Exendin-(9-39): Investigational Drug for the Treatment of Hyperinsulinism

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Disclosure

- Exendin-(9-39) is an investigational product
- Clinical research studies performed under an investigational new drug (IND)
- Currently, exendin-(9-39) is used only under research protocols and as a single dose intravenous dose in the inpatient setting
The Incretin Effect

IN - cre - tin
Intestine Secretion Insulin

N. McIntyre et al. Lancet 2:20-21, 1964
Incretin Hormones

- Gut-derived peptides that increase glucose-stimulated insulin secretion
- Glucose-dependent insulinotropic polypeptide (GIP) first incretin isolated (1970)
- Glucagon-like peptide-1 (GLP-1) more potent and physiologically important incretin
- GIP and GLP-1 account for 90% of incretin response
GLP-1 is Released from Gut Endocrine Cells
Glucose lowering effects of GLP-1

- GLP-1 is secreted in response to ingested nutrients and is a potent stimulator of insulin secretion
- GLP-1 has other glucose lowering effect including: inhibition of glucagon, gastric emptying and appetite
- GLP-1 acts through a receptor in the pancreatic beta cells to stimulate insulin secretion
- Therapies targeting the GLP-1 receptor are now approved for the treatment of type 2 diabetes
Exendin-(9-39)

- Exendin-4 -- Exenatide (Byetta®) is an analog of GLP-1 that stimulates insulin secretion and is approved for type 2 diabetes
- Exendin-(9-39) was derived from exendin-4 but has the opposite effect blocking insulin secretion
- Exendin-(9-39) increases fasting blood glucose in healthy humans and other species

Why Exendin-(9-39)?

- Need for exogenous glucose to maintain euglycemia decreases when babies with hyperinsulinism are kept without food for a few hours.
  - Suggest an enhanced "incretin" effect in hyperinsulinism.

![Graph showing GIR (mg/Kg/min) over time (hr)]
Why Exendin-(9-39)?

- The GLP-1 receptor is constitutively active in pancreatic islets lacking $K_{ATP}$ channels
- Exendin-(9-39) inhibits amino acids-stimulated insulin secretion in human HI islets

Calabria, Li, Gallagher, Stanley, De León. *Diabetes*, 2012
Preclinical proof-of-concept studies with Exendin-(9-39)

- Exendin-(9-39) prevents fasting hypoglycemia in mouse model of $K_{\text{ATP}}$ hyperinsulinism

Pilot Clinical Proof-of-Concept Study

- Pilot study to examine the effect of exendin-(9-39) on fasting blood glucose of subjects with $K_{\text{ATP}}$ Hyperinsulinism

- **Methods:**
  - 9 subjects
  - Randomized, open-label, two-period complete crossover
  - Fasted subjects received an intravenous infusion of exendin-(9-39) (100, 300 and 500 pmol/kg/min) or vehicle for 6 hours in 2 consecutive days (in random order)
  - Primary outcome: Blood glucose levels

www.Clinicaltrials.gov: NCT00571324
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*Dominant
Exendin-(9-39) increases fasting blood glucose

Calabria and De León. Diabetes, 2012
Exendin-(9-39) suppresses plasma insulin

Calabria and De León. *Diabetes*, 2012
GLP-1 Receptor Antagonist Exendin-(9-39) Elevates Fasting Blood Glucose Levels in Congenital Hyperinsulinism Owing to Inactivating Mutations in the ATP-Sensitive K⁺ Channel

Andrew C. Calabria,¹ Changhong Li,¹,² Paul R. Gallagher,³ Charles A. Stanley,¹,² and Diva D. De León¹,²
Summary:

- Exendin-(9-39) blocks the effects of the incretin hormone GLP-1
- In mouse and human $K_{ATP}$ pancreatic islets exendin-(9-39) inhibits insulin secretion
- In children, adolescents and adults with $K_{ATP}$ exendin-(9-39) is well tolerated and increases fasting blood glucose
- Next step – multiple dose study
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