Multi-Hormonal Therapy of Obesity

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Neuroendocrine Control of Energy Balance

Badman MK and Flier JS. *Science*, 5717, 1909-1914, 2005
Amylin

- Peptide hormone – co-localized and co-secreted with insulin
  - 37 amino acid peptide related to calcitonin, CGRP, adrenomedullin
  - Gene - chromosome 12
- Neuroendocrine peptide
  - Receptor identified
  - Binding sites in CNS
    - Area postrema
    - Dorsal raphae
    - Nucleus accumbens

Amylin

Amylin co-secreted with insulin

Amylin deficient in diabetes

Amylin’s Effect on Food Intake is Consistent With Increased Satiating Efficiency

A single dose of amylin (100 mcg/kg) was administered IP to rats prior to lights off.

Data show first meal analysis (N = 3-7/group)

*P < 0.05 compared to vehicle

Amylin Reversed Fasting-Induced Neuronal Activation in the Lateral Hypothalamus (LH)

24-h Fast

Refeeding

Amylin Injection (SC)

Lean adult male Wistar rats, standard chow (N = 4/group). C-fos staining after 24 h of food deprivation; amylin (20 mcg/kg; sc) or 2 h of refeeding 120 min prior to sacrifice.

Amylin-Mediated Weight Loss is Attributable to Food Intake Reduction, and is Fat-Specific

DIO (Levin) Prone rats; 32% fat diet (6 wk)
Ad-lib food except for Pair-fed Controls
Continuous SC Vehicle, amylin 300 mcg/kg/day

Body Weight

% of Baseline Body Weight

Days

Body Composition

Δ in Body Fat (g)

Δ in Protein (g)

Body Composition; Echo MRI
*P <0.05 compared to Vehicle;
#P <0.05 compared to Pair-Fed
Pramlintide: Synthetic Amylin Analog

- Synthetic analog of human amylin
  - soluble
  - equipotent
- Administered by SC injection prior to meals

Crossover Buffet Meal Pramlintide Study: Acute Effect on Food Intake and Satiety

Meal Size
-170 kcal (-16%)
P <0.05

Satiation Quotient
+58%
P <0.05

6 Week Mechanism of Action Study

- Randomized, single blind, placebo-controlled, multicenter study

- Population
  - 88 obese subjects (ITT), BMI 30-45 kg/m²
  - Males and postmenopausal females
  - No previous diagnosis of eating disorders

- Treatment
  - 6 weeks treatment with pramlintide 180 µg TID (sc 15 min prior to meals)
  - No lifestyle intervention
Pramlintide Reduced Body Weight and Food Intake

**Pramlintide Reduced Body Weight and Food Intake**

Baseline weight: Placebo 101.2 kg; Pramlintide 100.5 kg
Placebo lead-in (Day 1) 24-h total caloric intake: Placebo 3780 ± 178 kcal; Pramlintide 3932 ± 159 kcal

Pramlintide Dose-Escalation Study Design

- Randomized, double blind, placebo-controlled, multicenter study in obese subjects:
  - Without type 2 diabetes (N = 160)
  - With type 2 diabetes, treated with diet and exercise and/or metformin (N = 44)

- Study treatment: 16 weeks
  - One-week placebo lead-in period
  - Pramlintide initiated at 60 µg TID, escalated in 30-µg increments as tolerated to 240 µg TID
  - No lifestyle intervention

- Follow-up: 8 weeks
  - Subjects discontinued pramlintide and were monitored for an additional 8 weeks

Note: 88% of subjects randomized to pramlintide treatment escalated to 240 µg TID.

Data on file, Amylin Pharmaceuticals, Inc.
Pramlintide Decreased Body Weight Regardless of Presence or Absence of Diabetes

Without Type 2

Placebo (n = 35)
Pramlintide (n = 78)

-with Type 2

Placebo (n = 13)
Pramlintide (n = 19)

Evaluable; Mean ±SE; *P<0.05; **P<0.01; ***P<0.001; Baseline body weight = 106 kg (placebo), 104 kg (pramlintide).
Data from Weyer C, 87th Annual Meeting of the Endocrine Society. 2005; 344 (Abstract P1-701).
Data on file, Amylin Pharmaceuticals, Inc.
Dose-Ranging Phase 2B Study with Lifestyle Intervention

- Randomized, double blind, placebo-controlled, dose-ranging, multicenter study in obese subjects (ITT; N = 408)
- All subjects participated in structured lifestyle intervention (LSI) encompassing diet, exercise and behavior modification
- 270 completed 4-mo with no major protocol deviations (Evaluable)
- Pramlintide was generally well-tolerated up to 360 µg TID

Pramlintide Reduced Body Weight

**Δ Body Weight (kg)**

- **Placebo**
- **120 µg Pramlintide**
- **240 µg Pramlintide**
- **360 µg Pramlintide**

**BID Regimen**

- 360 µg BID: -6.1 ± 0.8 kg

**TID Regimen**

- 120 µg TID: -6.0 ± 0.9 kg

Evaluable N = 270;
Mean ± SE; *P<0.05; **P<0.01; Only 16-wk significance depicted in figures for clarity
16-Week Pramlintide Dose-Ranging Study: 
Double-Blind End-of-Study Questionnaire

Treatment with study medication made it easier for me to...

Control my Appetite
Control my Portions

% Strongly Agree

Placebo 120 mcg TID 360 mcg BID

Placebo 120 mcg TID 360 mcg BID

Evaluable
Data from Wadden T, et al. Obes Rev. 2006; 7:112-113
Study Design

- A single-blind, placebo-controlled extension of the previous Phase 2b dose-ranging study in obese subjects (N = 209)

- 77% of 4-mo Evaluable subjects opted to continue treatment

- All subjects continued with their pre-existing regimens
  - Three SC injections of study medication per day 15 min prior to meals
  - Pramlintide BID included placebo 15 min prior to midday meal

- Throughout extension, LSI geared towards weight maintenance
Pramlintide Elicited Sustained Weight Loss

Placebo
120 µg Pramlintide
240 µg Pramlintide
360 µg Pramlintide

BID Regimen
Evaluate N = 146; ITT N = 209; Mean ± SE; *P<0.05; **P<0.01; Only 12-mo significance depicted in figures for clarity.

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Pramlintide Reduced Waist Circumference

- **Placebo**
- **120 µg Pramlintide**
- **240 µg Pramlintide**
- **360 µg Pramlintide**

**BID Regimen**
- Evaluable

**TID Regimen**
- Evaluable
- ITT-LOCF

- Evaluable N = 146; ITT N = 209; Mean ± SE; *P<0.05; **P<0.01; Only 12-mo significance depicted in figures for clarity
Leptin: 1994 and 1995

“Researchers have discovered what they hope will be a magic bullet for obesity”

Mouse weighed down by genetics
Leptin Elicits Profound Weight Loss in Leptin-Deficient (Ob/Ob) Mice and Humans
Leptin: 1999 through 2001

• “Leptin not impressive in clinical trial”
  – Science, October 1999

• “What ever happened to leptin?”
  – WebMD, August 1999

• “Search for an obesity ‘cure’ fails”
  – BBC, September 2001
Amylin and Leptin: Synergy in DIO-Prone Rats

Diet-induced obesity prone rats (CRL; N = 6/group); *P <0.05 compared to all groups
Roth J, et al. 66th Annual Sessions of the American Diabetes Association, late-breaking Poster # 52-LB
Amylin + Leptin Synergy Not Explained by the Anorexigenic Effect of Amylin

Diet-induced obesity prone rats (CRL; N = 7/group); *P < 0.05 compared to all groups
Roth J, et al. 66th Annual Sessions of the American Diabetes Association, late-breaking Poster # 52-LB
Amylin + Leptin Body Composition: Weight Loss Is Fat-Specific and Lean-Sparing

Diet-induced obesity prone rats (CRL; N = 7/group); *P < 0.05 compared to vehicle control groups
Roth J, et al. 66th Annual Sessions of the American Diabetes Association, late-breaking Poster # 52-LB.
Amylin + Leptin + PYY(3-36): Marked Reduction in Body Weight and Adiposity

A+P+L: At 50% of the single-agent doses, weight was decreased by 16%, and body fat was reduced to 4%.

DIO rat (CRL; n = 5/group); minipump infusion; *P < 0.05 vs vehicle, *P < 0.05 vs all groups
Roth, et al. Submitted to NAASO 2006 (accepted)