Current Treatment Options and New Treatment Investigations

Diva D. De León-Crutchlow
Director, Congenital Hyperinsulinism Center

Goals of Therapy

- **Immediate:**
  - To promptly restore blood glucose to normal range (> 70 mg/dL)
- **Mid-term:**
  - To identify optimal treatment regimens according to type of hyperinsulinism
  - To maintain normal blood glucose levels while encouraging normal feeding/diet
  - Anticipation and prevention are key elements of intervention and management
- **Long-term:**
  - To prevent neurologic damage
  - To promote normal life and development

Treatment of Hypoglycemia: why is it important?

- **Inadequate cerebral glucose supply during neonatal period leads to serious long-term neurological impairments:**
  - Repeated low glucose in infants is associated with delayed neurological complications Lucas, *BMJ* 1988
  - Range of complications learning disabilities to cerebral palsy and persistent or recurrent seizure disorders, as well as intellectual disabilites of varying degrees

Current Medical Therapies

Diazoxide: *mainstay therapy for HI*

- **How does it work:**
  - Activates the potassium channel via the SUR subunit
  - Not effective in most potassium channel mutations
- **What types of hyperinsulinism can be treated with it:**
  - Hyperinsulinism/hyperammonemia - GDH-HI
  - HNFs hyperinsulinism
  - Glucokinase hyperinsulinism (some cases)
  - SCHAD hyperinsulinism
  - Some dominant K_{ATP} channel mutations

Current Medical Therapies

Diazoxide:

- **Dose:**
  - 5-15 mg/kg/day by mouth
  - Only suspension available in US - capsules
- **Side effects:**
  - Fluid retention (worse in neonates) – use of diuretics
  - Excessive body hair
  - Suppression of appetite
  - Suppression of blood count (less common)

Current Medical Therapies

Octreotide: *second line therapy for HI*

- **How does it work:**
  - Activates potassium channel, affects intracellular translocation of Ca, direct inhibition of insulin secretion
  - Response is good for a couple of days and then wears off
- **What types of hyperinsulinism can be treated with it:**
  - Diazoxide-unresponsive hyperinsulinism

Current Medical Therapies

Octreotide:

- **Dose:**
  - 5-20 mcg/kg/day by subcutaneous injection 2-4 times daily or as continuous intravenous or subcutaneous infusion (pump)
- **Side effects:**
  - Suppression of growth hormone, thyroid hormone or/and cortisol
  - GI side effects: nausea, anorexia, abdominal pain, loose stools, diarrhea
  - Gall stones
  - Necrotizing enterocolitis (1% in a series of 103 children with HI)

Current Medical Therapies

Glucagon:

- **How does it work:**
  - Increases glucose release from the liver
- **Dose:**
  - 1 mg/day continuous intravenous infusion or through subcutaneous pump
  - 1 mg intramuscularly for emergencies
- **Side effects/problems:**
  - Nausea/vomiting
  - Available preparation crystallizes in pump tubing

Current Medical Therapies

Enteral Dextrose:

- **How does it work:**
  - Provides continuous supply of glucose
- **Dose:**
  - Dextrose 10-20% up to 10 mg/kg/min continuously through gastrostomy tube
- **Side effects**
  - Vomiting/reflux
  - Suppression of appetite

Diet in the Management of Hyperinsulinism

- Diet:
  - Frequent high-carbohydrate feedings: formula supplemented with glucose polymer
  - Continuous feedings through nasogastric or gastric tube
  - Cornstarch: slow-release carbohydrate
  - Avoidance of protein-rich meals
- Side effects:
  - Reflux
  - Feeding aversion

Treatment Paradigm

Diagnosis of Hyperinsulinism

Mutation Analysis

Diazoxide Trial: 15 mg/kg/day for 5 days

Diazoxide Responsive

- Blood glucose monitoring at home
- Safety fast once a year

Diazoxide Unresponsive

Octreotide +/- Continuous Enteral Dextrose

response

fail

18FDOPA PET

SURGERY

Diffuse

Focal

Fasting Test

Not Cured

Cured

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New Therapeutic Options

Long acting Somatostatin Analogs:

- **Octreotide LAR: long half-life given IM every 4 weeks**
  - 10 children (age 1.3-8.5 years) transitioned from 3 SQ injections a day (or continuous) to 1 IM injection every 4 weeks for 6 months (Eur J Ped Endocrinol, 2012)
  - Well tolerated
  - Parent's questionnaires of general satisfaction were highly positive while children's QoL evaluation remained unchanged

	Octreotide	Octreotide + Octreotide LAR	Octreotide LAR
Blood glucose < 54 mg/dL	0	11	22
Total measurements of glucose	56	314	812

New Therapeutic Options

Long acting Somatostatin Analogs:

- **Lanreotide (Somatuline Autogel): long half-life given by deep SQ injection every 4 weeks**
  - 2 children age 4 yrs transitioned from short-acting octreotide to once monthly Lanreotide (J Clin Endocrinol Metab, 2011)
  - GOSH series: 8 children (age 3.5-16 yrs) transitioned from octreotide (6) and diazoxide (2) to Lanreotide every 28 days
  - Germany series: 6 children (7 months-4 yrs) mean duration 40.8 months in 3/6 lanreotide raised mean BG and reduced episodes of hypoglycemia

Sirolimus

- mTOR inhibitor
- Constitutive activation of mTOR pathway in hyperinsulinism
- 4 children with diazoxide-unresponsive hyperinsulinism treated with sirolimus
  - 1 with typical diffuse K_{ATP}HI weaned off fluids but required octreotide
  - 3 weaned off all other therapies
- Mechanism unknown
  - ↓ ß-cell replication vs. ↓ insulin signaling
- Non-controlled study
- Safety profile in young children unknown: immunosuppression, effect on growth?

Senniappan, et al. *N Engl J Med,* 2014

Exendin-(9-39)

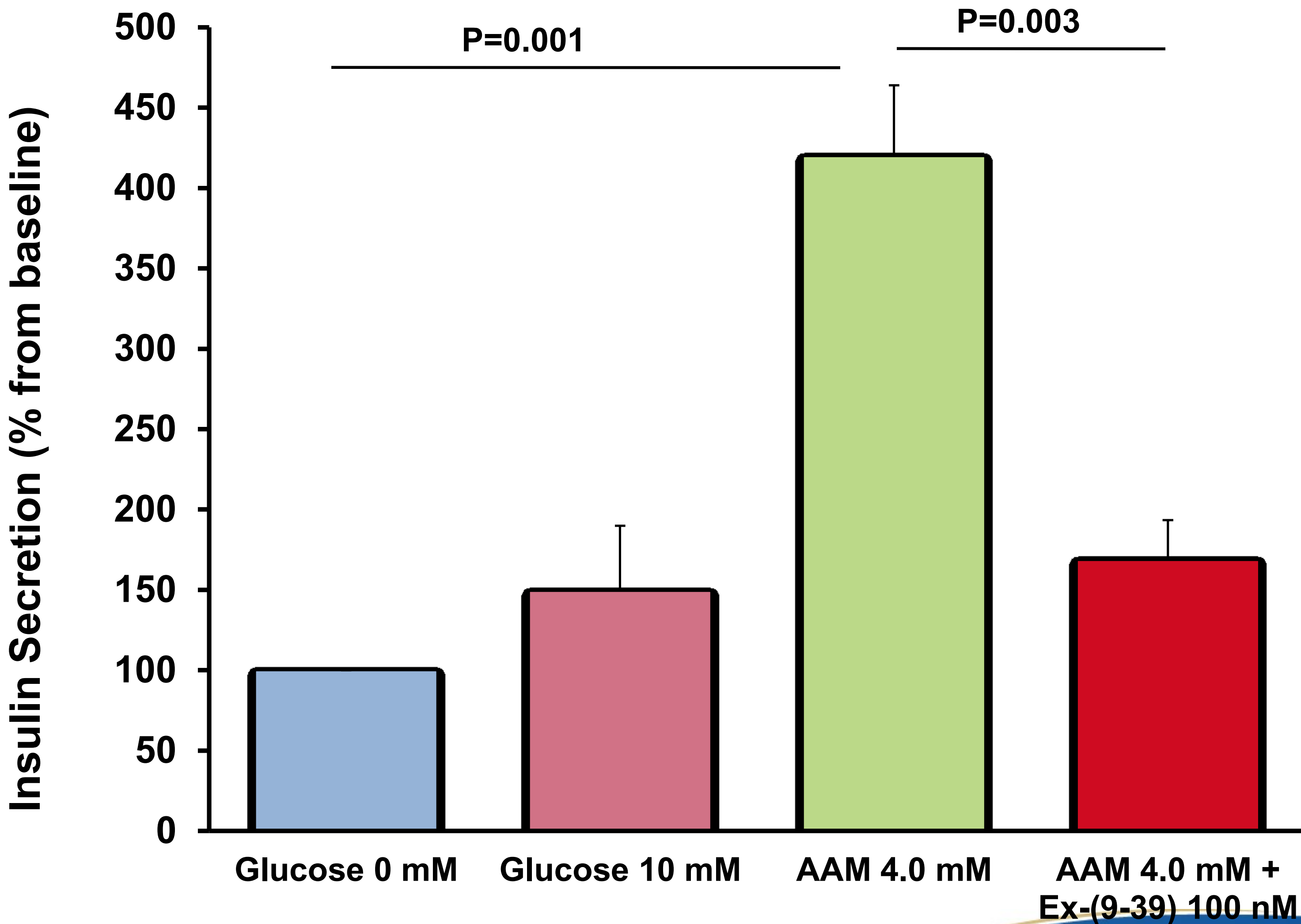
- Specific antagonist of the GLP-1 receptor
- Impairs glucose tolerance in humans and a variety of animal models Goke *JBC*, 1993; Thorens *Diabetes*, 1993
- N-terminus truncation of exendin-4 - - Exenatide (Byetta®) approved for type 2DM
- Inhibits insulin secretion and corrects fasting hypoglycemia in mouse model of K_{ATP} hyperinsulinism

De León, et al. *J Biol Chem*, 2008

Mouse model, subcutaneous infusion exendin-(9-39) for 2 weeks

Suppresses insulin secretion
Corrects fasting hypoglycemia

Exendin-(9-39) inhibits insulin Secretion in K_{ATP}HI Islets



Calabria, Li, Gallagher, Stanley, De León. *Diabetes, 2012*

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Pilot
Proof-of-Concept

- **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

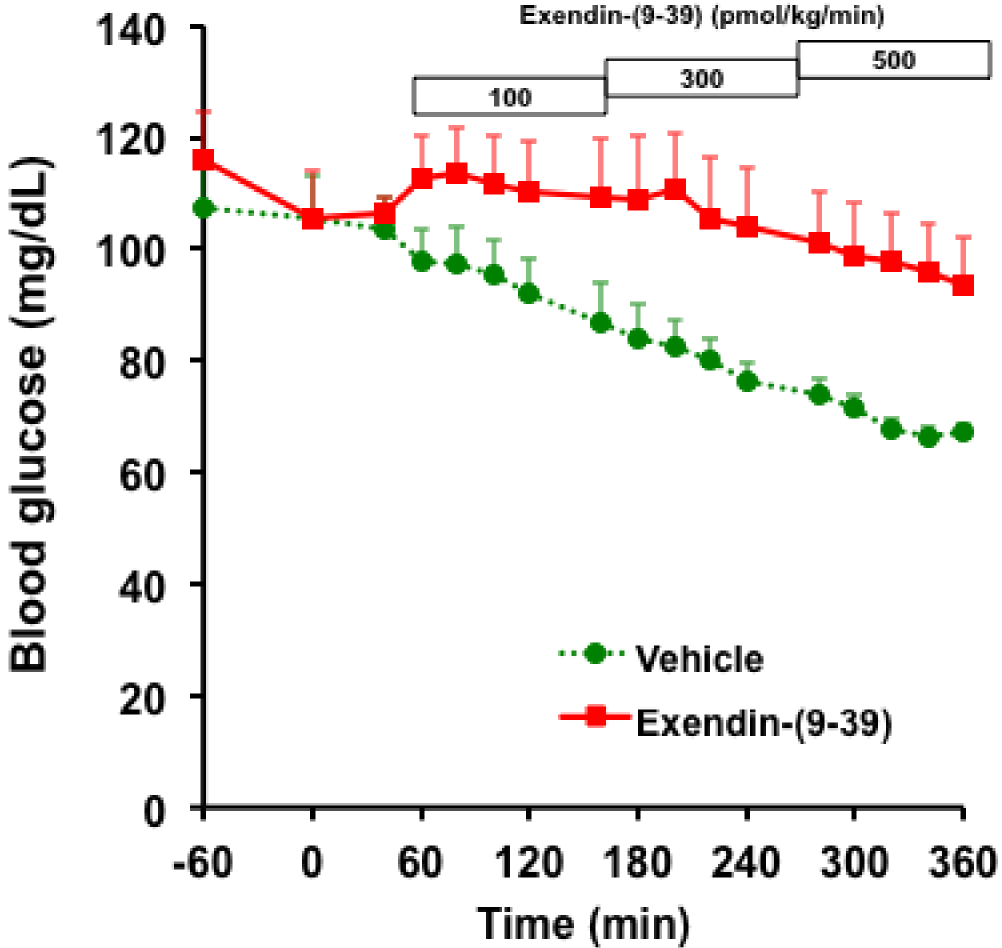
www.Clinicaltrials.gov: NCT00571324

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

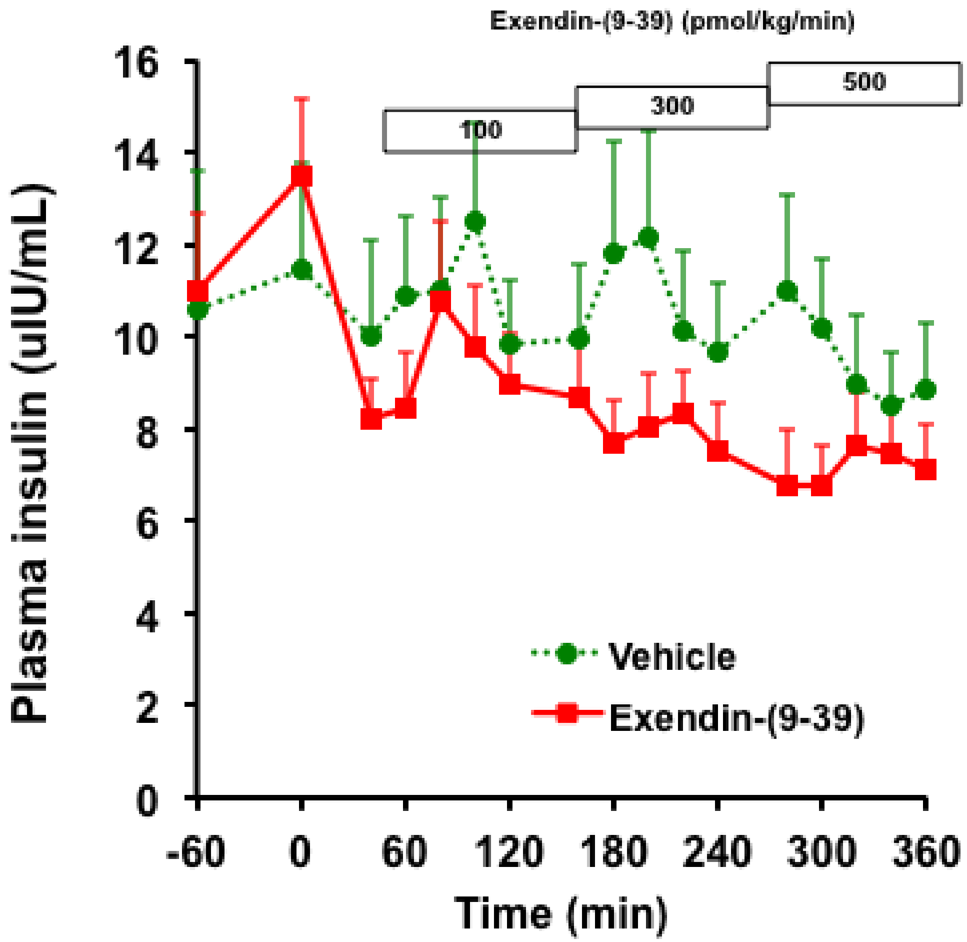
*Dominant

Exendin-(9-39) elevates fasting blood glucose



Calabria and De León. *Diabetes, 2012*

Exendin-(9-39) suppresses plasma insulin



Calabria and De León. *Diabetes, 2012*

Summary/Conclusions

- Medical treatment easy if the hyperinsulinism is diazoxide responsive, more challenging if not responsive
- Treatment decisions should be individualized and well informed
  - Genetics
  - 18-FDOPA PET scan
  - Severity of hyperinsulinism
- Great promise for new therapies in the near future

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