Targeting Insulin in Obesity

Robert H. Lustig, M.D., M.S.L.
Professor, Pediatric Endocrinology
Member, Institute for Health Policy Studies
University of California, San Francisco
President, Institute for Responsible Nutrition

I have no relevant financial relationships with the manufacturers of any commercial products and/or providers of commercial services discussed in this CME activity.

I intend to discuss an unapproved/investigative use of a commercial product/device in my presentation.

- octreotide for hypothalamic obesity

The neuroendocrinology of energy balance
**Effects of Insulin on the Adipocyte**

- Stimulates Glut4 mRNA and protein
- Stimulates Acetyl-CoA Carboxylase
- Stimulates Fatty Acid Synthase
- Stimulates Lipoprotein Lipase
- Hypothalamic actions inhibit lipolysis by suppressing SNS tone and Hormone-Sensitive Lipase
- Results in decreased energy expenditure


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**IVGTT-The Disposition Index**

- Intravenous glucose tolerance test
- The Disposition Index is a measure of insulin sensitivity


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Two insulin disorders in childhood obesity

**Insulin resistance**
- liver/muscle dysfunction
- defective insulin clearance
- fasting hyperinsulinemia
- seen in majority of obese children, esp. minorities

**Insulin hypersecretion**
- vagal/pancreatic dysfunction
- post-prandial hyperinsulinemia
- seen in children with CNS insult
- also seen in some obese adults

1. Insulin resistance
Factors Contributing to Insulin Resistance

1) Sex (F > M)
2) Race (African/Hispanic > Caucasian)
3) Puberty (Pubertal > Prepubertal)
Glucose

Fatty acid

Protein Synthesis

Glycogen

Protein

Diabetes / insulin resistance

Hyperglycemia

HbA1C

Hyperinsulinemia

Expression of High-Mobility Group A1 (HMGA1) and Insulin Receptor (INSR) Messenger RNA (mRNA) and Protein in Monocytes

Chiefari et al. JAMA 305:903, 2011
General Characteristics of the 3 Study Populations With or Without Type 2 Diabetes Mellitus (DM)a

<table>
<thead>
<tr>
<th>Table 1: General Characteristics of the 3 Study Populations With or Without Type 2 Diabetes Mellitus (DM)a</th>
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</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>-------------------------------------</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>BMI</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
</tr>
<tr>
<td>Diabetes risk factors</td>
</tr>
<tr>
<td>Physical activity</td>
</tr>
<tr>
<td>Smoking status</td>
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<tr>
<td>Family history of diabetes</td>
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Obesity can cause diabetes; but is obesity the only problem?

- Obesity is increasing worldwide by 1% per year
- Diabetes is increasing worldwide by 4% per year
NAFLD is a primary predictor of T2DM in Korean adults

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM</td>
<td>1.64</td>
<td>1.16</td>
</tr>
<tr>
<td>NO2</td>
<td>1.53</td>
<td>1.34</td>
</tr>
</tbody>
</table>

In exploratory analyses, C3c cut at the median predicted diabetes as well.

Traffic, Particulate Matter, Inflammation

- Study on the Influence of Air Pollution on Lung Inflammation and Aging (SALIA)
- Prospective study (1990—2006), n = 4000 women
- Measured Particulate Matter (PM) and NO2, from general monitoring stations, and from traffic, and soot and NO2, from land use at each address
- Measured Complement C3c levels as marker of subclinical inflammation
- These were correlated with diabetes incidence by questionnaire
- Covariates: distance from busy thoroughfare, education level of participants
  - (did not control for obesity or diet)
Traffic, Particulate Matter, Inflammation

- Danish Diet Cancer and Health Cohort
- 10 year prospective study, n = 57000
- Measured NO\textsubscript{2} at each address starting in 1971
- Correlated with diabetes incidence by Danish National Diabetes Registry
- Found greater correlations with women, and those who were healthier, non-smokers, and physically active
- Postulated these women spent more time outdoors in the polluted air

Andersen et al. Diab Care 35:92, 2012

Red meat consumption and risk for diabetes
NHS I and II, Physicians Health Study

Unprocessed (e.g. hamburger)
For every 100 gm:
Hazard ratio 1.12

Processed (e.g. bacon)
For every 50 gm:
Hazard ratio 1.51

Pan et al. AJCN epub Aug 17, 2011

Detrimental Effects of Fructose
**Metformin**

- Most obese children are hyperinsulinemic and insulin resistant
- Insulin resistance worsens with worsening obesity
- Insulin resistance is a primary risk factor for the Metabolic Syndrome in children
- Hepatic insulin resistance can be improved with metformin
  - activates hepatic AMP kinase
  - decreases hepatic gluconeogenesis

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**Mechanism of Metformin Action**

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**Metformin in obese adolescents**

- 32 obese adolescents with insulin resistance and positive family history of T2DM (29 completed)
- Double-blind, randomized to metformin vs. placebo x 6 months
- No dietary restriction

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Metformin in obese adolescents

- 98 obese adolescents with obesity
- Double-blind, randomized to metformin vs. placebo x 12 months, then d/c'ed and observed for another 12 months
- No dietary restriction

Metformin x 3 years

2. Insulin hypersecretion
IVGTT-The Disposition Index

Feature STORY

DOES INSULIN DRIVE OBESITY?

A new study shows that reduced insulin levels protect mice from metabolic problems

Transgenic manipulation of insulin dosage protects against obesity

IVGTT

The Disposition Index


Transgenic manipulation of insulin dosage protects against obesity

Hypothalamic Obesity


Lustig, Rev Endo Metab Dis 4:23, 2003

Autonomic innervation of the Adipocyte

Vagal modulation of insulin secretion
OGTT vs. IVGTT or euglycemic clamp

- Ease, especially in children
- Screening for diabetes mellitus by ADA criteria
- Measurement of β-cell secretion AND insulin resistance
- Takes advantage of incretin effect, related to secretion
- Standardized indices of β-cell function, insulin sensitivity
- Utilizes gastrointestinal afferents and efferents
- Exportability to clinical venues

Hypothalamic Obesity Pilot Study—Purpose

1. To assess the insulin secretory dynamics of patients with hypothalamic obesity
2. To assess the efficacy of octreotide in reducing basal and glucose-stimulated insulin release in patients with hypothalamic obesity
3. To assess the efficacy of octreotide in promoting weight loss in patients with hypothalamic obesity

Hypothalamic Obesity Pilot Study—Weight and BMI Change

Hypothalamic Obesity Pilot Study—
Effects on Glucose and Insulin Responses


Hypothalamic Obesity Pilot Study—
Weight Loss Versus:


Octreotide treatment of hypothalamic obesity
Demographics

- Double-blinded, 6 month placebo-controlled trial of octreotide
- 20 subjects with pediatric hypothalamic obesity
  - ages 8-18, 11M, 9F
  - 2 from St. Jude
  - 18 from other institutions
  - 13 with craniopharyngioma
  - 4 with hypothalamic astrocytoma, optic pathway glioma
  - 1 with suprasellar germinoma
  - 2 with ALL, S/P cranial XRT and chemotherapy
- Weight 96.8 ± 5.7 kg, BMI 36.9 ± 1.3 kg/m2, annualized weight gain 15.9 ± 2.9 kg

Lustig et al. JCEM 88:2586, 2003
Octreotide treatment of hypothalamic obesity

1st Window (6 Months)

<table>
<thead>
<tr>
<th></th>
<th>ΔΔΔΔΔΔΔΔ</th>
<th>ΔΔΔΔΔΔΔΔ</th>
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<tbody>
<tr>
<td>Octreotide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight P</td>
<td>0.0008</td>
<td>0.0005</td>
</tr>
<tr>
<td>BMI</td>
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</tbody>
</table>

Octreotide (n = 9) Placebo (n = 9)

Lustig et al. JCEM 88:2586, 2003

Insulin dynamics during OGTT (1st Window)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Octreotide</td>
<td>Placebo</td>
</tr>
<tr>
<td>n = 9</td>
<td>n = 9</td>
</tr>
<tr>
<td>0 months</td>
<td>0 months</td>
</tr>
<tr>
<td>6 months</td>
<td>6 months</td>
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</tbody>
</table>

Insulin (µU/ml)

Minutes

0 40 80 120 160 200 240 0 6 15 30 90 120 150 180 280

Lustig et al. JCEM 88:2586, 2003
Insulin hypersecretion and weight gain in Quebecois

Pilot Study of Octreotide-LAR for Adult Obesity

Hypotheses:

- Insulin hypersecretion occurs in a subset of obese adults
- Insulin suppression using the once-a-month octreotide-LAR will:
  - Slow or reverse adipogenesis
  - Promote weight loss
  - Improve insulin sensitivity

Octreotide-LAR 40 mg IM q 28d
Effects on Weight and BMI Stratified By Response

Patients who completed 24 weeks (n=44)

<table>
<thead>
<tr>
<th>BMI Response</th>
<th>Non-responders (BMI &gt; 35) (n = 11)</th>
<th>Low responders (23 &lt; BMI &lt; 35) (n = 25)</th>
<th>High responders (BMI &lt; 23) (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>BMI</td>
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ANOVA with repeated measures

Use of OGGT to distinguish Insulin Hypersecretion vs. Resistance

- CIR
  - Computed Insulin Response
  - Measure of β-cell activity
  \[ \text{CIR} = \frac{\text{Int}_\text{Glycaemia} \times \text{Int}_\text{Glycaemia}}{\text{Int}_\text{Glycaemia} \times \text{Int}_\text{Glyce}

- GSI
  - Composite Insulin Sensitivity Index
  - Measure of endogenous insulin sensitivity
  \[ \text{GSI} = \frac{\int_0^t \text{Insulin} \times \text{Glucose} \, dt}{\text{Glucose}} \]
Randomized dose-finding trial of octreotide-LAR in adult obesity due to insulin hypersecretion

- Randomized, double-blind, placebo-controlled, dose-finding trial of octreotide-LAR in adult obesity due to insulin hypersecretion (as measured by baseline CIR > 1.0)
- 19 centers nationwide

Inclusion criteria:
- Age 18–65
- BMI > 30
- CIR > 1.0 on screening OGTT

Exclusion criteria:
- Diabetes mellitus
- Previous voluntary weight loss
- Use of weight loss medications
- Use of any autonomically active or psychoactive medications
- Gallstones, hepatic disease, renal disease

Role of Race and CIR in Prediction of Response to Octreotide-LAR

<table>
<thead>
<tr>
<th>CIR (Non-Caucasian)</th>
<th>Treatment Group Comparison</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>&lt;1.43</td>
<td>Placebo</td>
<td>NS</td>
</tr>
<tr>
<td>&gt;1.43</td>
<td>Placebo</td>
<td>NS</td>
</tr>
</tbody>
</table>

Non-Caucasians, CIR < 1.43—Treatment Group Comparison, P=0.046

Octreotide-LAR x 6 months

Lustig et al. NAASO, Oct. 2003, OR-103
Differentiation of insulin resistance from insulin hypersecretion

Insulin is a primary target of obesity therapy. Insulin resistance and insulin hypersecretion are two separate phenomena, but can overlap. Insulin responses can be used to predict treatment responses in obese children (and adults). Environmental changes (food) or drugs that target insulin can be effective—sugar restriction or metformin for insulin resistance, carbohydrate restriction or octreotide for insulin hypersecretion.

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**Targeting Insulin: Conclusions**

- Insulin is a primary target of obesity therapy.
- Insulin resistance and insulin hypersecretion are two separate phenomena, but can overlap.
- Insulin responses can be used to predict treatment responses in obese children (and adults).
- Environmental changes (food) or drugs that target insulin can be effective—sugar restriction or metformin for insulin resistance, carbohydrate restriction or octreotide for insulin hypersecretion.

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**Which comes first? It depends on the disease**

- Hypothalamic Obesity
- Insulin secretion
- Insulin resistance
- OBESITY

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The graph shows the association between insulin sensitivity (CIrt) and insulin resistance (CRrt) in 120 obese children. The scatter plot indicates that a high CIrt is associated with low CRrt, suggesting that targeting insulin can be effective in treating obesity-related insulin resistance and hypersecretion. The graph highlights the importance of insulin sensitivity and resistance in the context of obesity treatment.