha cell ratio)
    - Insulin & Ki67 (beta cell proliferation)
    - Insulin & TUNEL (beta cell apoptosis)

Results

- GLP-1 promoted an initial reduction in blood glucose in WT and Akita mice. Random blood glucose levels remained lower in WT (A) and Akita mice (B) treated with GLP-1. Akita mice treated with GLP-1 also had lower fasting glucose (C) and higher fasting insulin levels (corrected for glucose).

- Akita islets had more proliferating beta cells than WT islets at baseline. GLP-1 treatment increased proliferation rates in both WT and Akita groups but had no effect on apoptosis.

- GLP-1 did not improve the abnormal alpha cell topography and had no effect on fasting plasma glucagon levels in WT or Akita mice.

Summary

- Mice treated with GLP-1 had an initial reduction in blood glucose and body weight. Blood glucose, but not body weight, remained decreased in these mice.
- Mice treated with GLP-1 had higher fasting insulin levels but no difference in fasting glucagon levels.
- GLP-1 treatment increased beta cell proliferation in WT and Akita mice but had no effect on apoptosis.

Conclusions

- GLP-1 exerts both acute and chronic effects that improve glycemic control in Akita mice. The mechanism appears to involve stimulation of insulin secretion and beta cell proliferation.
- These findings suggest some therapeutic benefit of a GLP-1 agonist in preserving beta cell function and reducing hyperglycemia in neonatal diabetes.

Background

- The Akita mouse:
  - contains a missense mutation in the Insulin 2 gene
  - produces misfolded, nonfunctional insulin
  - severe hyperglycemia by 2-3 weeks old
  - increasing hyperglycemia with age due to ER stress

- Glucagon-like Peptide-1 (GLP-1):
  - hormone secreted in response to oral glucose
  - acutely, increases insulin secretion, decreases glucagon secretion, and promotes satiety
  - chronically, may preserve beta cell mass in mice by promoting beta cell proliferation and inhibiting beta cell apoptosis

- GLP-1 administered by pump promoted weight loss in WT and Akita mice in the first week of treatment, but mice regained weight in the following weeks.

- GLP-1 will preserve beta cell mass in Akita mice via promoting beta cell proliferation and inhibiting beta cell apoptosis.

- These findings suggest some therapeutic benefit of a GLP-1 agonist in preserving beta cell function and reducing hyperglycemia in neonatal diabetes.