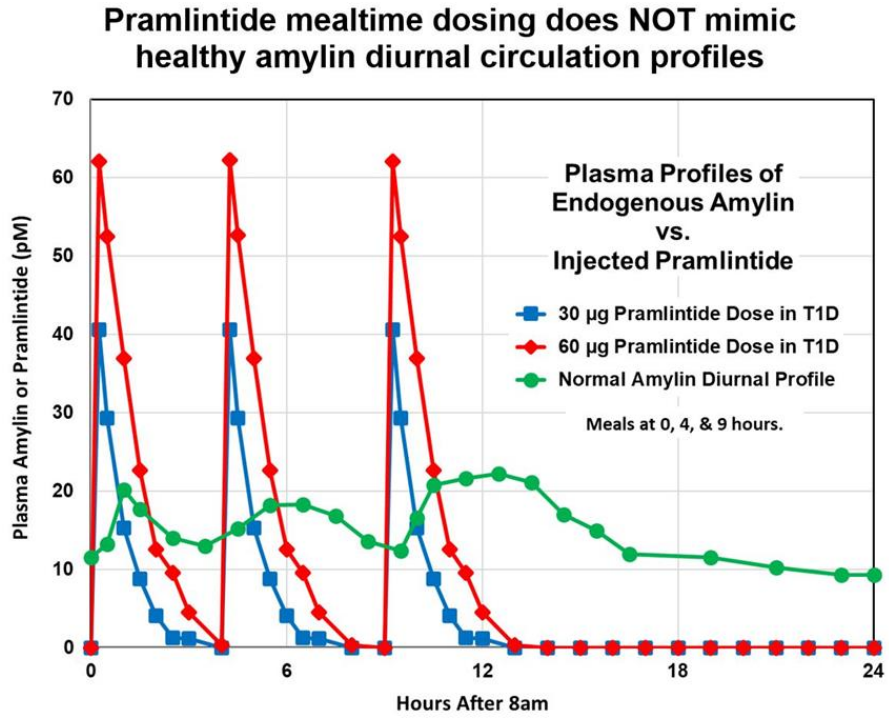
The Amylin Circuit Breaker: Restoring Glucagon Counterregulation in T1D

A novel hypothesis to explain how islet alpha-cells detect changes in blood glucose, and a proposal for a novel amylin/insulin infusion regimen to correct defective glucagon secretion in Type 1 Diabetes.

Note: The data, analyses, and concepts summarized in this presentation are explained, with supporting references, in the longer document of the same title.

Amylin replacement therapy has been disappointing because dosing is all wrong

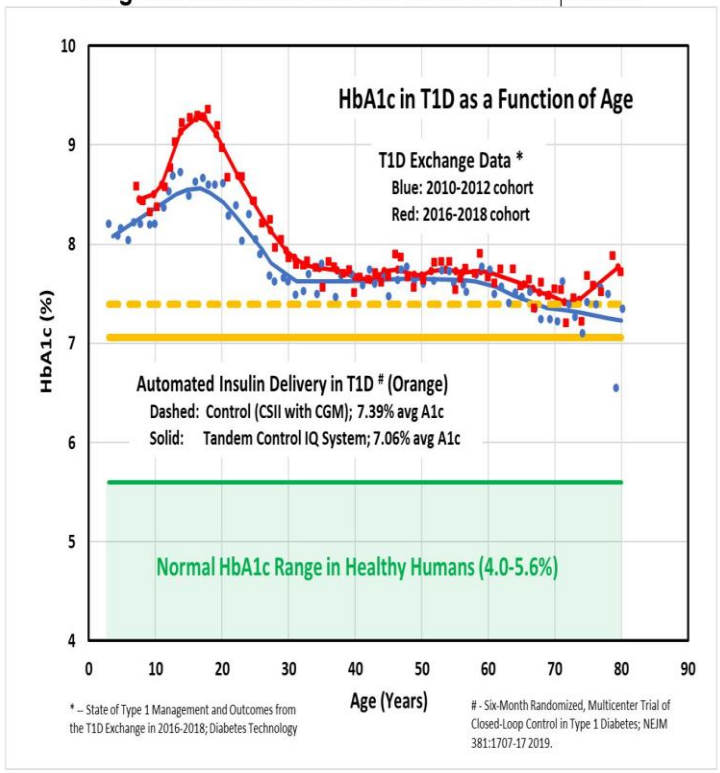
- Mealtime injections are titrated to maximum tolerated dose
- Supraphysiological levels at mealtimes cause nausea
- Clearance between meals eliminates the basal component
- Full benefits of beta-cell hormone replacement are not achieved



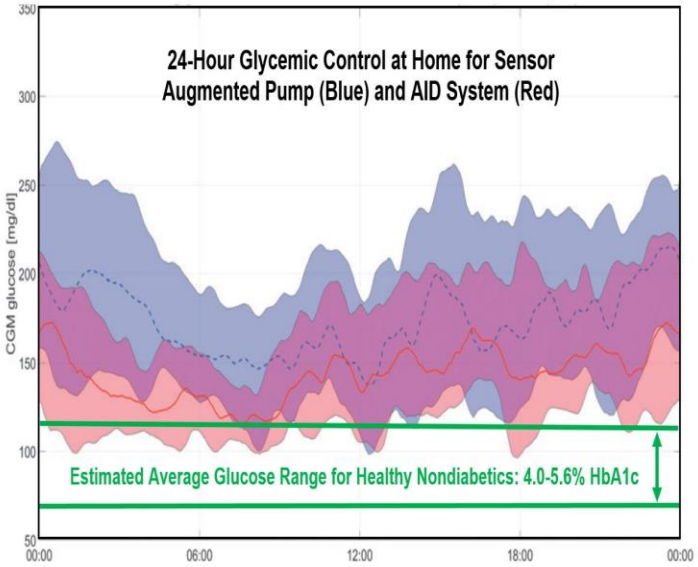
Why is this relevant? Because a breakthrough is still needed for treating Type 1 Diabetes

- HbA1c progress has stalled
- AID systems fail to normalize glucose
- Main barrier: risk of hypoglycemia
- Hypos cause morbidity & mortality

Progress toward normal HbA1c in T1D has stalled



The most advanced AID system does not bring T1D blood glucose values into the healthy range

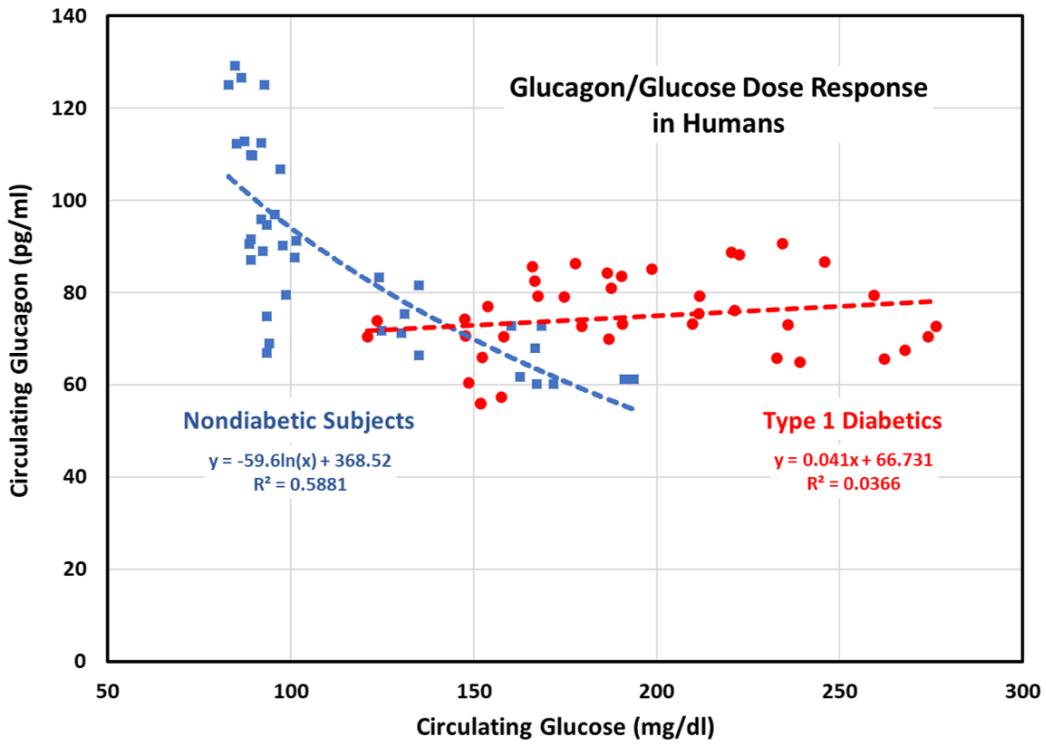


Full-day glycemic control during home use. The red line and shaded area represent Automated Insulin Delivery use, and the blue line and shaded area represent Sensor Augmented Pump use. The shaded area represents the 25th to 75th percentile for glucose values in each group. The center lines (plain and dotted) represent the mean.
Source: Successful at-home use of the Tandem Control-IQ artificial pancreas system in young children during a randomized controlled trial: Diabetes Technology & Therapeutics 21:1-11 2019.

Alpha-cell dysregulation should be the target of the new amylin replacement regimen

- Glucagon response to changes in blood glucose is absent in T1D
- Excessive glucagon secretion amplifies hyperglycemia
- Lack of counterregulation increases the risk of iatrogenic hypoglycemia
- No known adjunctive therapy appears promising
- A new model of alpha-cell sensing should focus on amylin

Type 1 Diabetics have lost glycemic control of glucagon



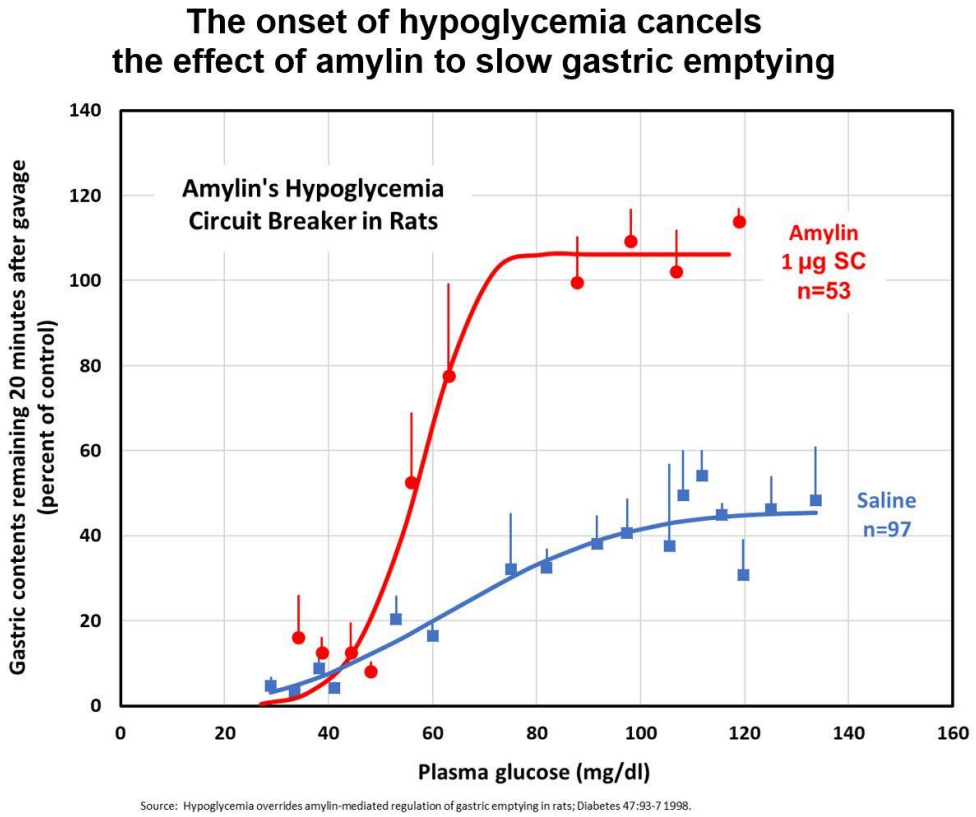
Source: Diurnal pattern to insulin secretion and insulin action in healthy individuals; Diabetes 61:2691-700 2012.

Might the T1D problem be the lack of proper amylin replacement dosing?

- Teleologically, a second amidated peptide hormone secreted by beta-cells must play an important role in glucose homeostasis
- Amylin receptors are in the area postrema, the metabolic control center of the brain
  - Amylin is a neuroendocrine hormone
- Amylin constrains blood glucose influx via alpha-cell secretion, gastric emptying, and satiety, all of which are mediated by the CNS
  - Since Claude Bernard, autonomic activation has been considered a key player in glucose counterregulation
- How could amylin's suppression of alpha-cells lead to an increase in glucagon secretion in response to hypoglycemia?...

Answer: A CNS “circuit-breaker” interrupts amylin’s restraint on blood glucose influx

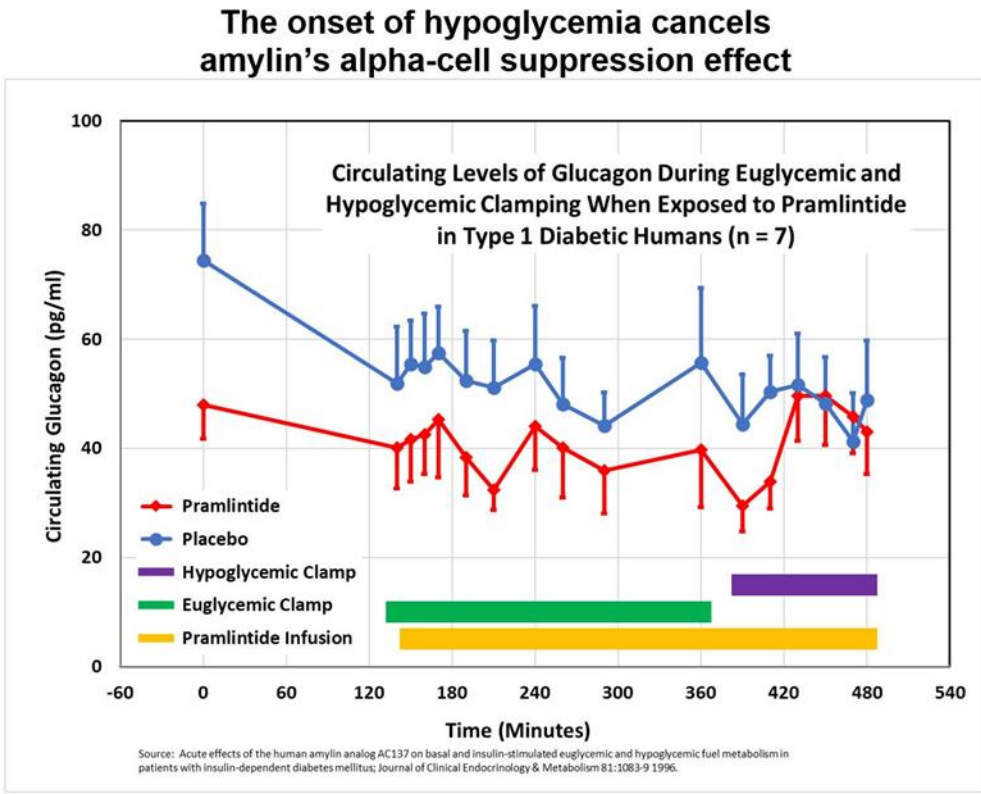
- Hypoglycemia cancels amylin’s slowing of gastric emptying
  - This chart shows gastric contents 20 minutes after gavage in rats injected with either amylin or saline
  - At low blood glucose levels amylin has no effect on gastric emptying
- The onset of hypoglycemia thus accelerates exogenous blood glucose influx from the gut



Source: Hypoglycemia overrides amylin-mediated regulation of gastric emptying in rats; Diabetes 47:93-7 1998.

This circuit-breaker also interrupts tonic inhibition of alpha-cells and causes glucagon to rebound

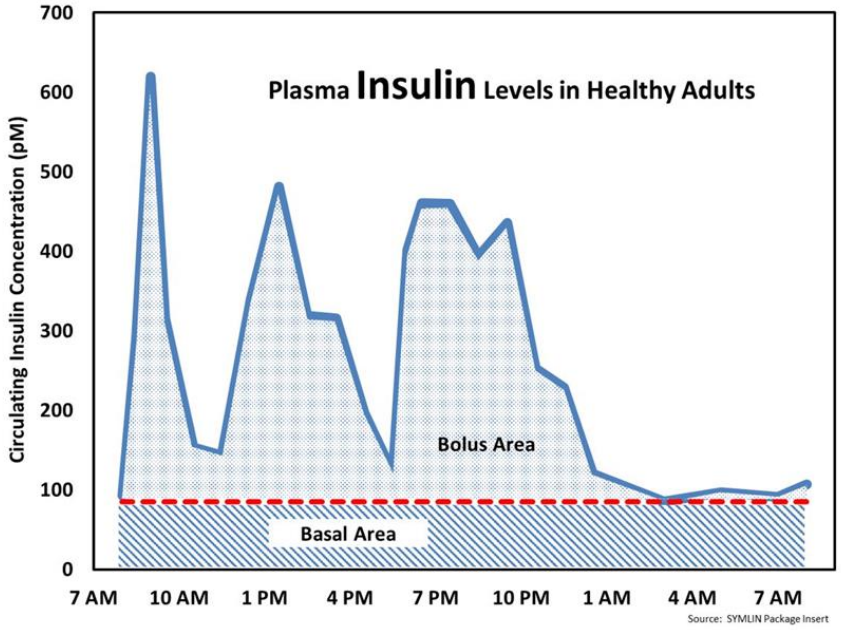
- The onset of hypoglycemia releases glucagon from amylin suppression
  - In this study in T1D subjects…
  - When a euglycemic clamp is replace by a hypoglycemic clamp…
  - Pramlintide suppression of glucagon is terminated
- By overriding the amylin signal, the brain raises blood glucose from two sources:
  - Exogenous from the gut
  - Endogenous from the liver



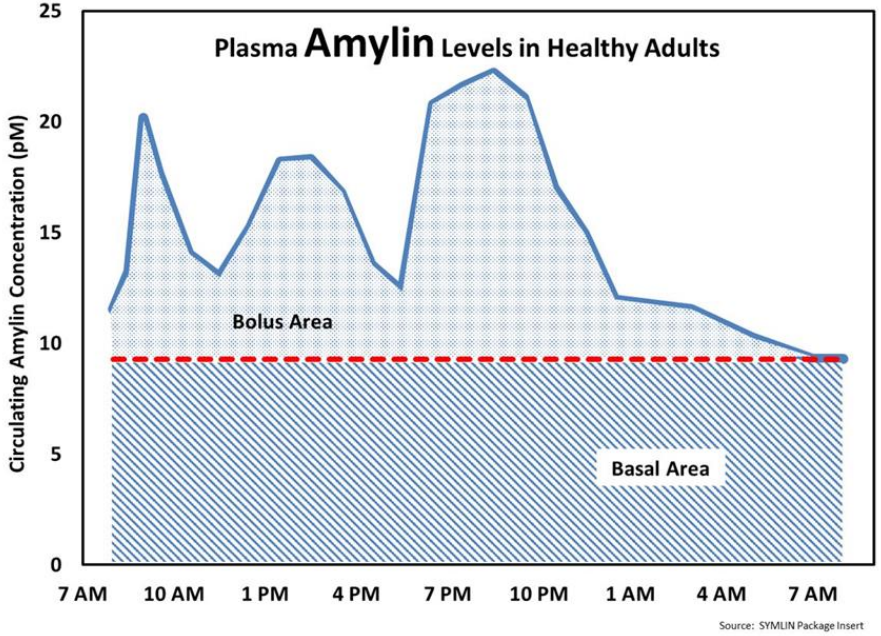
Amylin's diurnal profile is consistent with tonic inhibition of alpha-cells in euglycemia

- Amylin's circulating profile has a large basal component compared to that of insulin, and this would act to inhibit secretion of glucagon

Circulating insulin is dominated by mealtime boluses

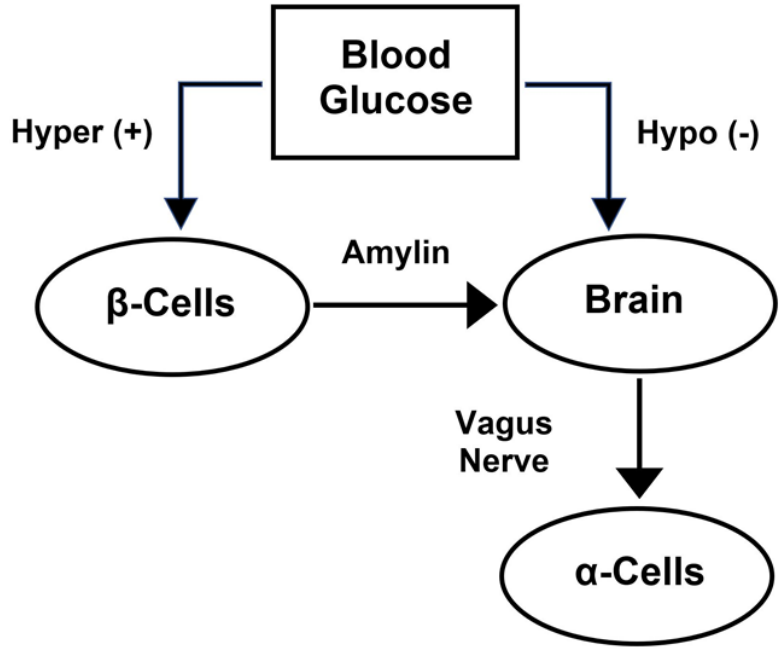


Circulating amylin has a large basal component



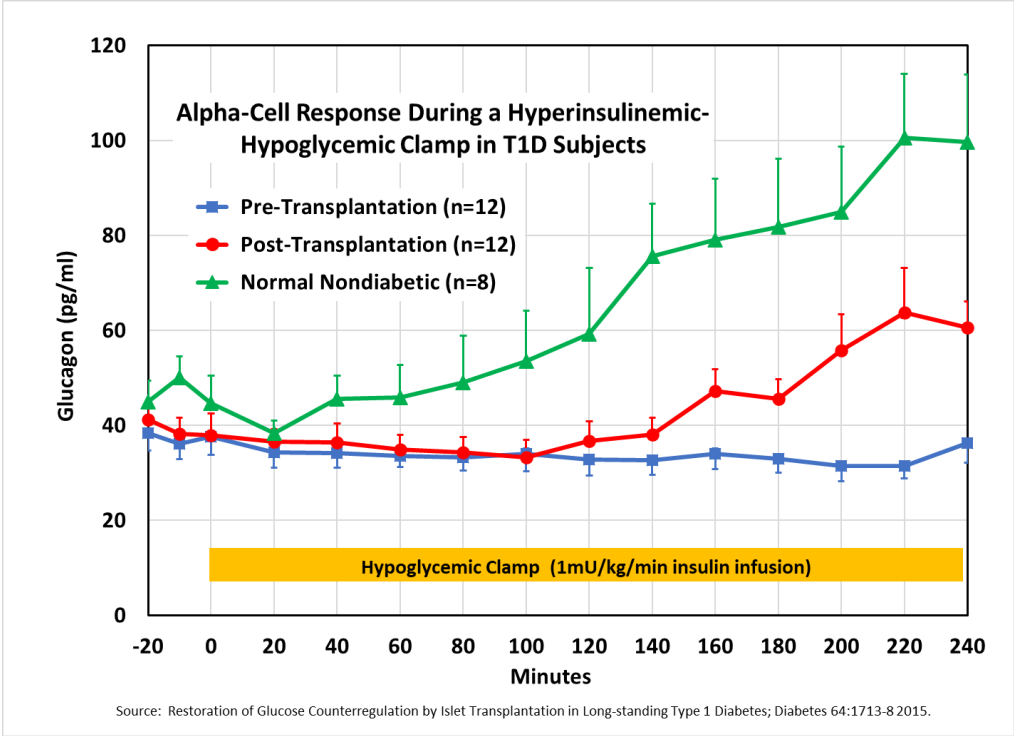
Introducing: The circuit-breaker model of alpha-cell regulation

- Blood glucose sensing is directionally determined
  - Onset of hyperglycemia: beta-cells respond
  - Onset of hypoglycemia: brain responds
- In euglycemia, basal amylin provides tonic inhibition of alpha-cells via the CNS
- At mealtimes amylin levels rise to further constrain glucagon secretion
- At the onset of hypoglycemia, the CNS circuit-breaker activates glucagon rebound



Islet cell transplants demonstrate the potential for correctly replacing amylin in T1D

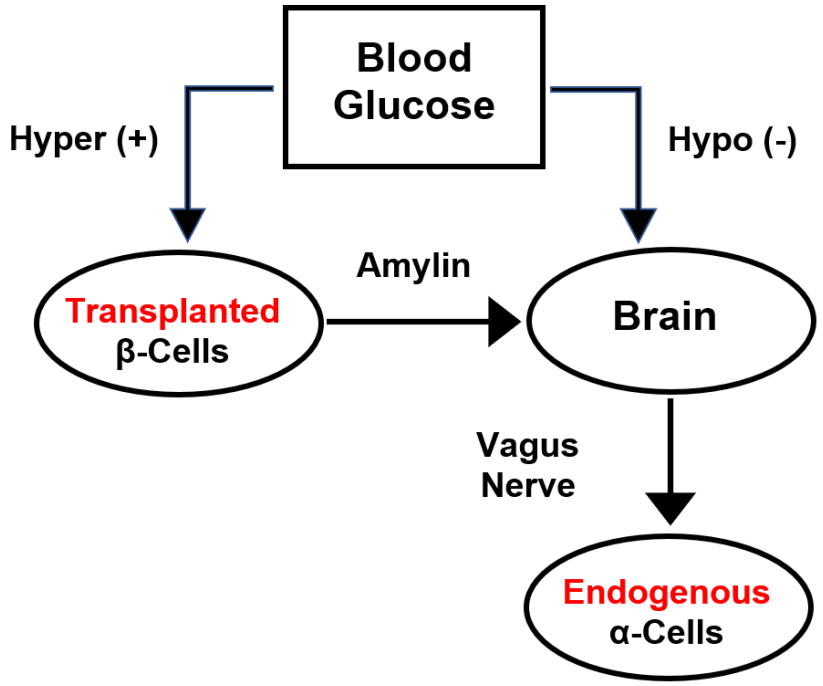
- Intrahepatic islet transplantation partially restores counterregulation
- Transplanted beta-cells must sustain a correct diurnal amylin profile
- But, the transplanted alpha-cells are not connected to the CNS
- Does this contradict the circuit-breaker model?...



Source: Restoration of Glucose Counterregulation by Islet Transplantation in Long-standing Type 1 Diabetes; Diabetes 64:1713-8 2015.

Answer: The circuit-breaker model predicts reactivation of counterregulation by islet transplants

- Transplanted beta-cells provide proper diurnal amylin profiles:
  - **Endogenous** alpha-cells are tonically inhibited via the CNS
- Hypoglycemia activates the amylin circuit-breaker:
  - **Endogenous** alpha-cells rebound with increased glucagon secretion

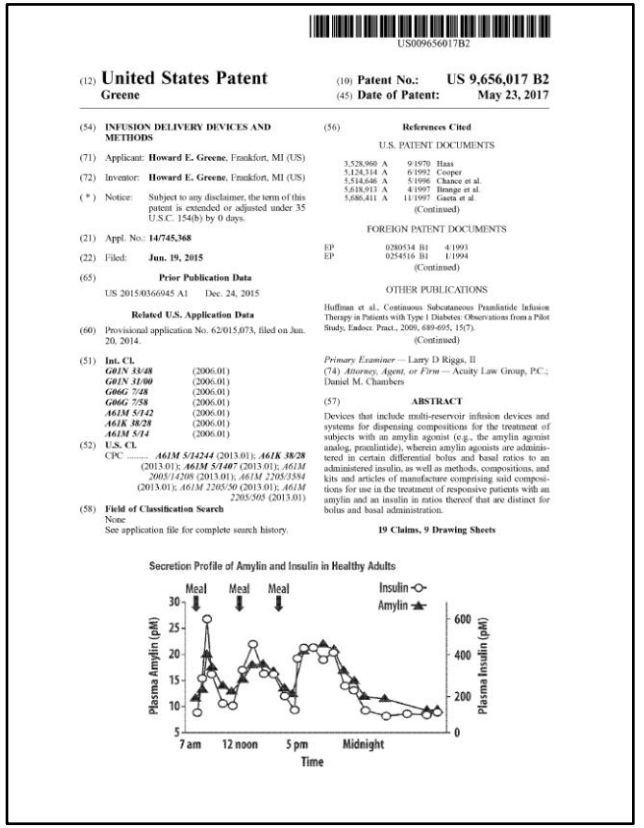


Solution to the amylin dosing problem: A dual hormone AID system

- Dual hormone pumping systems are already under development
- Pramlintide can be substituted for glucagon
- Clinical trials could be started with separate pumps
  - Studies using multiple pumps already done
- Primary endpoint would mimic transplant studies:
  - Improved HbA1c, and
  - Reduction of time in hypoglycemia

Key to success would be an appropriate infusion algorithm for pramlintide

- Studies are already underway for fixed ratio amylin/insulin infusions
- An improvement would be **dual** ratio infusions, e.g.:
  - 6 µg / Unit for basal infusion rates
  - 2 µg / Unit for bolus infusion rates
- This approach is the subject of an issued US Patent 9,656,817



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(54) **INFUSION DELIVERY DEVICES AND METHODS**

(71) Applicant: **Howard E. Greene**, Frankfort, MI (US)

(72) Inventor: **Howard E. Greene**, Frankfort, MI (US)

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G06G 7/58	(2006.01)
A61M 5/142	(2006.01)
A61K 38/28	(2006.01)
A61M 5/14	(2006.01)

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(58) **Field of Classification Search**
None
See application file for complete search history.

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Primary Examiner — Larry D Riggs, II
(74) *Attorney, Agent, or Firm* — Acuity Law Group, P.C.; Daniel M. Chambers

(57) **ABSTRACT**

Devices that include multi-reservoir infusion devices and systems for dispensing compositions for the treatment of subjects with an amylin agonist (e.g., the amylin agonist analog, pramlintide), wherein amylin agonists are administered in certain differential bolus and basal ratios to an administered insulin, as well as methods, compositions, and kits and articles of manufacture comprising said compositions for use in the treatment of responsive patients with an amylin and an insulin in ratios thereof that are distinct for bolus and basal administration.

19 Claims, 9 Drawing Sheets

Secretion Profile of Amylin and Insulin in Healthy Adults

Bottom line: The amylin circuit-breaker model warrants testing in the clinic

- Even partial restoration of glucagon counterregulation would be of huge benefit in T1D
- All the components needed to test the idea are readily available
  - Pramlintide
  - Smart phone controllable pumps using CGM-driven algorithms
  - Experience with implementing multi-pump clinical studies
- For an in-depth discussion of the data and logic supporting this hypothesis, please see the detailed documentation
  - Located at www.amylin.online
  - A downloadable PDF version of the documentation is also available