Insights from Rare Obesity Disorders

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Disclosures

• Research funding: Zafgen, AstraZeneca, Rhythm

• Member, Zafgen Hypothalamic Injury Assoc. Obesity Advisory Board (2015)

• I will discuss off label drug use
Objectives

• Why syndromic obesity matters
• Review of the leptin-melanocortin pathway
• Novel treatments for POMC deficiency
• Lessons from pseudohypoparathyroidism
Syndromic Obesity

Effect size

Variant frequency

Very rare

Common

Mendelian diseases
Rare variant
Large effect

Common disease
Rare variant
Moderate effect

Common disease
Common variant
Small effect

Fig. modified from Kaiser J. Science. 2012
Common Variants Associated with Obesity

Speliotes EK et al. Nat Genet. 2010
Why are rare diseases important?

• Syndromic obesity accounts for more than 5% of childhood obesity → 625,000 children

• Furthers our understanding of the pathophysiology underlying common obesity

• Potential to develop targeted treatments
Leptin-Melanocortin Pathway

Hypothalamus

MC4R

PVN

POMC

Agrp/Npy

Hypothalamus

Ghrelin

Ghrelin Receptor (Ghsr)

Leptin Receptor (Lepr)

Stomach

Adipose Tissue

Leptin

Energy Expenditure

Food intake

α-MSH

Energy intake

POMC

Leptin

Agrp/Npy

MC4R
Leptin-Melanocortin Pathway

**Stomach**

**Adipose Tissue**

**Hypothalamus**

**PVN**

**MC4R**

**POMC**

**Agrp/Npy**

**Ghrelin**

**Ghsr**

**Lepr**

**Energy Expenditure**

**Food intake**

Dehghani et al. *Euro J Med Gen* 2018

Farooqi et al. *Endocrine Reviews* 2006

Krude et al. *Nat Genetics* 1998
Leptin

- 1994: Defects in leptin secretion cause obesity in the ob/ob mouse
- 1997: Congenital leptin deficiency reported in two children
- 1998: Leptin receptor mutation reported in humans
- 2002: Recombinant human leptin treats leptin deficiency

Farooqi et al. *JCI* 2002
Leptin-Melanocortin Pathway

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Energy Expenditure

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Dehghani et al. Euro J Med Gen 2018
Farooqi et al. Endocrine Reviews 2006
Krude et al. Nat Genetics 1998
POMC

Enzyme: Proprotein convertase 1 (PCSK1)

γ-MSH
ACTH
β-MSH
βend
α-MSH

Setmelanotide

Jackson et al. Nat Genetics 1997
Philippe et al. IJO 2014
Krude et al. Nat Genetics 1998
Leptin-Melanocortin Pathway

- Stomach
- Adipose Tissue
- Hypothalamus
- Arcuate
- POMC
- MC4R
- PVN
- Leptin
- Ghrelin
- Agrp/Npy
- Lepr

Dehghani et al. *Euro J Med Gen* 2018
Farooqi et al. *Endocrine Reviews* 2006
Krude et al. *Nat Genetics* 1998
Setmelanotide for POMC and LEPR

Clement et al. Nature Medicine 2018
Setmelanotide - Skin changes

Kuhnen et al. NEJM 2016
Setmelanotide – PWS

- Orphan drug designation

Bischof et al. *J Pharmacol* 2016
Common Variants Associated with Obesity

Speliotes EK et al. Nat Genet. 2010
Setmelanotide for General Obesity

\[
\text{REE}_c \pm \text{SD (kcal/day)} \\
1856 \pm 369 \text{ kcal/d} \\
1745 \pm 359 \text{ kcal/d}
\]

\[p = 0.028\]
Melanocortin 4 receptor

Asai et al. Science 2013
Ramachandrappa et al. JCI 2013
Pseudohypoparathyroidism

Weight

Height
Pseudohypoparathyroidism

Abnormal expression of $G_s\alpha$

GNAS - 20q13.2

Weinstein et al. 2009
PHP Types

PPHP

PHP type 1A

PHP type 1B

Elli et al. JCEM, 2016
Treating PHP

- PTH resistance $\rightarrow$ Calcitriol
- TSH resistance $\rightarrow$ Levothyroxine
- GHRH resistance $\rightarrow$ Growth hormone
- LH/FSH resistance $\rightarrow$ OCPs
Treating PHP

NO TREATMENT FOR ...

• Obesity
• Cognitive impairment
• Subcutaneous ossifications
• Premature closure of the epiphyses
Why do patients with PHP become obese despite adequate hormone replacement?
Obesity is a feature of maternally inherited PHP

### TABLE 2. Weight and BMI data for PHP1a and pseudoPHP

<table>
<thead>
<tr>
<th></th>
<th>PHP1a</th>
<th>pseudoPHP</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weight SDS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (n = 40)</td>
<td>1.84 ± 0.22</td>
<td>−0.18 ± 0.29</td>
<td>0.000015</td>
</tr>
<tr>
<td>Children (n = 28)</td>
<td>2.23 ± 0.26</td>
<td>−0.60 ± 0.63</td>
<td>0.0019</td>
</tr>
<tr>
<td>Adults (n = 12)</td>
<td>0.93 ± 0.27</td>
<td>−0.06 ± 0.34</td>
<td>0.033</td>
</tr>
<tr>
<td><strong>BMI z-score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (n = 40)</td>
<td>2.31 ± 0.18</td>
<td>0.65 ± 0.31</td>
<td>0.000032</td>
</tr>
<tr>
<td>Children (n = 28)</td>
<td>2.58 ± 0.23</td>
<td>−0.41 ± 0.87</td>
<td>0.00045</td>
</tr>
<tr>
<td>Adults (n = 12)</td>
<td>1.69 ± 0.18</td>
<td>0.97 ± 0.26</td>
<td>0.031</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SEM.
Melanocortin-4 Receptor

- G-protein coupled receptor
- Important role in hypothalamic control of energy balance → “Adipostat”

Diagram:
- MC4R
- Agrp/Npy
- POMC

Food Intake vs. Energy Expenditure
Leptin-Melanocortin Pathway

Stomach

Adipose Tissue

Hypothalamus

POMC

Agrp/Npy

MC4R

PVN

Ghrelin

Ghsr

Leptin

Lepr

Energy expenditure

Food intake

Arcuate

Ghrelin

Leptin

Adipose Tissue
MC4R Mutations Cause a Human Obesity Syndrome
PHP mouse model shows imprinting in the hypothalamus

Quantification of in situ hybridization using a gnas exon-1 probe

Melanocortin 4 receptor

↑Sympathetic Tone
↑Energy Expenditure
↓Food Intake

cAMP

MC4R
Neuron

Resting Energy Expenditure is Decreased in PHP

Shoemaker et al. IJO 2012
Perez et al. JCEM 2018
Hyperphagia

- PHP1A patients may have mild hyperphagia
  - Breakfast buffet: 99 ± 49 vs. 63 ± 23 %REE, p= 0.01
  - Dinner buffet: 93 ± 22 vs. 79 ± 30 %REE, p= 0.25
  - Similar to MC4R deficiency (~40 kcals/kg FFM)

Perez et al. *JCEM* 2018
HEALTH CONSEQUENCES OF OBESITY
Glucose intolerance occurs prior to onset of obesity

Adults with PHP have reduced insulin sensitivity

IV glucose tolerance test

Mixed meal

Muniyappa et al. JCEM, 2013
Children with PHP are less insulin resistant than obese controls

Shoemaker unpublished data
Children vs. Adults

Perez et al. *JCEM*, 2018

Muniyappa et al. *JCEM*, 2013
Children with PHP have impaired glucose tolerance

Perez et al. JCEM, 2018
HbA1c may be decreased in PHP

Perez et al. JCEM, 2018
Repurposing drugs for PHP

MC4R Neuron

Kir 7.1

K+

cAMP

AMP

PDE inhibitors
Summary

• Understanding the pathophysiology of syndromic obesity provides opportunity for novel treatments

• Repurposing drugs is a viable option for orphan diseases
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