ARTIFICIAL ENDOCRINE PANCREAS: FROM BENCH TO BEDSIDE

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Learning Objectives

- Identify knowledge gaps in carbohydrate physiology in type 1 diabetes
- Identify pitfalls and knowledge gaps in glucose sensing in type 1 diabetes
- Discuss state of the art approaches / components / trials of artificial pancreas in type 1 diabetes

Biostator GCIIS
The Technology Timeline

- **1920s**: Insulin discovered by Frederick Banting
- **1960s**: Backpack insulin & glucagon pump
- **1970s**: First use of CSII by Pickup et al.; BMJ, 1978
- **1970s**: Second use of CSII by Tamborlane et al.; NEJM, 1979
- **1980s**: Blood glucose meters becoming smaller and faster
- **1980s**: Insulin pumps becoming more reliable and portable
- **1990s**: Diabetes Technology & Therapeutics Vol 1, 1999
- **2000s**: 2001: First U.S. Diabetes Technology Meeting

The AP System

- **Patient**
- **Sensor**
- **Attending Physician**
- **Model Predictive Control**
- **Insulin Management System**
- **Frequent YSI provides reference BG**
Why do We Need to Improve Current Closed Loop Systems?

- Current systems
  - are generic
  - not based on understanding of physiology
  - hence limited in coping with challenges of meals, activities of daily living, exercise etc
  - studies have shown that one size algorithm does not fit all
  - hence limited applicability

Mind the Gaps

1. Post Prandial physiology: Diurnal pattern
   - Post prandial glucose flux
     - Insulin dose
     - Meal composition and size
     - Insulin action
   - Gastric emptying
   - Intra-individual variability
2. Physical activity (energy expenditure)
   - Activities of daily living
   - Moderate/high grade activity
   - Sinusoidal activity
3. Hepatic Glucagon sensitivity
4. Post absorptive physiology: Dawn phenomenon
5. Glucose sensing and kinetics
Diurnal Pattern of Insulin Action

Insulin Sensitivity

Implications:

- Diurnal pattern of insulin sensitivity and inter-day, intra-individual changes in insulin sensitivity incorporated and tested in T1DM simulator.
- Based on these data, algorithms have being developed to accommodate diurnal pattern and variability of insulin sensitivity.
- FDA approves IDEs for phase II/III clinical trials testing informed algorithm: July 17, 2013 and June 2015.
- IRB approvals obtained; studies ongoing.

Effects of Gastric Emptying: Pramlintide
Effects of Activities of Daily Living on Post-Prandial Glucose Excursions
Low grade activity
Activity level: 1.2 mph
Healthy: 2.5 ± 0.1 kcal/kg/hr
T1D: 2.6 ± 0.1 kcal/kg/hr

Effects of Moderate Intensity Exercise on Insulin Sensitivity
Implications

- Studies have just been completed in T1DM subjects to determine the effects of high grade exercise (both immediate and delayed) on insulin sensitivity before simulation testing and subsequent incorporation into next generation algorithms.

Hepatic Glucagon Sensitivity
Artificial Pancreas: Role of Glucagon

- FDA suggested consideration of glucagon use in artificial pancreas systems (Zimliki C, 2011).
- Glucagon maybe used for rescue and prevention of hypoglycemia.
- Dual hormone (insulin-glucagon) control has been recently tested in artificial pancreas.

Critical Questions about Glucagon Use in Artificial Pancreas

In Type 1 Diabetes:
- Is there a dose response of EGP to glucagon?
- Does hepatic glucagon sensitivity vary with prevailing glucose concentrations?
- Is there a relationship between glucagon concentrations and clearance?
**Plasma Glucagon**

Euglycemia

- High Dose Glucagon
- Medium Dose Glucagon
- Low Dose Glucagon

Hypoglycemia

**Endogenous Glucose Production**

Euglycemia

- High Dose Glucagon
- Medium Dose Glucagon
- Low Dose Glucagon

Hypoglycemia
Summary

1. There is a dose response of EGP to glucagon at both euglycemia and hypoglycemia.
2. The difference in the dose response profile based on glycemia was not significant, implying that the slope of EGP response to glucagon did not differ between euglycemia and hypoglycemia.
3. Glucagon clearance did not change with increasing dosing at both euglycemia and hypoglycemia.
Conclusion

The glucagon controller of a dual hormone closed loop control system for T1D may not need to adjust glucagon sensitivity, and hence glucagon dosing, based on prevailing glucose concentrations.
Nocturnal Phenomenon

- The effect size of nocturnal rise in glucose concentrations is now being incorporated into the T1D simulator for further validation and testing in clinical trials
Clinical Testing – Comparison (Overnight)
[UVA and SDRI, October 2013]

02-29101

Control

Adaptive

Control

Adaptive

Clinical Testing – Longer Duration Pump Suspension
[UVA and SDRI, October 2013]

02-29101A

Dinner: 71g

Exercise
Clinical Testing – Longer Duration Pump Suspension
[UVA and SDRI, October 2013]

Clinical Testing – Short Duration Suspension
[UVA and SDRI, October 2013]
Clinical Testing – Short Duration Pump Suspension
[UVA and SDRI, October 2013]

Clinical Testing – Comparison (Lunch)
[UVA and SDRI, October 2013]
Safety of Outpatient Closed-Loop Control: First Randomized Crossover Trials of a Wearable Artificial Pancreas

Diabetes Care 2014;37:1789-1796 | DOI: 10.2337/dc13-2076
But..this “Bang-bang” algorithm strategy...

- ...resulted in ~ 30% more insulin delivered during closed loop than conventional open-loop in all study subjects
- ...resulted in daily additional dose of ~750 µg of glucagon in every subject!
- ...and this approach does NOT restore normal prandial physiology in T1DM
Current Limitations in Closed-Loop Control Algorithms in T1D

Postprandial Hyperglucagonemia in T1D
Possible Remedies

1. Correction of postprandial hyper-glucagonemia

2. Alignment of prandial insulin action profile (after subcutaneous administration) with appearance of meal glucose

Watch for This Space for Update Next Year!!
Also…..what about CGM glucose sensing, glucose kinetics, accuracy of CGM etc?

**Importance of CGM in T1D management**

- Accurate estimation of physiological time lag of glucose between plasma and Interstitial fluid (ISF) is **essential** for sensor-augmented open-loop therapy and for all closed loop algorithms.
- This knowledge would help refine the next generation CGM algorithms, thus improving safety and efficacy of T1D therapeutic strategies that include CGM.
- There are prior reports that suggest a time lag between plasma to ISF of approximately **2- 45 minutes** based on indirect evidence in humans.
We have recently applied innovative glucose isotope methods, combined with microdialysis techniques to directly estimate physiological time-lag of glucose transport from plasma to ISF.

This time-lag signifies the time taken for glucose tracer to appear in ISF after a bolus administration directly into the vascular space.

In these studies under steady-state conditions (i.e., after an overnight fast), physiological time-lag of glucose transport in healthy subjects was ~ 5.7 minutes and in T1D subjects, ~ 6.8 minutes.

Another possible interpretation is that of system and control engineering, where the “lag” is the equilibration time between the two compartments, i.e. a parameter representing the time it takes the ISF compartment’s response to a unit step input in plasma to reach the 63% of its asymptotic value.

How can we measure it?
**Model of Plasma-ISF Kinetics**

Tracer theory in steady-state:
Linear time-invariant compartment models

Equilibration time can be calculated from model parameters

Median (IQR) equilibration time was 9.1 (2.3) and 11.0 (3.3) min in healthy and T1D subjects, respectively

Schiavon et al, DTT (accepted)

**Question:** Is the Time-lag Altered During Meals?
Results:

- Time-lag of glucose appearance from plasma to ISF:
  - Non-diabetic
    - IV Meal: 7.1 ± 2.7 min
    - Oral Meal: 11.2 ± 5.4 min
  - Type 1 Diabetes
    - IV Meal: 9.7 ± 5.5 min
    - Oral Meal: 13.1 ± 6.5 min
- Time-lag was greater during meal ingestion vs. intravenous administration
- Time-lag values did not differ between T1D and nondiabetic subjects.

Further Analyses and Studies

- Equilibration times are being currently estimated by creating and applying a new meal model of SQ glucose kinetics
- The role of insulin in this model is being explored.
- The effect of exercise on time-lag and equilibration time is also being determined.
Implications and Relevance

- These studies will provide the scientific basis for CGM manufacturers to revise and eventually for the FDA to approve next generation CGM algorithms for both open-loop and closed-loop therapies for type 1 diabetes.

**Time Lag of Glucose From Intravascular to Interstitial Compartment in Humans**

Ananda Basu,1 Simmi Dube,1 Michael Slama,1 Isabel Errazuriz,1 Jose Carlos Amezgua,1 Yogish C. Kudva,1 Thomas Peyser,2 Rickey E. Carter,3 Claudio Cobelli,4 and Rita Basu1


**Time Lag of Glucose From Intravascular to Interstitial Compartment in Type 1 Diabetes**

Ananda Basu, Simmi Dube, Sona Veetil, Michael Slama, Yogish C. Kudva, Thomas Peyser, Rickey E. Carter, Claudio Cobelli and Rita Basu

*J Diabetes Sci Technol* published online 10 October 2014

**Modeling Plasma to Interstitial Glucose Kinetics from Multi-Tracer Plasma and Microdialysis Data**

Schiavon, Dallaman, Dube, Slama, Kudva, Peyser, Basu A, Basu R, Cobelli

*Diabetes Technology & Therapeutics* accepted
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