Pediatric Obesity: Clinical and basic questions, and some answers

Pediatric Grand Rounds
University of Florida
February 26, 2015

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Disclosures

Joseph Majzoub, M.D.  None
The expanding girth of Henry VIII

Age 25: 32”

Age 45: 52”
gluttony
Socioeconomic Disparity in Obesity Prevalence Among American Adolescents (NHANES)

Parent high school education or less
Parent college education or more

Frederick et al. PNAS, 111:1338-42 (2014)
Genetic studies of body mass index yield new insights for obesity biology

97 loci from >300,000 subjects account for < 3% of BMI variation

Most obesity SNP variants located in genes expressed in CNS

500 eggs per capita

1909  1945  2012

1984 USDA Food Guide Pyramid
Glycemic Index
A physiological basis for classifying carbohydrate

Area under the glycemic curve after consumption of 50 g CHO from test food divided by area under curve after 50 g CHO from control food

David Ludwig
GI & Regulation of Food Intake

GI & Regulation of Food Intake

Serum Insulin

Plasma Glucagon

GI & Regulation of Food Intake

Plasma Epinephrine

Serum Growth Hormone

GI & Regulation of Food Intake

Time to put eggs back on the menu  (Deb Lindsey for The Washington Post)
Increasing Adiposity: Consequence or Cause of Overeating?

A  Prevailing model

Environment of convenient, highly palatable, energy-dense food

Environment that encourages a sedentary lifestyle

Energy intake

Energy expenditure

Circulating metabolic fuels (glucose, lipids, ketones)

Fat storage

Obesity

↑ Insulin secretion

Low Glycemic Index Approach to Obesity Treatment

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Sugar-Sweetened Beverages and Adolescent Body Weight

Cara B. Ebbeling, Ph.D., Henry A. Feldman, Ph.D., Virginia R. Chomitz, Ph.D., Tracy A. Antonelli, M.P.H., Steven L. Gortmaker, Ph.D., Stavroula K. Osganian, M.D., Sc.D., and David S. Ludwig, M.D., Ph.D.
Leptin Resistance in Obesity

Decreased food intake

MC4R neurons

αMSH stimulates MC4R

Npy inhibits MC4R

(+) POMC

Fed (leptin ↑)

Modified from O’Rahilly et al. Nat Med, 10:351, 2004
Decreased food intake

Second-order neurons

MC4R

αMSH

Stimulates MC4R

(+) POMC

Fed (leptin ↑)

Inhibits MC4R

Npy AgRP (−)

Modified from O’Rahilly et al. Nat Med, 10:351, 2004
Human *LEP* Mutation

- Autosomal recessive, high penetrance
- Very rare monogenic cause of obesity
- Hyperphagia

3yr old weighing 42kg

7yr old weighing 32kg
Decreased food intake

Second-order neurons

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αMSH

Stimulates MC4R

(+) POMC

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Inhibits MC4R

Npy

AgRP (−)
Human *LEPR* Mutation

- Autosomal recessive, high penetrance
- Very rare monogenic cause of obesity
- Hyperphagia

Human *POMC* Mutation

- Autosomal recessive, high penetrance
- Very rare monogenic cause of obesity
- Hyperphagia

*Krude and Gruters Nat Genetics 19:155, 1998*
Increased food intake

Stimulates MC4R

(+) POMC

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Fed (leptin ↑)

Second-order neurons

MC4R

aMSH

Decreased food intake
Human **MC4R Mutation**

- Autosomal dominant, high penetrance
- Most common (3-5%) monogenic cause of obesity
- Hyperphagia

*O’Rahilly et al. Nat Med, 10:351, 2004*
Mutations in *MRAP*, encoding a new interacting partner of the ACTH receptor, cause familial glucocorticoid deficiency type 2

Louise A Metherell¹, J Paul Chapple², Sadani Cooray¹, Alessia David¹, Christian Becker³, Franz Rüschendorf³, Danielle Naville⁴, Martine Begeot⁴, Bernard Khoo¹, Peter Nürnberg³,⁵, Angela Huebner⁶, Michael E Cheetham² & Adrian J L Clark¹
Melanocortin Receptor Family Leads to MRAP2

Skin Pigmentation-MC1R

Energy Balance-MC3R, MC4R

Exocrine Gland-MC5R

Energy Balance

α-MSH

MC4R

MRAP2

Adrenal MC2R

MRAP

Adrenal Steroidogenesis

α-MSH

ACTH
Ligand = αMSH

GPCR = Mc4r

Mrap2

Gα

Gγ

Gβ

GDP
Mrap2 enhances αMSH signaling via Mc4r

Asai et al. Science 341, 275, 2013
Mrap2KO Mice are Obese

Asai et al. Science 341, 275, 2013
Mutations in **MRAP2** in obese humans

Rare (loss of function) mutations → important biology

More common mutations → important pathophysiology?
Rationale for Metabolic Surgery in Adolescents

• Curative and preventive strategy

• Most effective (but also most invasive) treatment available
Adolescent Bariatric Surgery Referral Guidelines

- Obesity BMI > 35 + severe co-morbidities
  -(e.g., Type 2 DM, Severe NASH, Pseudotumor, Severe OSA)
- Severe Obesity BMI > 40 + co-morbidities
- Mature, motivated adolescent
- Able to give informed assent (parental consent)
- Failed a 6 month organized weight loss program
- Near complete linear growth
- Supportive family
- Adheres to pre-bariatric evaluation and preparation
- If psychological problem, stable and in treatment
Available Surgical Options

- Lifestyle/Meds
- AGB
- SGx
- RYGB

Effectiveness vs. Invasiveness

Ideal Treatment

Nicholas Stylopoulos
Challenges of Bariatric Surgery in Adolescents

• No definitive data supporting effectiveness and safety in adolescents
• No long-term follow up
• No consensus on ideal surgical option
• Mechanisms of surgical efficacy are unknown
Reprogramming of Intestinal Glucose Metabolism and Glycemic Control in Rats After Gastric Bypass
Increased Glucose Uptake in the Roux Limb of RYGB

Pharmacotherapy for Obesity

- **Pharmaceuticals on market**
  - **Orlistat**, Xenical (Roche). Pancreatic lipase inhibitor
    - Steatorrhea
  - **Lorcaserin**, Lorqess/Belviq (Arena). **ADULTS ONLY.** Serotonin HT2c receptor agonist. 3% weight loss over placebo.
    - Adverse events - memory, attention, language problems, depression, euphoria, valvular heart disease.
  - **Topiramate-phentermine**, Qsymia (Vivus). **ADULTS ONLY.** Anti-epileptic-catecholamine stimulant. 7% weight loss over placebo.
    - Adverse events - memory, attention, language problems, depression, metabolic acidosis, increased heart rate, anxiety, insomnia, elevated creatinine levels, cleft palate.
Pharmacotherapy for Obesity

• Pharmaceuticals removed from market
  – (Fenfluramine-phentermine, Fen-Phen, 1997). Nonselective serotonin receptor agonist-catecholamine stimulant.
    • Mitral valve disease, pulmonary hypertension
  – (Sibutramine, Meridia, 2010). Serotonin reuptake inhibitor.
    • Heart attack, stroke
Pharmacotherapy for Obesity

• Pharmaceuticals in development
  – **Beloranib** (Zafgen). MetAP2 inhibitor, decreased fatty acid production.
    • Diarrhea, nausea, headache
    • Not orally active
    • Concern about cardiovascular toxicity. FDA requires very large outcomes study prior to approval.
  – **SR01**. Leptin sensitizer (ERX, Umut Ozcan, BCH).
    • Preclinical. Mice, monkeys
Leptin Resistance in Obesity

Leptin

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MRAP2

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AgRP

SR01

(+ ) POMC
Reassessment of obesity as a disease, rather than a lifestyle choice

- 2004: Medicare removed language from its coverage manual saying obesity was not a disease (but Medicare Part D denies drug coverage).

- 2013: AMA recognized obesity as a disease.
  - Should allow payment for obesity-related care
    - Diagnostic evaluations
    - Therapies
      - Food and Exercise
      - Bariatric Surgery
      - Pharmaceuticals
My Colleagues at Boston Children’s Hospital

- Joel Hirschhorn
  ✓ Common variant obesity genetics
- David Ludwig
  ✓ Dietary macronutrients
- Nick Stylopoulos
  ✓ Gastric bypass mechanisms
- Umut Ozcan
  ✓ New obesity pharmacotherapy

My Collaborators

MRAP2

- Masato Asai
  - Yuan Shen
  - Rong Zhang
  - Nikhil Nuthalapati
  - Visali Ramanathan
  - David Strochlic
  - Caroline Ho
  - Kirsten Linhart
- Sadaf Farooqi
- Li Chan