GLP-1 and metabolic syndrome.
Bench to bedside.

Kevin Niswender MD, PhD
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The incretin effect.

Control Subjects
(n=8)

Incretin Effect

IR Insulin, mU/L

Oral glucose load
Intravenous (IV) glucose infusion

Time, min

The Incretin Axis

Hormonal signals
- GLP-1
- GIP

Glucagon (GLP-1)

Insulin (GLP-1, GIP)

Neural signals

Nutrient signals

Pancreas

alpha cells
beta cells

Gut


Adiposity Negative Feedback Signaling

i.e. regulation of “metabolic drive”

Schwartz MW et al., Nature 2000
Does GLP-1 work in a similar way?
GLP-1 given ICV lowers food intake..

Turton et al., Nature 1996
...and blunts NPY induced feeding.

Turton et al., Nature 1996
Reward Circuitry

Cami NEJM 2003
GLP-1 analogue decreases candy and increases chow intake. (and decreases weight gain)

Raun et al., Diabetes 2007
GLP-1 as an adiposity signal?

• GLP-1 can act in hypothalamic areas to control feeding.
• In rodent models, this is not required for an effect on feeding and weight gain.
• GLP-1 is not produced in proportion to fat mass.
• Rather, energy in the form of food stimulates GLP-1 production.
Feeding occurs in meals: satiation and meal termination.

Schwartz MW et al., Nature 2000
CCK reduces meal size

Geary Phys. Beh. 2004
GLP-1 induces satiety and reduces meal size

Flint et al., JCI 1990
GLP-1 works in periphery as a satiety factor.

Williams et al., Endocrinology 2008
Energy homeostasis and GLP-1: potential sites/mechanisms of action

Schwartz MW et al., Nature 2000
GLP-1 and GIP Are Degraded by DPP-4

Meal

Intestinal GIP and GLP-1 release

GIP-(1–42)
GLP-1(7–36)
Intact

GIP and GLP-1 Actions

DPP-4 Enzyme

GIP-(3–42)
GLP-1(9–36)
Metabolites

Rapid Inactivation

Half-life*
GLP-1 ~ 2 minutes
GIP ~ 5 minutes

Therapeutic approaches: exenatide and liraglutide.

GLP-1 (amidated form)

Exenatide

Liraglutide

Proteolytic inactivation (DPP-4)

C-16 free fatty acid

Albumin
Does the promise translate: glucose?

Buse et al., Lancet 2009
Does the promise translate: weight?

Buse et al., Lancet 2009
Liraglutide (Victoza) and obesity

Astrup, Lancet 2009
<table>
<thead>
<tr>
<th></th>
<th>Liraglutide</th>
<th>Exenatide</th>
<th>Estimated treatment difference (liraglutide–exenatide) (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Islet function</strong></td>
<td></td>
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<tr>
<td>Fasting insulin (pmol/L)</td>
<td>12.43 (6.93)</td>
<td>-1.38 (6.92)</td>
<td>13.81 (0.94 to 26.68)</td>
<td>0.0355</td>
</tr>
<tr>
<td>Fasting C-peptide (nmol/L)</td>
<td>0.05 (0.05)</td>
<td>-0.02 (0.05)</td>
<td>0.07 (0.02 to 0.16)</td>
<td>0.1340</td>
</tr>
<tr>
<td>Fasting proinsulin-to-insulin ratio</td>
<td>0.00 (0.03)</td>
<td>-0.02 (0.03)</td>
<td>0.002 (0.03 to 0.08)</td>
<td>0.4309</td>
</tr>
<tr>
<td>HOMA-B</td>
<td>32.12% (6.75%)</td>
<td>2.74% (6.75%)</td>
<td>29.37% (16.81% to 41.93%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fasting glucagon (ng/L)</td>
<td>-19.44 (5.18)</td>
<td>-12.33 (5.12)</td>
<td>-7.12 (-16.66 to 2.43)</td>
<td>0.1436</td>
</tr>
<tr>
<td><strong>Blood pressure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>-2.51 (1.15)</td>
<td>-2.00 (1.18)</td>
<td>-0.51 (-2.66 to 1.64)</td>
<td>0.6409</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>-1.05 (0.71)</td>
<td>-1.98 (0.71)</td>
<td>0.93 (-0.37 to 2.23)</td>
<td>0.1610</td>
</tr>
<tr>
<td><strong>Lipid profiles</strong></td>
<td></td>
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</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>-0.20 (0.07)</td>
<td>-0.09 (0.07)</td>
<td>-0.11 (-0.23 to 0.02)</td>
<td>0.0946</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>-0.44 (0.06)</td>
<td>-0.40 (0.06)</td>
<td>-0.04 (-0.15 to 0.06)</td>
<td>0.4412</td>
</tr>
<tr>
<td>VLDL cholesterol (mmol/L)</td>
<td>0.20 (0.04)</td>
<td>0.27 (0.04)</td>
<td>-0.07 (-0.13 to -0.01)</td>
<td>0.0277</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>-0.04 (0.02)</td>
<td>-0.05 (0.02)</td>
<td>0.01 (-0.02 to 0.04)</td>
<td>0.5105</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>-0.41 (0.10)</td>
<td>-0.23 (0.10)</td>
<td>-0.18 (-0.37 to 0.00)</td>
<td>0.0485</td>
</tr>
<tr>
<td>Free fatty acids (mmol/L)</td>
<td>-0.17 (0.02)</td>
<td>-0.10 (0.02)</td>
<td>-0.07 (-0.11 to -0.03)</td>
<td>0.0014</td>
</tr>
<tr>
<td>Apolipoprotein B (g/L)</td>
<td>-0.06 (0.02)</td>
<td>-0.03 (0.02)</td>
<td>-0.02 (-0.05 to 0.01)</td>
<td>0.1119</td>
</tr>
</tbody>
</table>

Data are least square means (SE). HOMA-B = homeostasis model assessed β-cell function. LDL = low-density lipoprotein. HDL = high-density lipoprotein. VLDL = very low-density lipoprotein.

*Table 2*: Change in indices of islet function and cardiovascular risk from baseline to week 26.
Does the promise translate: exenatide 82 weeks?

**Systolic BP**

- Quartile I: 2
- Quartile II: 1
- Quartile III: 3
- Quartile IV: 4

**Diastolic BP**

- Quartile I: 0
- Quartile II: 1
- Quartile III: 2
- Quartile IV: 3

**Triglycerides**

- Quartile I: 0
- Quartile II: -2
- Quartile III: -4
- Quartile IV: -6

**HDL-C**

- Quartile I: 8
- Quartile II: 7
- Quartile III: 6
- Quartile IV: 5

Blonde, DOM 2006