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

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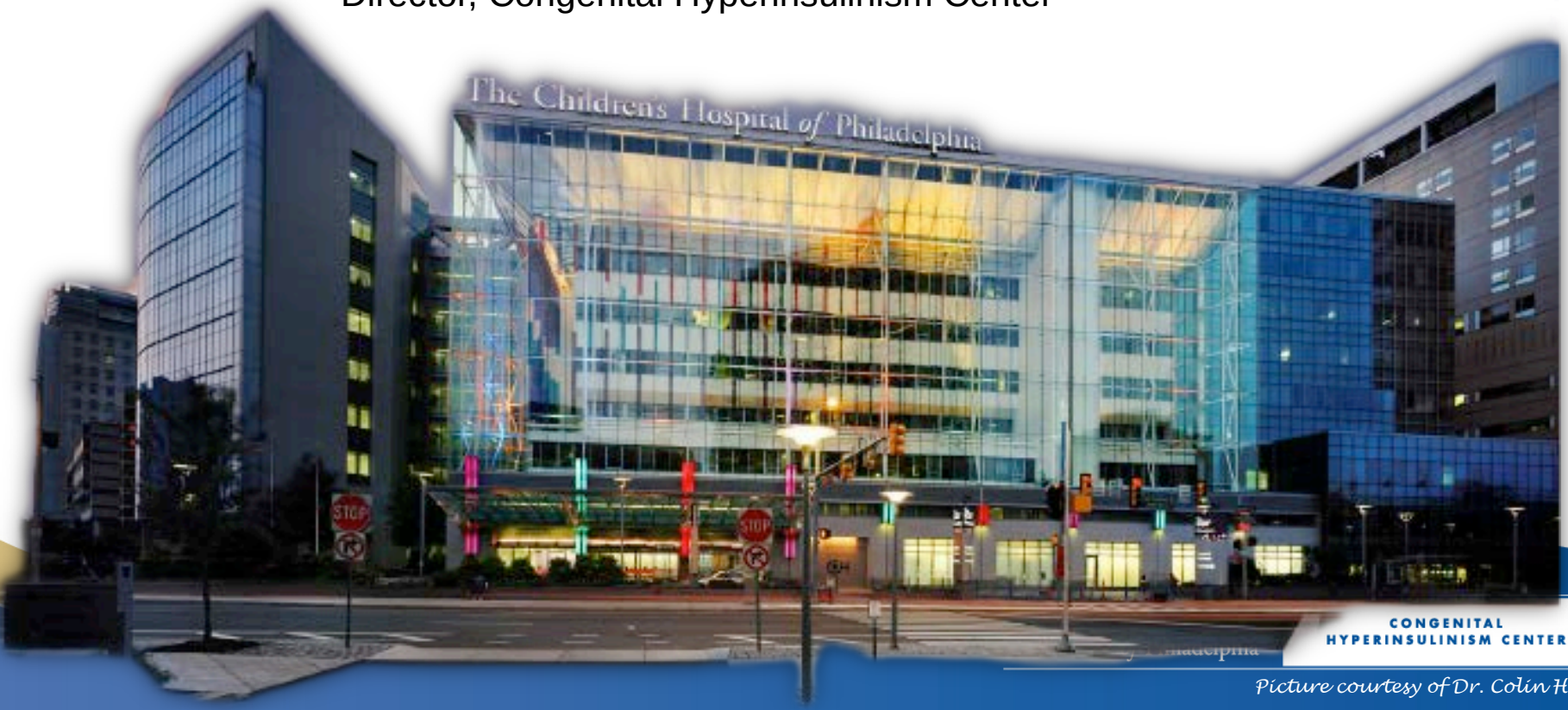


Picture courtesy of Dr. Colin Hawkes

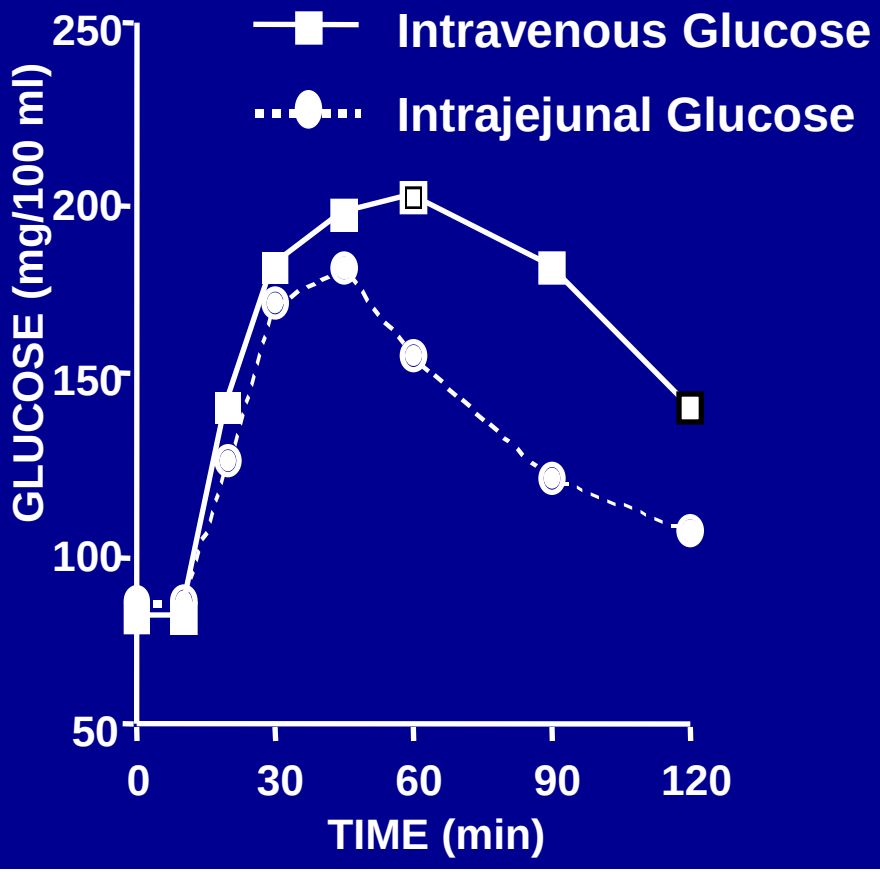
Disclosure

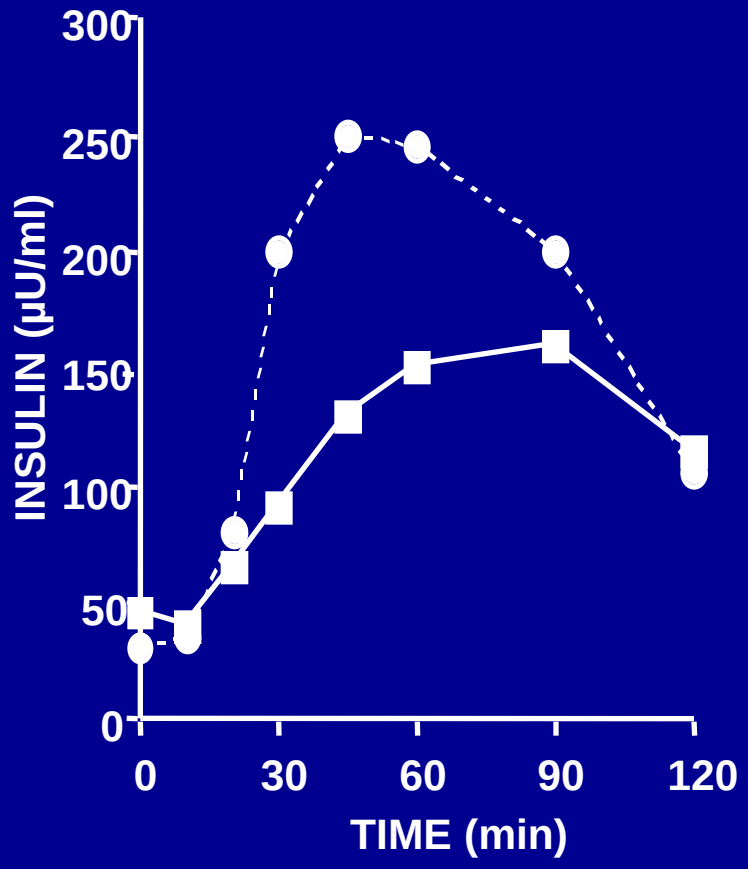
- Exendin-(9-39) is an investigational product
- Clinical research studies performed under an investigational new drug (IND)
- Currently, exendin-(9-39) is used only under research protocols and as a single dose intravenous dose in the inpatient setting

The Incretin Effect

In - cre - tin

Intestine Secretion Insulin



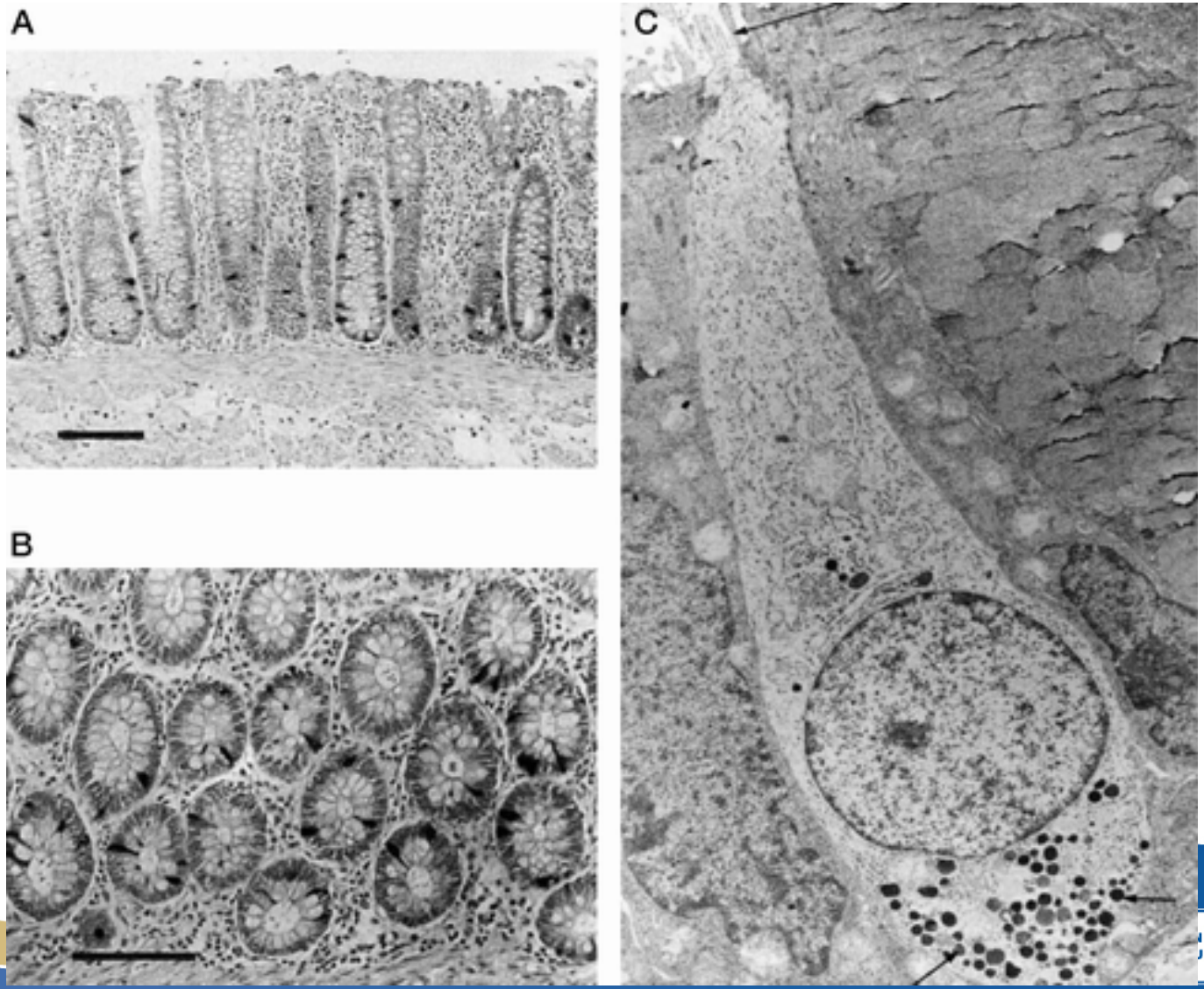


N. McIntyre *et al.* Lancet 2:20-21, 1964

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

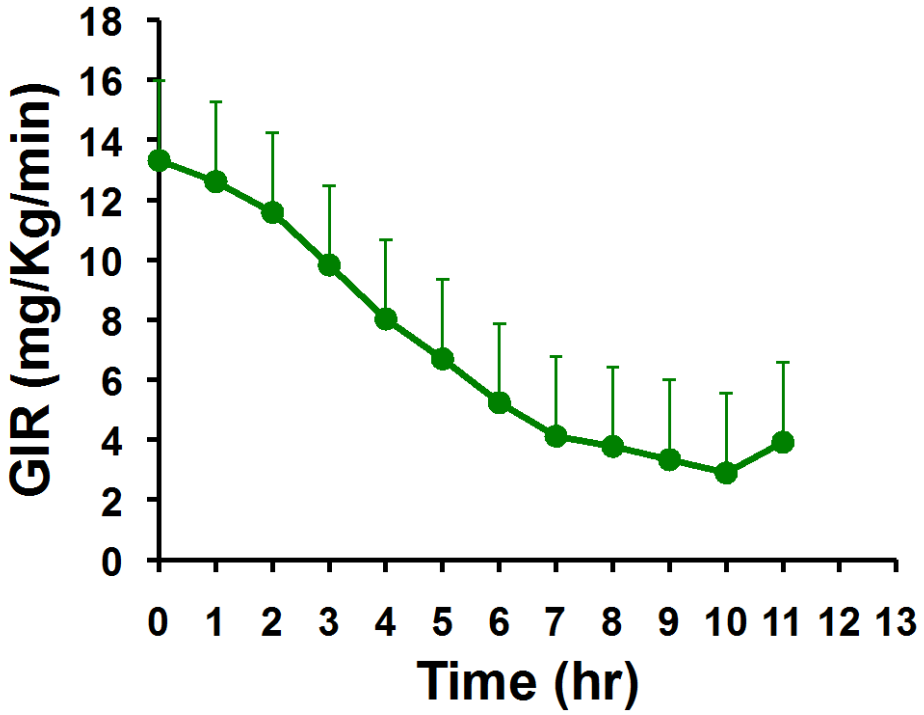
Exendin-(9-39)

- 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

De León, et al. *J Biol Chem,* 2008

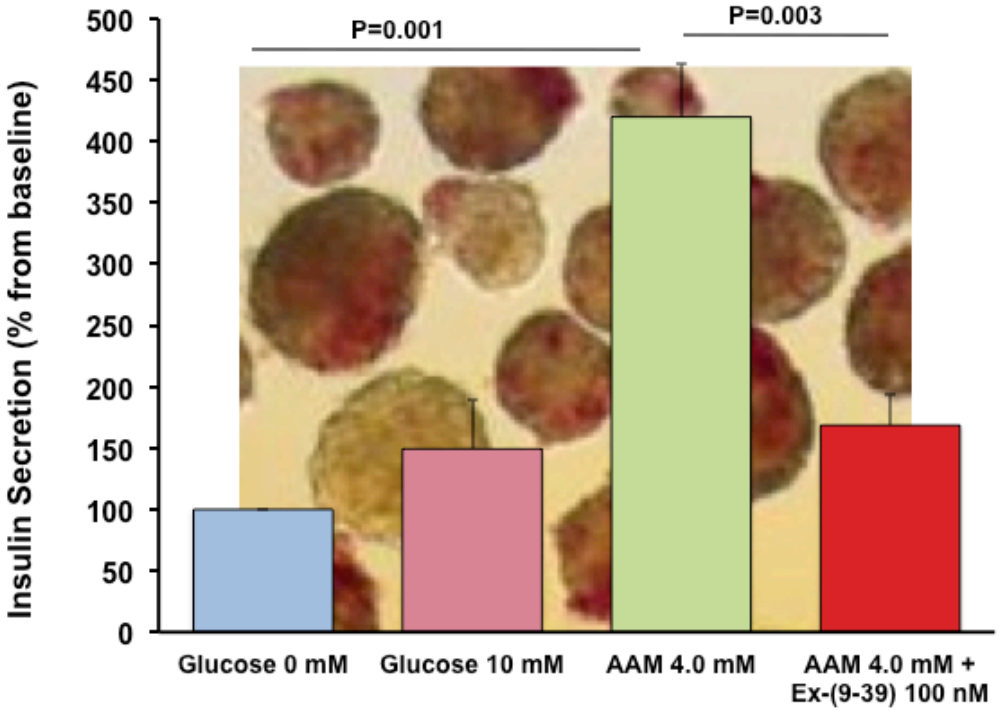
Why Exendin-(9-39)?

- 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



Why Exendin-(9-39)?

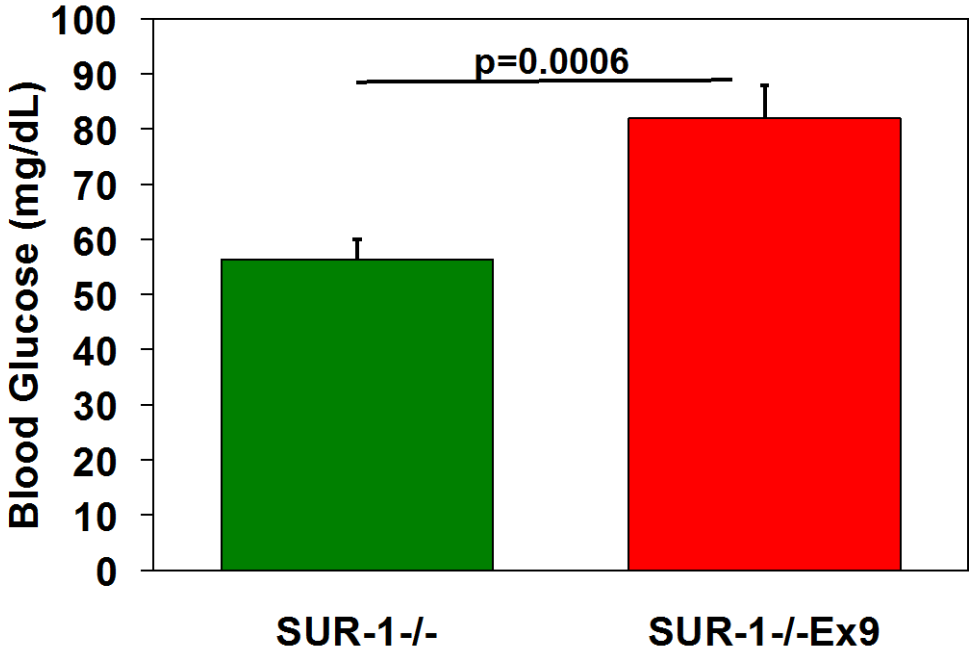
- The GLP-1 receptor is constitutively active in pancreatic islets lacking K_{ATP} channels
- Exendin-(9-39) inhibits amino acids-stimulated insulin secretion in human HI islets



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_{ATP} hyperinsulinism



De León, et al. *J Biol Chem,* 2008

Pilot
Clinical Proof-of-Concept Study

- **Pilot study to examine the effect of exendin-(9-39) on fasting blood glucose of subjects with K_{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

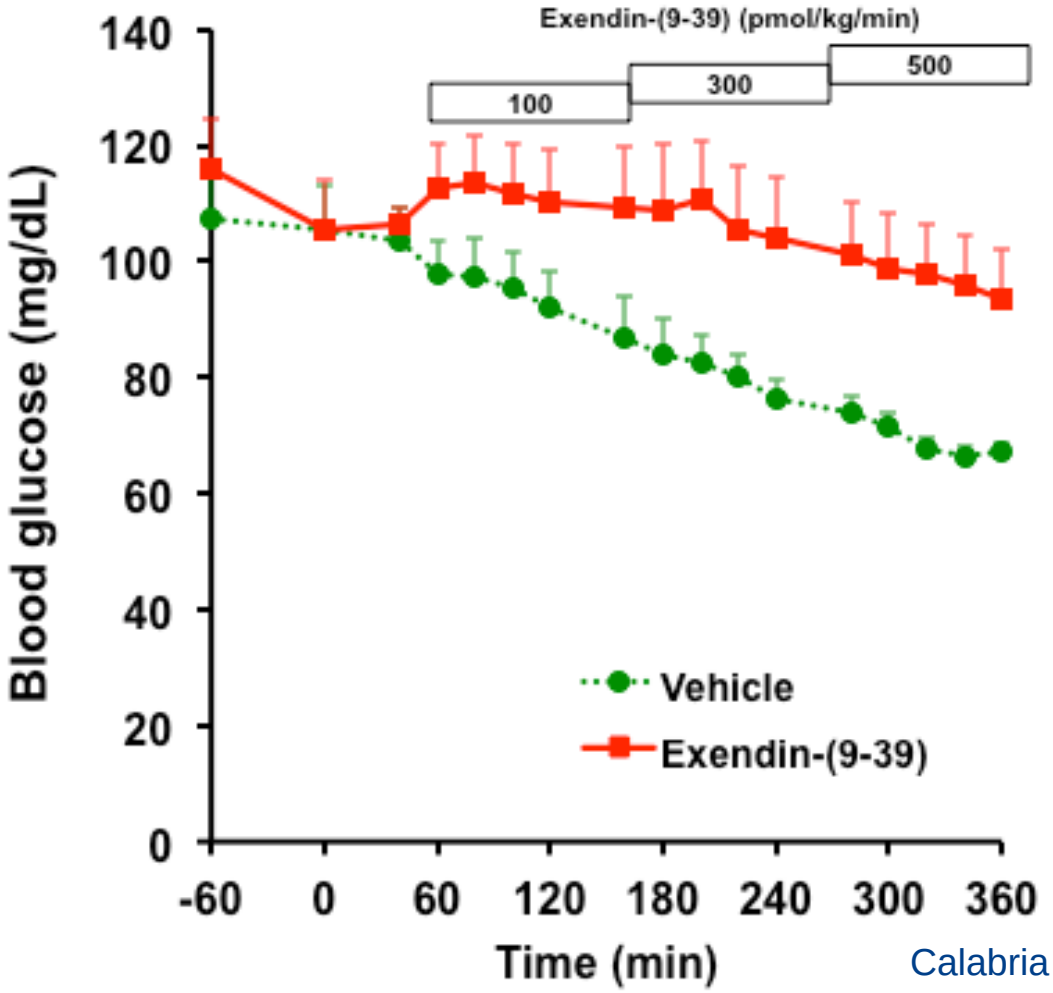
www.Clinicaltrials.gov: NCT00571324

Subject Characteristics

Subject	Age	Gender	Mutation (*ABCC8*)	Pancreatectomy
1	29	F	delF1388 + 3992-9 G>A	85%
2	44	M	delS1387*	None
3	35	M	S408P*	None
4	17	F	3992-9 G>A	95 %
5	15	F	3992-9 G>A	95%
6	18	M	delS1387*	None
7	16	F	delS1387*	None
8	47	F	R1353H*	None
9	37	F	R521Q*	None

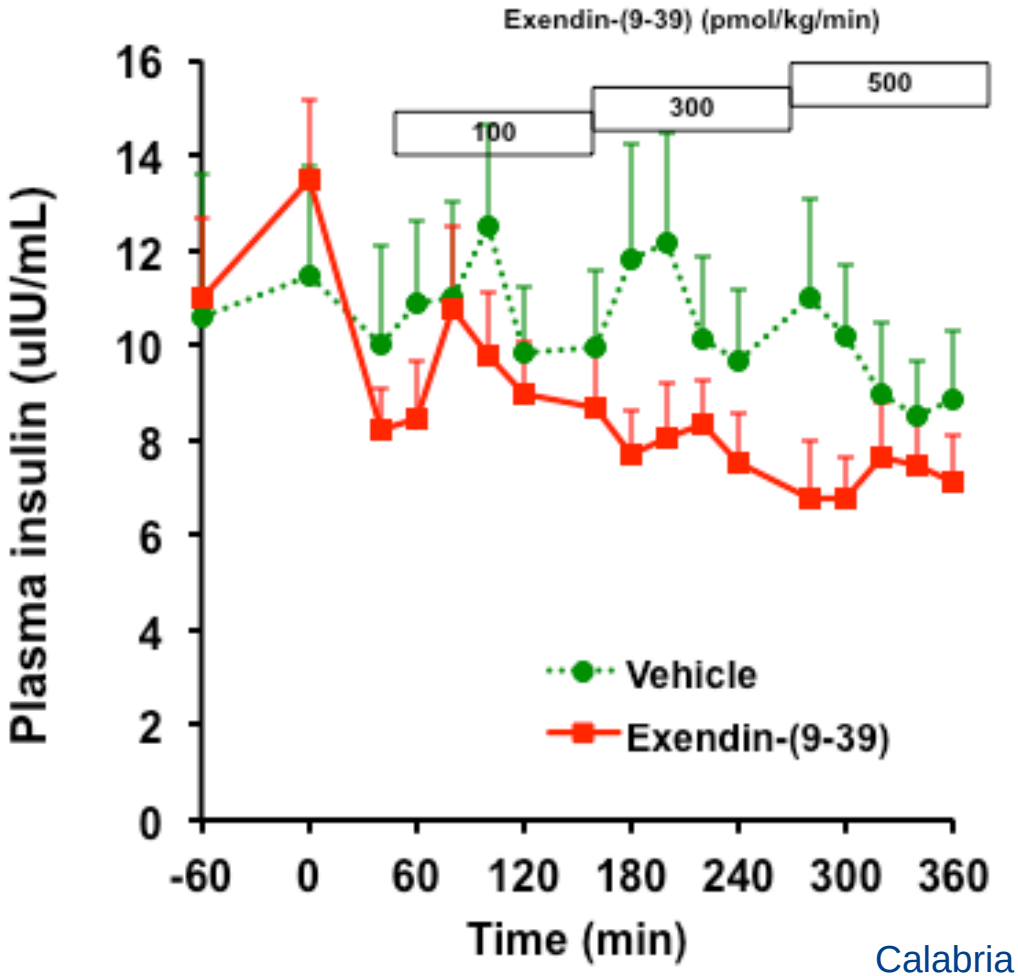
*Dominant

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*

ORIGINAL ARTICLE

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 León[1,2]

Summary:

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

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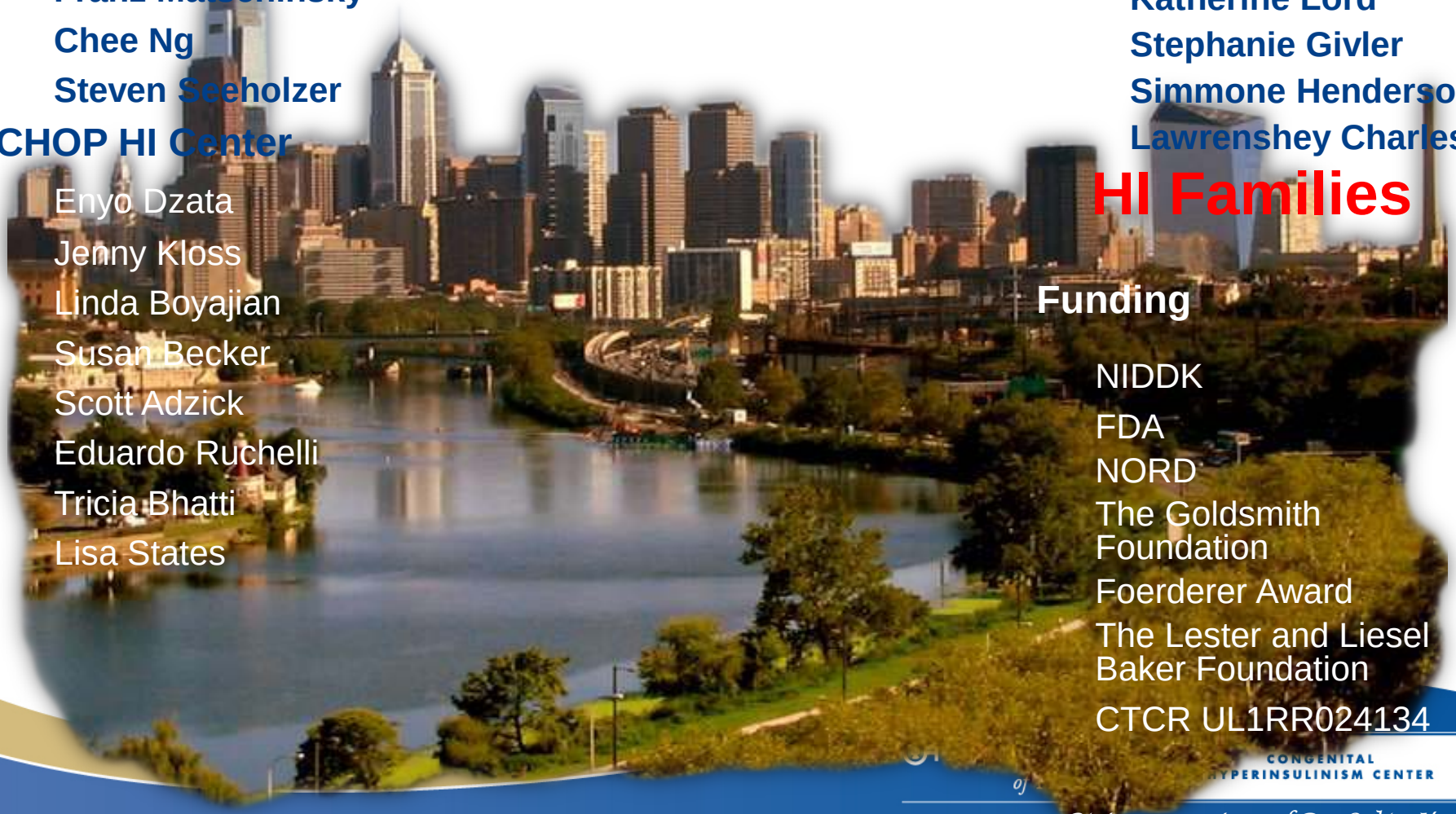

CONGENITAL HYPERINSULINISM CENTER

Picture courtesy of Dr. Colin Hawkes

Congenital Hypoglycemia Disorders: Hyperinsulinism and GSD

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Ruth and Tristram Colket, Jr. Translational Research Building
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