NEUROLOGICAL COMPLICATIONS OF LEPTIN RESISTANCE/OBESITY

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Insulin ↔ Leptin ↔ Hippocampal Plasticity

Mechanisms?
Lentivirus construct

SPWGrIR14R
10808 bp

PGK-1p

IR antisense

GFP

ampR

HIV LTR'

WPRE

HIV Sequence

LTR

Psi

IRES

EGFP

rIR antisense
Targeting of hypothalamic IRs with lentivirus

GFP immunohistochemistry
Targeting of hypothalamic IRs with lentivirus

Grillo et al, 2007
# Plasma endocrine parameters

<table>
<thead>
<tr>
<th></th>
<th>LV-Con</th>
<th>LV-IRAS</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mg/dl)</td>
<td>107.3 ± 7.4</td>
<td>114.8 ± 4.5</td>
<td>0.388</td>
</tr>
<tr>
<td>Insulin (ng/ml)</td>
<td>0.41 ± 0.054</td>
<td>0.317 ± 0.035</td>
<td>0.167</td>
</tr>
<tr>
<td>Leptin (ng/ml)</td>
<td><strong>1.03 ± 0.13</strong></td>
<td><strong>1.57 ± 0.19</strong></td>
<td><strong>0.043</strong></td>
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<tr>
<td>Adiponectin (ng/ml)</td>
<td>2.58 ± 0.25</td>
<td>3.89 ± 0.76</td>
<td>0.144</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td><strong>109.2 ± 19.2</strong></td>
<td><strong>171.5 ± 14.9</strong></td>
<td><strong>0.028</strong></td>
</tr>
</tbody>
</table>

Grillo et al, 2007
Peripheral leptin cannot stimulate phosphorylation of STAT3 in the hypothalamus of IRAS rats.

Grillo et al., 2011
Neurological consequences of obesity

- Increased risk of dementia independent of diabetes and cardiovascular comorbidities.
- Association with decreased cognitive function.
- There is a reciprocal link between depression and obesity. Obesity was found to increase the risk of depression. In addition, depression was found to be predictive of developing obesity.
Hippocampal neuroplasticity?

↑ Adiposity

↓ Hypothalamic IRs

↑ Leptin

↑ TGs

BBB
Downregulation of hypothalamic IRs impairs hippocampal LTP

Grillo et al., 2011
Sucrose preference

Grillo et al., 2011
Depressive-like phenotype in LV-IRAS rats: Forced Swim Test

Grillo et al., 2011
Conclusions

Specific downregulation of hypothalamic insulin receptor produces:

- Increases in body weight, body adiposity, plasma leptin, and plasma triglycerides levels in absence of other metabolic and/or neuroendocrine abnormalities.

- Cognitive deficits and adverse effects on hippocampal synaptic transmission.

- Depression-like behavior and decreases in BDNF levels.

- All these undesired effects were ameliorated or restored by food restriction.
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Questions?
Contextually conditioned freezing behavior

Graph A: Freezing behavior over time during acquisition.

Graph B: Percent of time freezing for LV-Con and LV-IRAS groups.

Graph C: Freezing behavior over time during retention.

Graph D: Percent of time freezing for Mins 1-3 and Mins 6-8.

Legend:
- LV-Con
- LV-IRAS
BDNF levels

**PLASMA**

LV-Con  
LV-IRAS

**HIPPOCAMPUS**

LV-Con  
LV-IRAS

* indicates statistical significance.
Body Weight in LV-IRAS rats subjected to Food Restriction
Leptin and BDNF plasma levels and food restriction

3 weeks post-surgery

6 weeks post-surgery
Correlation between Leptin and BDNF levels

$r^2 = 0.2418$
$p < 0.01$
Sucrose preference

- LV-Con
- LV-IRAS
- LV-IRAS Prevention
- LV-IRAS Reversal
Food restriction restores LTP
Summary

Food restriction restores:

- Body weight and body composition.
- Plasma leptin levels.
- Plasma BDNF levels.
- Sucrose preference.
- Long term potentiation.
Summary

- Deficit in associative learning, accompanied by lack of activation of CA1 hippocampal neurons.
- Hippocampal synaptic transmission is adversely affected.
- Developed depression-like behavior:
  - Anhedonia to a palatable sucrose solution.
  - Exhibit behavioral despair.