Is Glucagon Ready For Prime Time?

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My objectives today

1. glucagon physiology in health and disease
2. glucagon as a therapeutic target in type 1 diabetes
3. glucagon as a therapeutic target in type 2 diabetes

What is Glucagon and What Does It Do?

- Glucagon is a 29 aminoacid polypeptide hormone
- regulated by endocrine, paracrine, and autonomic mechanisms
- along with insulin is principal regulator of glucose homeostasis
- it opposes insulin action
- under hypoglycemia, pancreatic α cells secrete glucagon → glycogen breakdown and raise glucose
- under hyperglycemia, pancreatic β cells secrete insulin → stimulates glucose uptake from blood, glycogen formation and lowers blood glucose

Milestones in the Discovery and Renaissance of Glucagon

1922 Banting and Best administer pancreatic extract to diabetic dogs and observe decreased blood glucose; a transient increase in blood glucose is noted
1923 Hyperglycemic substance in pancreatic extracts named “glucagon”
1923 Banting and Macleod awarded Nobel Prize for discovery of insulin treatment, establishing its primary role in diabetes
1957 Bromer identifies amino acid sequence, paving the way for commercially available glucagon
1959 Unger develops glucagon radioimmunoassay
1975 Valverde and Unger identify 2 distinct glucagon-like peptides, GLP-1 & GIP
1984 Unger recognizes glucagon’s role as counterregulatory partner to insulin in Banting Lecture
1989 DeFronzo includes alpha cell as part of “Ominous Octet”
1991 International Symposium focuses on glucagon’s role in diabetes
2008 Unger receives 2014 Rolf Luft Award from Karolinska Institutet for work on glucagon
Cytoarchitecture of Human Islets

- Human islets
  - Alpha, beta, and delta cells are intermingled throughout islet
  - Fewer beta cells, more alpha and delta cells
- Cytoarchitecture of human islet suggests paracrine interactions


Crosstalk between α and β cells in the pancreatic islet

Glucagon and Type 1 Diabetes

- In health: insulin/glucagon ratio strictly regulated, both reach liver via splanchnic circulation simultaneously
- In T1DM: s.c. insulin first absorbed, then systemic circulation —> glucagon acts unopposed, lower insulin/glucagon ratio —> hyperglycemia
- If injecting more s.c. insulin —> hypoglycemia
- No α cells but β cells still there —> fasting + postprandial hyperglycemia

The Liver Is Glucagon’s Target Organ

- Glucagon is the primary regulator of hepatic glucose production, which consists of:
  - Glycogenolysis – breakdown of stored glycogen into glucose
  - Gluconeogenesis – glucose synthesis from non-carbohydrate sources

Glucagon and Type 1 Diabetes

- Glucagon physiology is disturbed in both type 1 and type 2 diabetes
  - Patients have inappropriately elevated levels of glucagon, both in fasting and postprandial states
  - In addition, insulin resistance contributes to hyperglycemia

So, What Does This Have to with Diabetes and My Patients?
**Ok, So What Can We Do With Glucagon in Type 1 Diabetes Now?**

- Use for rescue in hypoglycemic emergencies
- Inhibit to lower hyperglycemia
- In dual hormone “bionic pancreas”

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**Glucagon to the Rescue**

In the midst of Phase 3 trials

The current emergency kit on the market involves dry powder in a vial that has to be manually mixed up and is a 9-step process

This one is premixed; take off the cap and press it against the skin and it delivers the drug right away.

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**Dasiglucagon (ZP4207)**

- Glucagon peptide analog
- Phase II results support its potential for use in a ready-to-use rescue pen to treat severe hypoglycemia in diabetes
- All subjects treated with dasiglucagon or with the approved glucagon product achieved a blood glucose concentration of >70 mg/dL within 30 minutes of dosing
- Time to clinically relevant plasma glucose increases of >20 mg/dL similar for dasiglucagon and approved glucagon with a median time of 9-10 minutes
- Dasiglucagon was well tolerated and had a similar safety profile compared to approved glucagon

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**Glucagon? Show it up your nose?**

**Is This the Future of Glucagon Rescue?**

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**Intranasal Glucagon (AMG504-1/Locemia Solutions)**

- T1D Exchange: 2 studies
  - 75 adults (mean age 33 years)
  - Randomized, crossover trial (3 mg intranasal vs. 1 mg IM)
  - Success = rise of glucose to 70 mg/dL or above within 30 min of nadir
  - Mean time for intranasal: 16 min, for IM: 13 min
  - Head/facial discomfort in 25% intranasal, 9% IM
  - Nausea 35% vs. 38%
- In children (4-17 years)
  - 48 participants (3 mg intranasal vs. 1 mg IM)
  - Nadir 67-75 mg/dL
  - All produced rise of 25 mg/dL within 20 minutes
  - Nausea 42% vs. 67%

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**It Works!**
Intranasal Glucagon (AMG504-1/Locemia Solutions)

Glucagon Inhibition in Type 1 Diabetes Treatment

- pramlintide (synthetic amylin, on-label)
- GLP-1 receptor agonists (off-label)
- DPP-4 inhibitors (off-label)

Pramlintide Reduces Postprandial Glucose

Amylin is Deficient in Diabetes

Suppressing Glucagon With Amylin Analog
Components of Bihormonal Bionic Pancreas

Dual hormone closed loop system (insulin and glucagon)

Formulating Soluble Glucagon
Towards Pumpable Glucagon for Artificial Pancreas

Stable, Liquid Glucagon Formulation Discovered for Potential Use in Artificial Pancreas Systems

---JDRF-funded researchers from Oregon Health & Science University and Legacy Health discovered a method to stabilize liquid glucagon for automated pump delivery that could accelerate the development of a multi-hormonal fully-automated closed loop artificial pancreas system.

New York, NY, June 11, 2013—JDRF-funded researchers at Oregon Health & Science University (OHSU) and Legacy Health have discovered a liquid glucagon formulation that may be usable in standard diabetes pumps. Such a formulation could broaden the use of glucagon to help prevent hypoglycemia in people with type 1 diabetes (T1D) who are treated with insulin. It could also open a path to future-generation artificial pancreas systems that dispense more than just insulin for optimizing glucose control.

JDRF Announces Two Partnerships to Develop Stable, Pumpable Glucagon to Support Advanced Generation Artificial Pancreas Systems

Jun 20, 2013, 16:07 ET
Glucagon as Target in Type 2 Diabetes

**Glucagon suppression**
- pramlintide (alongside meal-time insulin injections)
- incretin effect
- DPP-4 inhibition
- GLP-1 receptor agonism

**Glucagon receptor antagonism**
Enhancing Incretin Effects

GLP-1 effect is diminished in type 2 diabetes
Natural GLP-1 has short half-life (1-2 min)

Injection
Add GLP-1 agonist with longer half-life
- Exenatide
- Liraglutide
- Albiglutide
- Dulaglutide

Oral
Block DPP-4, the enzyme that degrades GLP-1 and GIP
- Linagliptin
- Saxagliptin
- Sitagliptin
- Vildagliptin
- Alogliptin

Pharmacologic (supraphysiologic) GLP-1 Levels

Ingestion of food
GLP-1 receptor agonists
Exenatide, Liraglutide, Albiglutide, Dulaglutide
(GLP-1 remains active by DPP-4)

Pancreas
Glucose-dependent
- Insulin

Alpha cells
Glucose-dependent
- Glucagon

DPP-4 inhibitors
Saxagliptin
Linagliptin
Vildagliptin

Inactive GLP-1
Inactive GIP

Glucose Control With Sitagliptin
(DPP-4 inhibitor)

GLP-1 Receptor Agonists on the U.S. Market

EFFECT OF EXENATIDE AND SITAGLIPTIN ON POSTPRANDIAL PLASMA GLUCAGON CONCENTRATION OVER TIME

Glucose Control With Liraglutide
(GLP-1 RA)
LY2409021 decreases serum glucose by preventing glucagon receptor activation and alleviating excess gluconeogenesis.

CNS, central nervous system; GABA, γ-aminobutyric acid.

Pearson et al. 2016 Diabetes Care 39:1075-1077

So, Is Glucagon Ready For Prime Time?

Glucagon physiology is disturbed in both type 1 and type 2 diabetes.
Glucagon is being used as a therapeutic target in type 1 diabetes.
Glucagon is being used as a therapeutic target in type 2 diabetes.

You be the judge!