Amylin:
The Other $\beta$ Cell Hormone

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Amylin

- Peptide hormone – co-localized and co-secreted with insulin
  - 37 amino acid peptide related to calcitonin, CGRP, adrenomedullin
  - Amylin gene - chromosome 12

- Neuroendocrine peptide
  - Receptor identified
  - Binding sites in CNS
    - Area postrema
    - Dorsal raphae
    - Nucleus accumbens

Amylin Is Co-Secreted With Insulin

Healthy adults; n = 6
Hepatic Glucose Output in Diabetes is Abnormally Increased After Meals

Type 2 Diabetes: $P<0.01$ AUC$_{0-120\,\text{min}}$; *$P<0.05$

Data from Wahren J, et al. *J Clin Invest* 1976; 57:987-999

Deficient Insulin and Hypersecreted Glucagon

Defects in diabetes:
- Deficient insulin release
- Glucagon not suppressed (postprandially)
- Hyperglycemia

Gastric-Emptying Rate Is an Important Determinant of Postprandial Glycemia

Subjects without diabetes; n = 16
r = 0.58; P<0.05
Data from Horowitz M, et al. Diabetologia 1993; 36:857-862
Gastric Emptying Is Accelerated in Diabetes

Type 2

Type 1

Type 2: without diabetes, n = 9; type 2 diabetes, n = 9; *P<0.05
Type 1: without diabetes, n = 12; type 1 diabetes, n = 11; **P = 0.0005
Amylin Is Deficient in Diabetes

Without diabetes; n = 27
Late-stage type 2; n = 12
Type 1; n = 190

Multihormonal Regulation of Glucose

APPEARANCE AND DISAPPEARANCE

• Insulin helps regulate glucose disappearance

• Amylin helps regulate glucose appearance

Model derived from animal studies
Pramlintide

- An analog of amylin that overcomes the tendency of human amylin to:
  - Aggregate, form insoluble particles
  - Adhere to surfaces
- Pharmacokinetic and pharmacodynamic properties similar to human amylin

Adapted from Westermark P, et al. Proc Natl Acad Sci 1990; 87: 5036-5040
Pramlintide Reduces Postprandial Glucagon

Type 1 Diabetes

Time (h)

Placebo
Pramlintide

-20
0
10 20
30

Insulin
Sustacal®

Type 2 Diabetes, Insulin treated

Time (h)

Plasma Glucagon (pg/mL)

0
1
2
3
4
5

Placebo or 100 µg/h pramlintide infusion

Type 1 Diabetes

Time (h)

Plasma Glucagon (pg/mL)

0
1
2
3
4
5

Placebo or 25 µg/h pramlintide infusion

Type 2 diabetes, n = 12; AUC_{1-4 h}: P = 0.005
Type 1 diabetes, n = 9; AUC_{1-5 h}: P<0.001;
Effect of Pramlintide on Gastric Emptying in Type 1 Diabetes

Mean Half-Emptying Time (h)

Breakfast

- Placebo
- Insulin + Placebo
- Insulin + Pramlintide

Single SC pramlintide doses: n = 11, crossover; *P<0.004; 99m Tc labelled pancake; solid component measured
Data from Kong MF, et al. Diabetologia 1998; 41:577-583
Pramlintide Reduces Caloric Intake in Type 2 Diabetes

Ad-Libitum Caloric Intake (kcal)

-202 kcal
(-23%)

\[ P < 0.01 \]

n = 11; subjects given buffet meal
Pramlintide (single SC injection, 120 μg)
Pramlintide Clinical Effects
TYPE 2 DIABETES COMBINED PIVOTALS

△ A1C (%)

△ Insulin Use (%)

△ Weight (kg)

Placebo + Insulin
120 μg Pramlintide BID + Insulin

ITT; Mean (SE); *P<0.01, **P<0.0001
Placebo + insulin, N = 284, Baseline A1C = 9.3%; Pramlintide + insulin, N = 292, Baseline A1C = 9.1%
Pramlintide Reduces Fasting and Postprandial Glucose

TYPE 2 DIABETES

Baseline
6 Months

Glucose (mg/dL)

pre-bf post-bf pre-lu post-lu pre-di post-di bedtime

N = 166; *P<0.05; Clinical-Practice Study, 120 μg pramlintide
bf, breakfast; lu, lunch; di, dinner
Pramlintide Clinical Effects

TYPE 1 DIABETES COMBINED PIVOTALS

\[ \Delta \text{A1C} \% \]  \[ \Delta \text{Insulin Use} \% \]  \[ \Delta \text{Weight (kg)} \]

Placebo + Insulin  
30 or 60 \( \mu \)g Pramlintide TID or QID + Insulin

ITT; Mean (SE); *P<0.05, **P<0.01, ***P<0.0001;
Placebo + insulin, N = 538, Baseline A1C = 9.0%; Pramlintide + insulin, N = 716, Baseline A1C = 8.9%
Pramlintide Acetate Prescribing Information, 2005; Data on file, Amylin Pharmaceuticals, Inc.
Pramlintide Reduces Fasting and Postprandial Glucose

TYPE 1 DIABETES

N = 265; *P<0.5; Clinical-Practice Study: all pramlintide doses
bf, breakfast; lu, lunch; di, dinner
Pramlintide Reduces Postprandial Glucose

TYPE 1 DIABETES

Pre-Breakfast

Mean Glucose (mg/dL)

Placebo
Pramlintide

Post-Breakfast

Mean Glucose (mg/dL)

Placebo
Pramlintide

Placebo, n = 147
Pramlintide, n = 148
Study Design

• 16-week, randomized, double-blind, placebo-controlled, multicenter study in patients with type 2 diabetes

• Pramlintide or placebo added to insulin glargine (±OAs)
  – Administered immediately prior to major meals
  – Initiated at 60 μg for 3-7 days, then increased to 120 μg as tolerated

Insulin Glargine Dose Titration (FPG target ≥70 and <100 mg/dL)

<table>
<thead>
<tr>
<th>Pramlintide 120 μg + Insulin Glargine</th>
<th>Placebo + Insulin Glargine</th>
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Screening

Study Visits

Time (Weeks)

0  4  8  12  16
Change in A1C From Baseline to Week 16

Mean±SE; ITT LOCF: Placebo N = 106; Pramlintide N = 105
*p <0.05 vs. Placebo

Riddle, et al. Diabetes 2007; 56(Suppl 1):A143-144
Change in Glucose Fluctuations

**Placebo + Insulin Glargine**

**Pramlintide + Insulin Glargine**

**Blood Glucose (mg/dL)**

Mean±SE; ITT observed

**p<0.01 and *** p<0.001 vs. Baseline**
Change in Body Weight From Baseline to Week 16

Mean ± SE; ITT LOCF: Placebo N = 106; Pramlintide N = 105
***p < 0.001 vs. Placebo
Riddle, et al. Diabetes 2007; 56(Suppl 1):A143-144
Proportion of Patients Achieving the Composite Endpoint At Week 16

ITT LOCF: Placebo N=106; Pramlintide N=105;
#Patients had to achieve each of the following components: A1C ≤7.0% or ≥0.5%, PPG excursions ≤40 mg/dL, no weight gain, and no severe hypoglycemia

***p < 0.001 vs. Placebo
Riddle, et al. Diabetes 2007; 56(Suppl 1):A143-144
Conclusions

♦ Amylin, a newly discovered islet-hormone, has an important role in glucose regulation, particularly postprandial hyperglycemia

♦ Synthetic amylin (pramlintide), provides an opportunity to replace this peptide to both improve glycemia and reduce weight.

♦ Careful patient selection, in addition to physicians comfortable with insulin use, are both important for success