Pediatric Obesity: Clinical and basic questions, and some answers

Pediatric Grand Rounds
University of Florida
February 26, 2015

Joseph A. Majzoub, MD
Chief, Division of Endocrinology
Boston Children's Hospital
Harvard Medical School

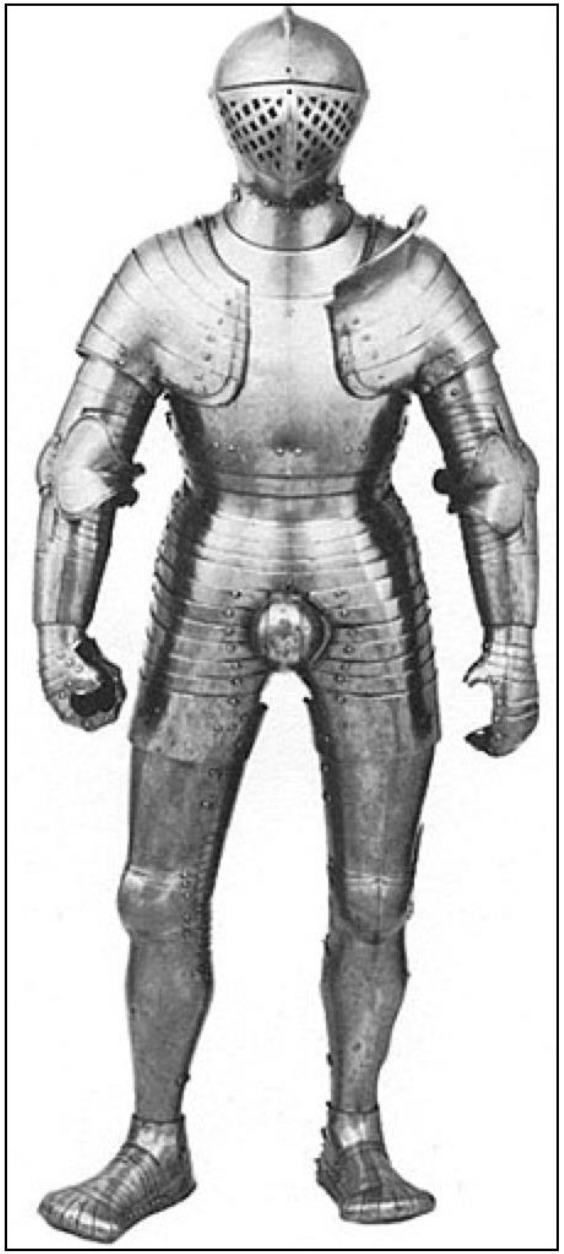
Disclosures

Joseph Majzoub, M.D. None

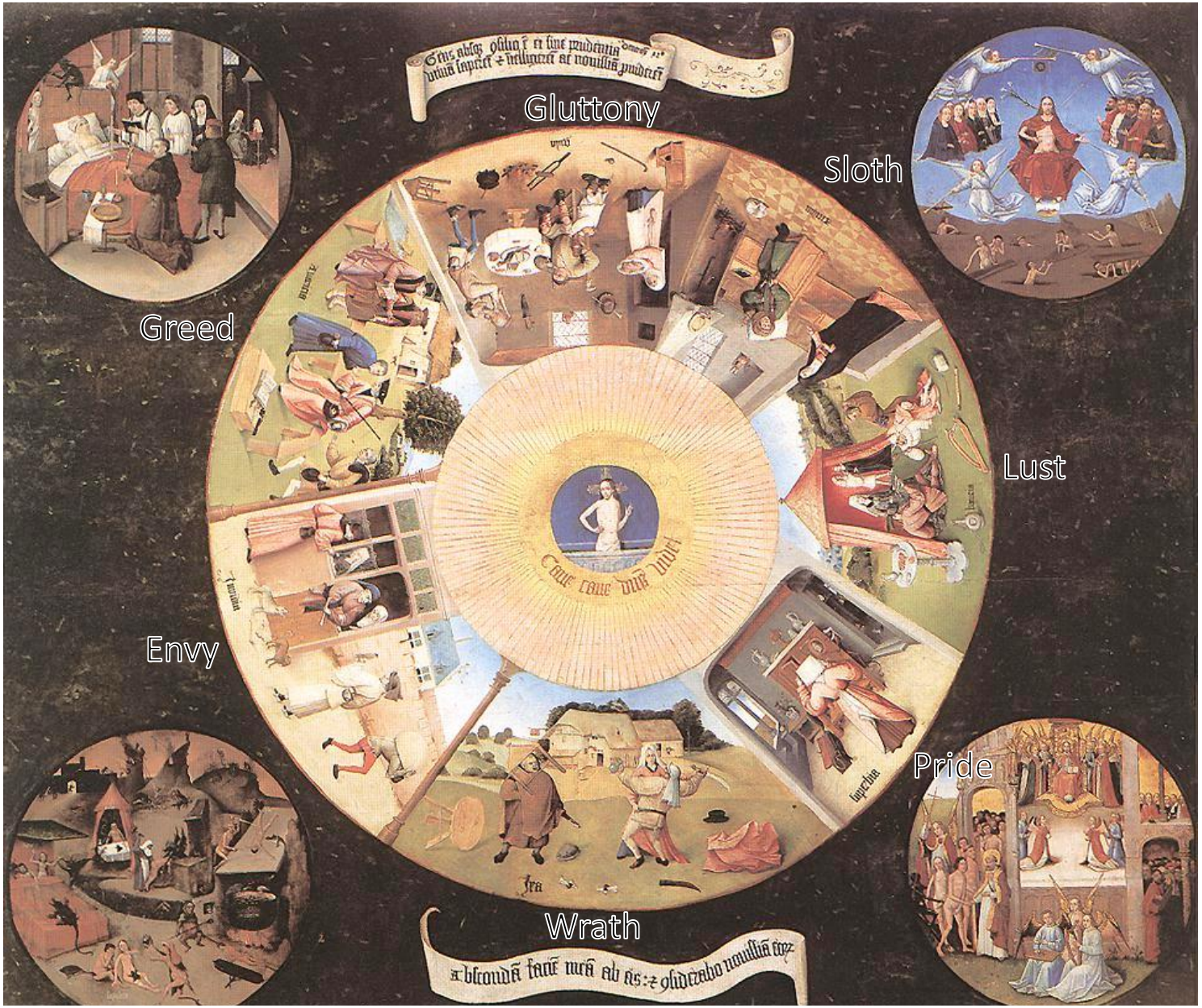
HENRY VIII

The expanding girth of Henry VIII

Age 25: 32”



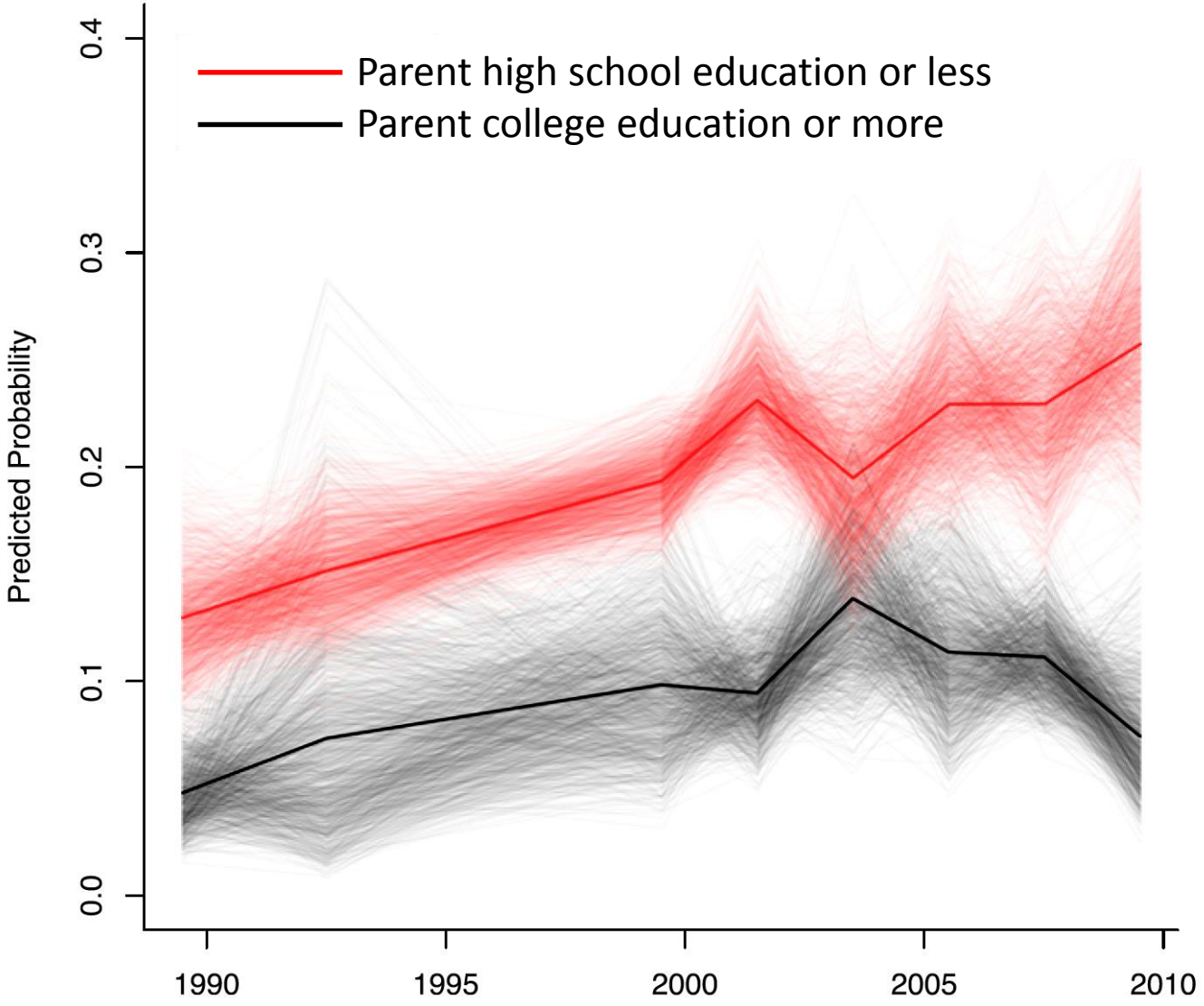
Age 45: 52”



The Seven Deadly Sins
Hieronymus Bosch

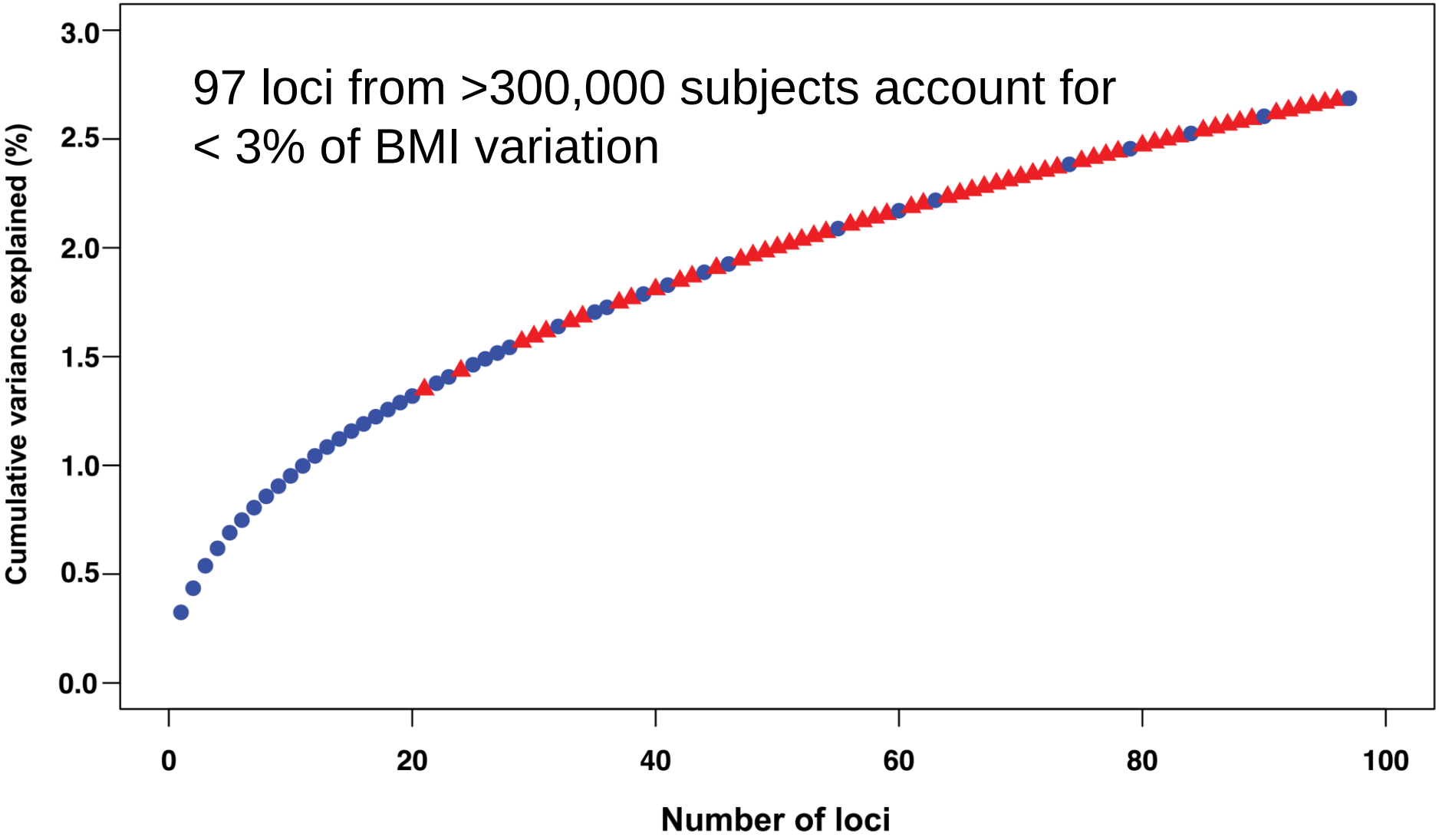
gluttony

Socioeconomic Disparity in Obesity Prevalence Among American Adolescents (NHANES)



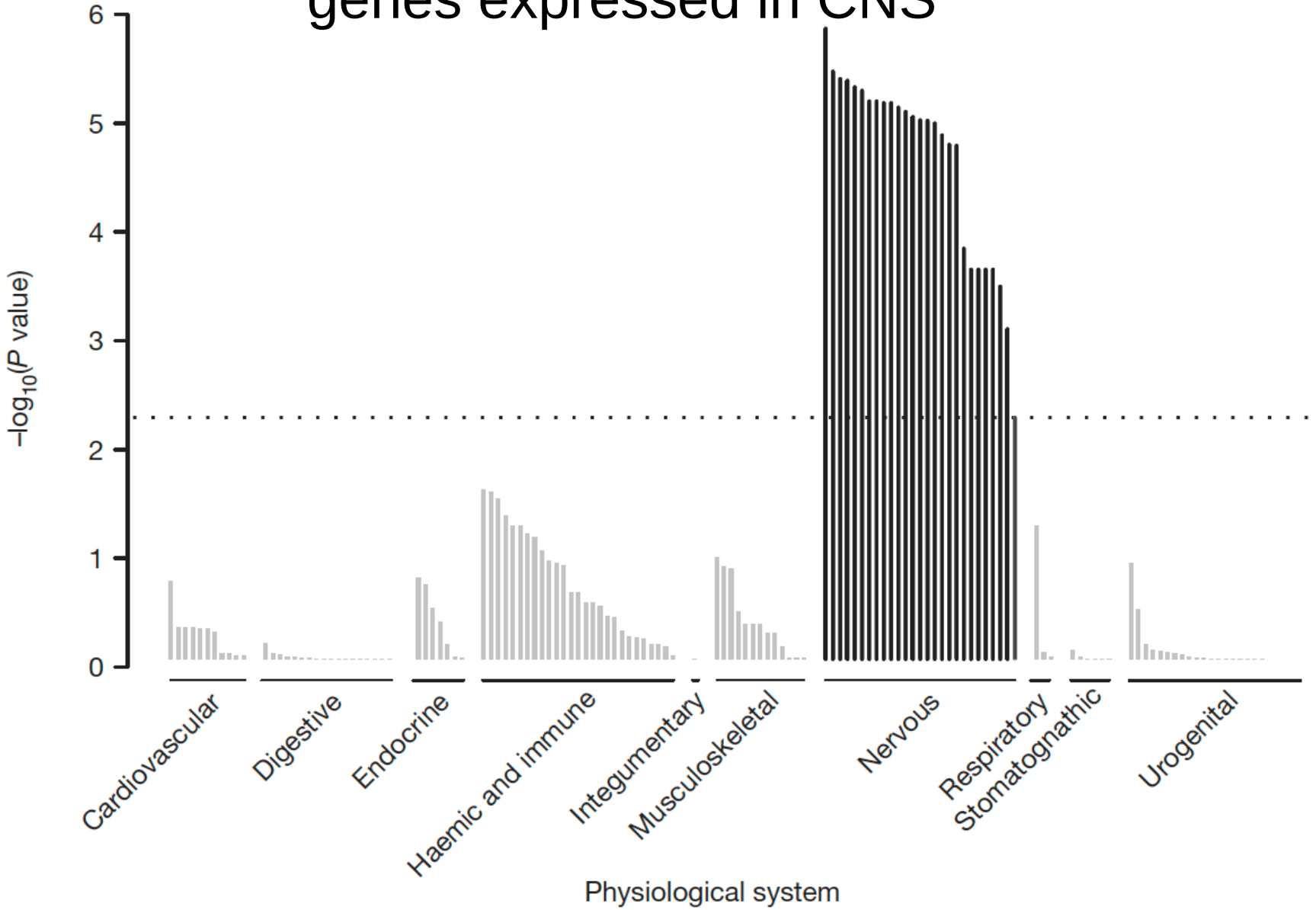
Frederick et al. PNAS, 111:1338-42 (2014)

Genetic studies of body mass index yield new insights for obesity biology



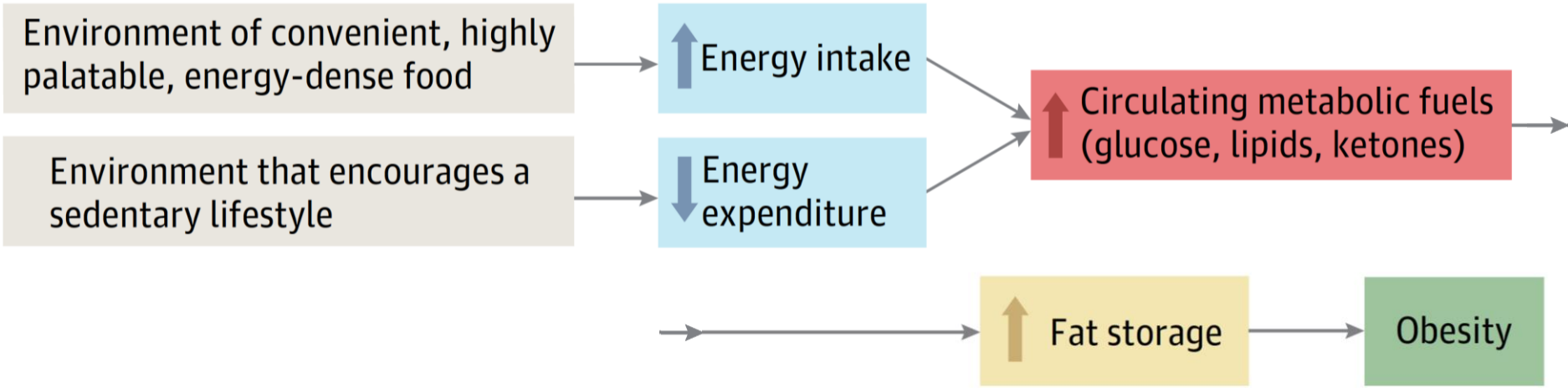
Locke, Hirschhorn et al. Nature, 518: 197–206 (2015)

Most obesity SNP variants located in genes expressed in CNS

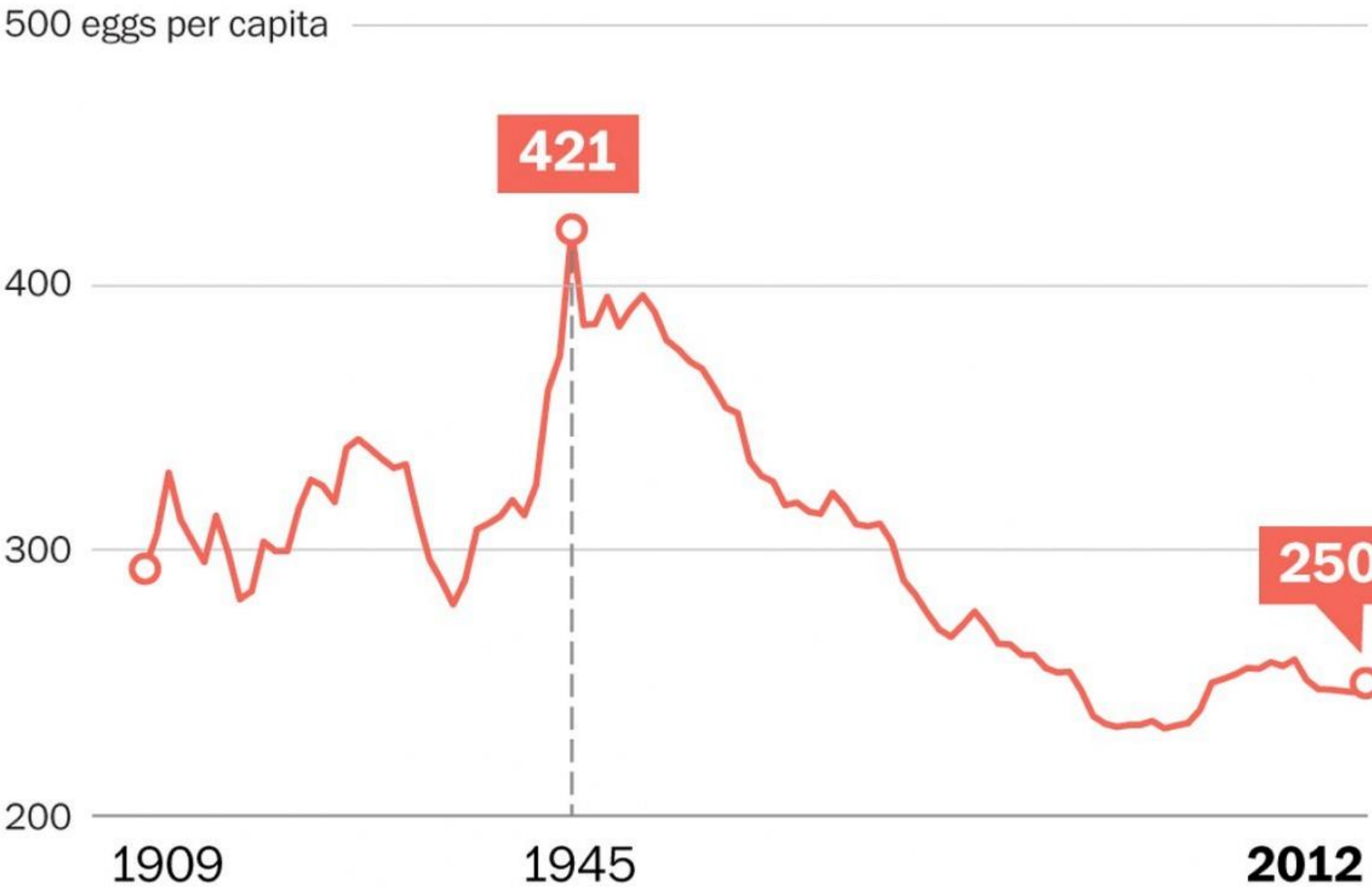


Locke, Hirschhorn et al. Nature, 518: 197–206 (2015)

Prevailing Model of Cause of Recent Obesity Epidemic



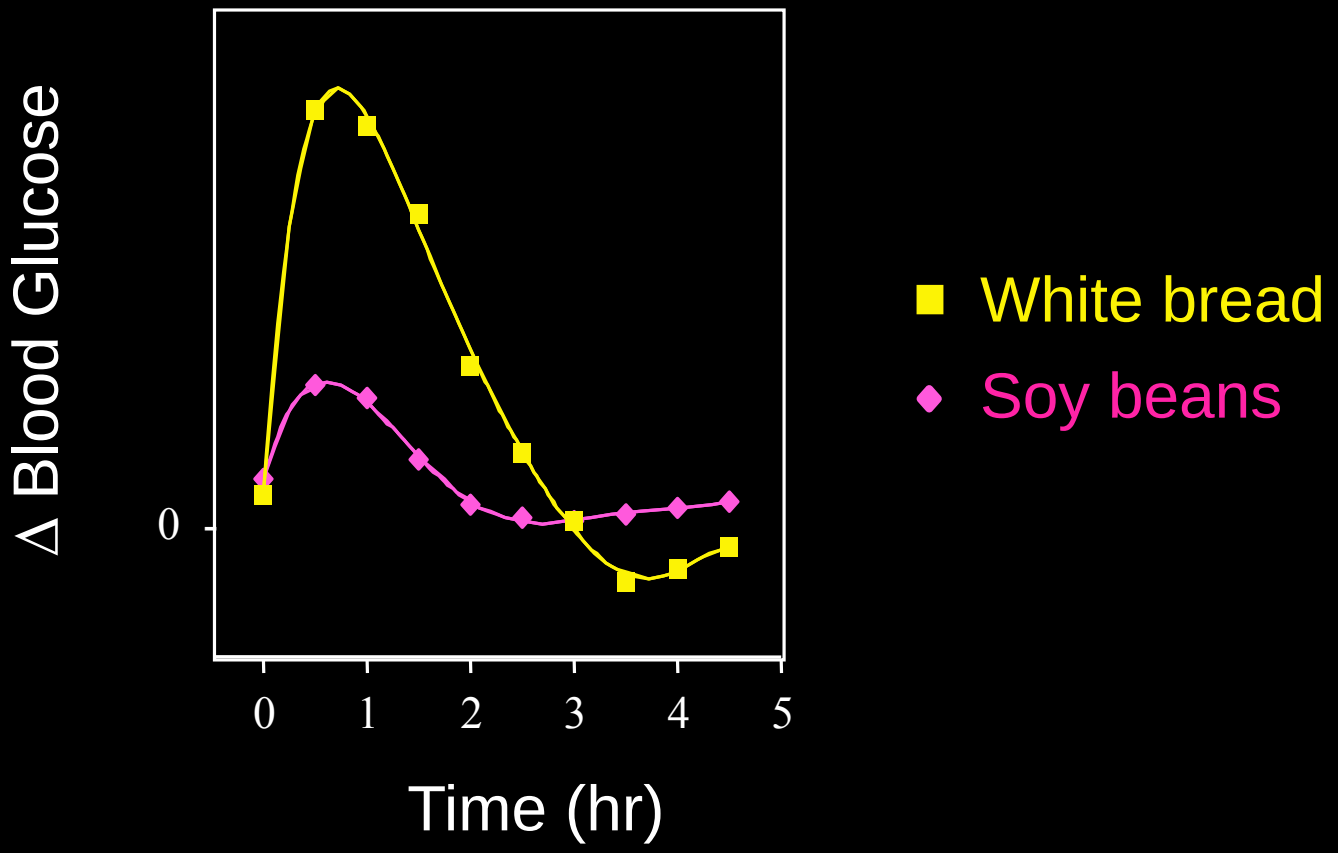
Ludwig et al. JAMA. 311:2167. (2014)



1984 USDA Food Guide Pyramid

Glycemic Index

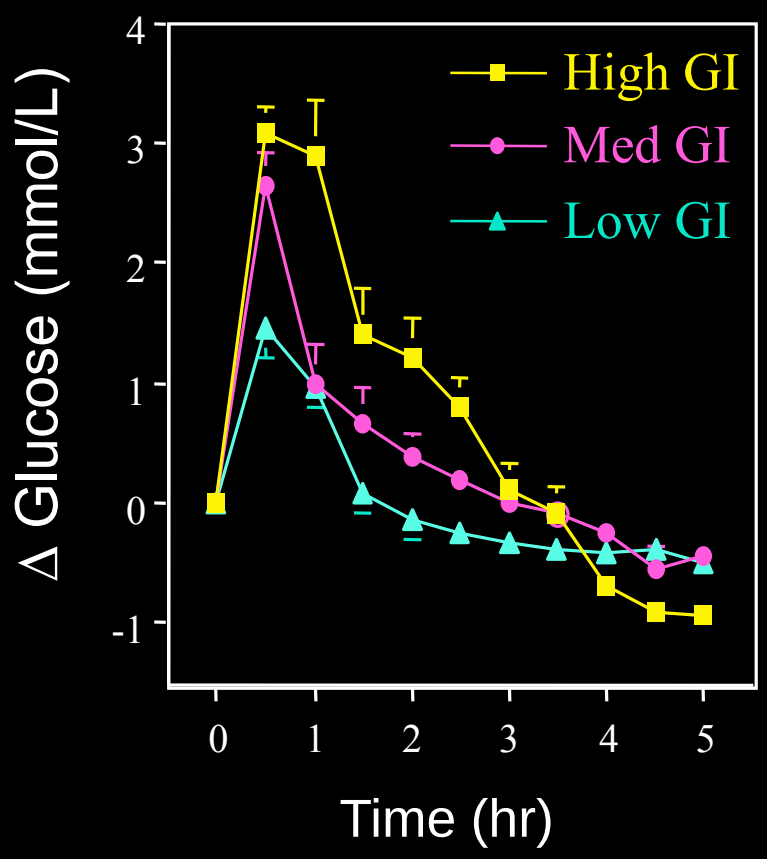
A physiological basis for classifying carbohydrate



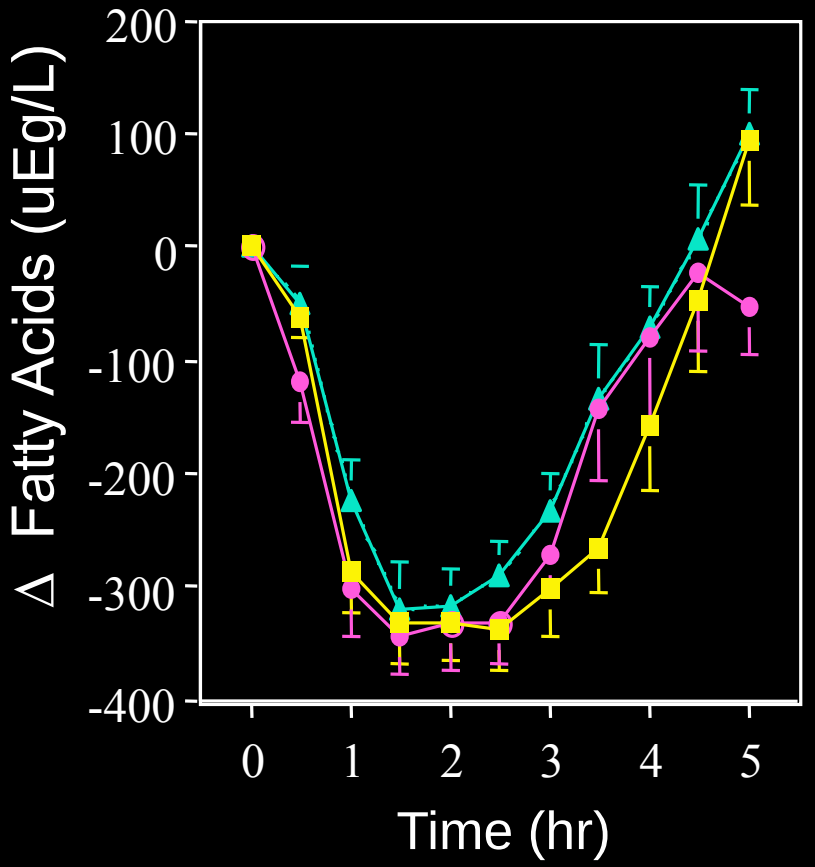
Area under the glycemic curve after consumption of 50 g CHO from test food divided by area under curve after 50 g CHO from control food

David Ludwig

GI & Regulation of Food Intake



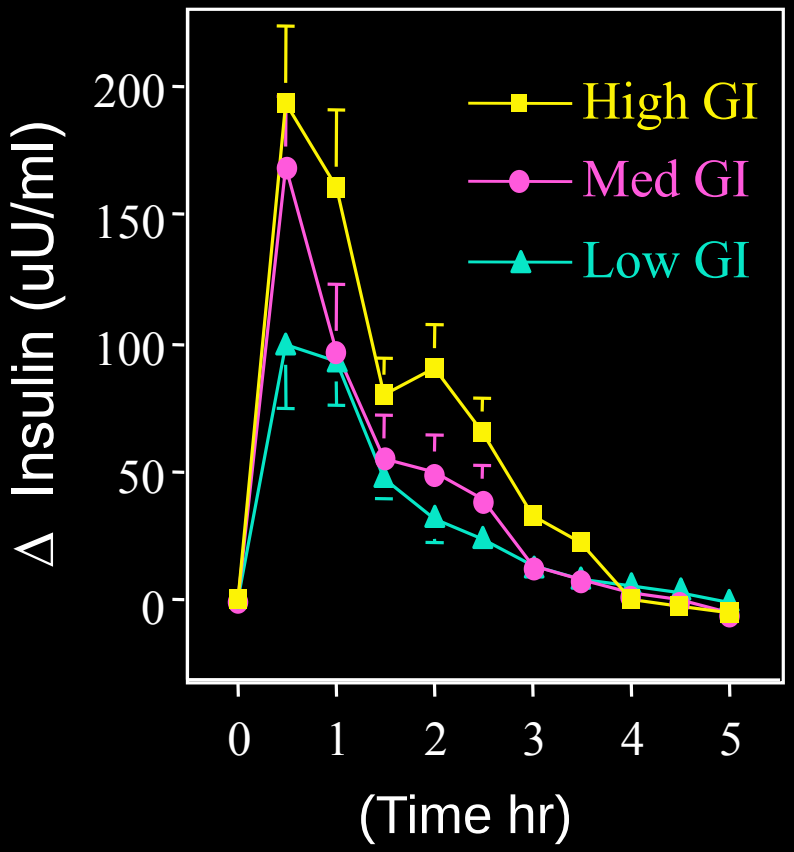
Blood Glucose



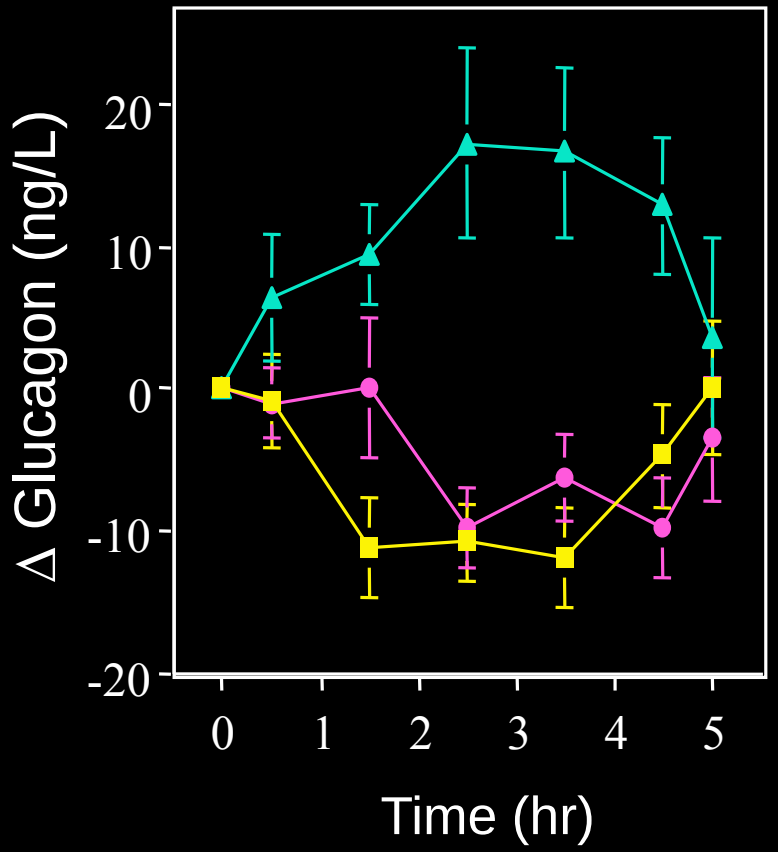
Plasma Free Fatty Acids

Ludwig et al. Pediatrics, 103:e261. (1999)

GI & Regulation of Food Intake



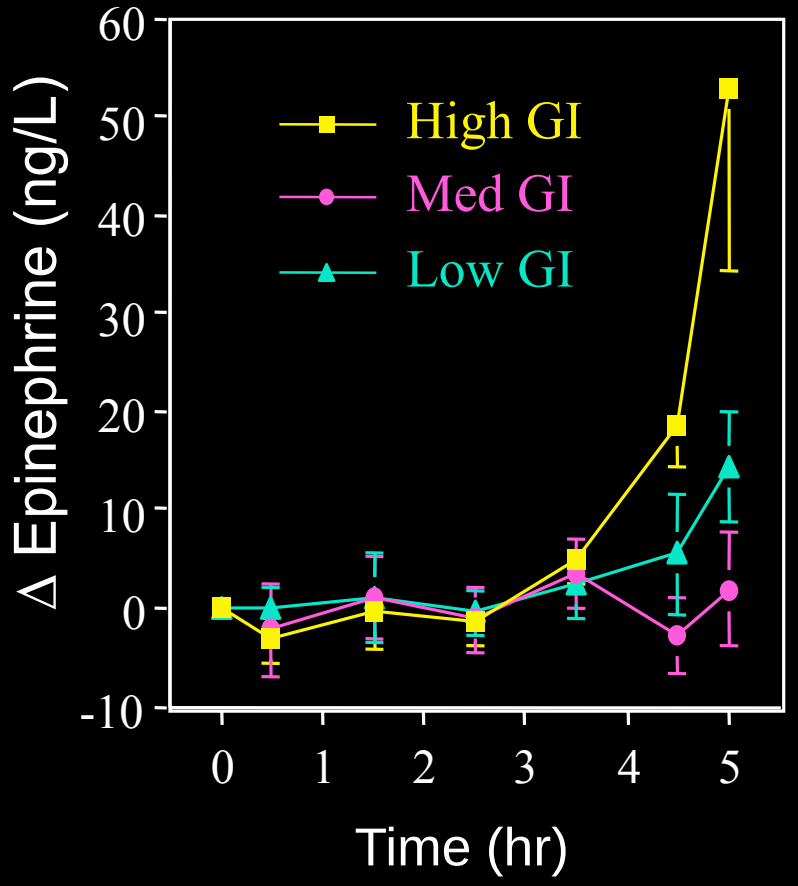
Serum Insulin



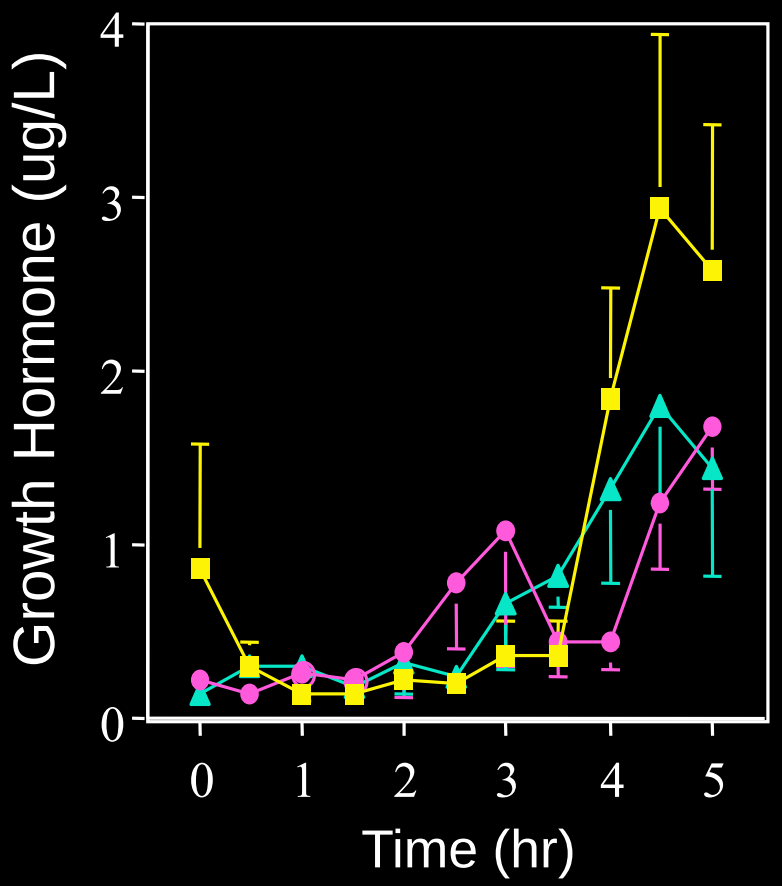
Plasma Glucagon

Ludwig et al. Pediatrics, 103:e261. (1999)

GI & Regulation of Food Intake



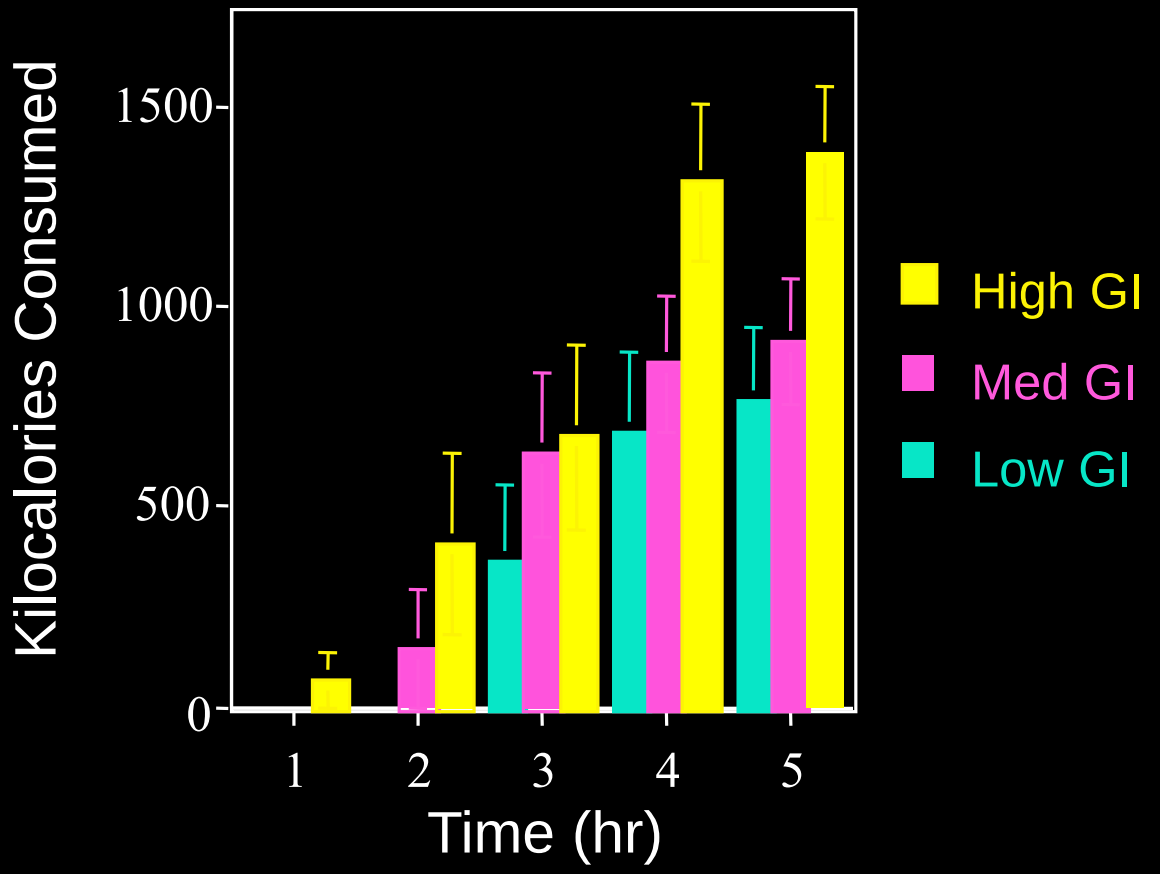
Plasma Epinephrine



Serum Growth Hormone

Ludwig et al. Pediatrics, 103:e261. (1999)

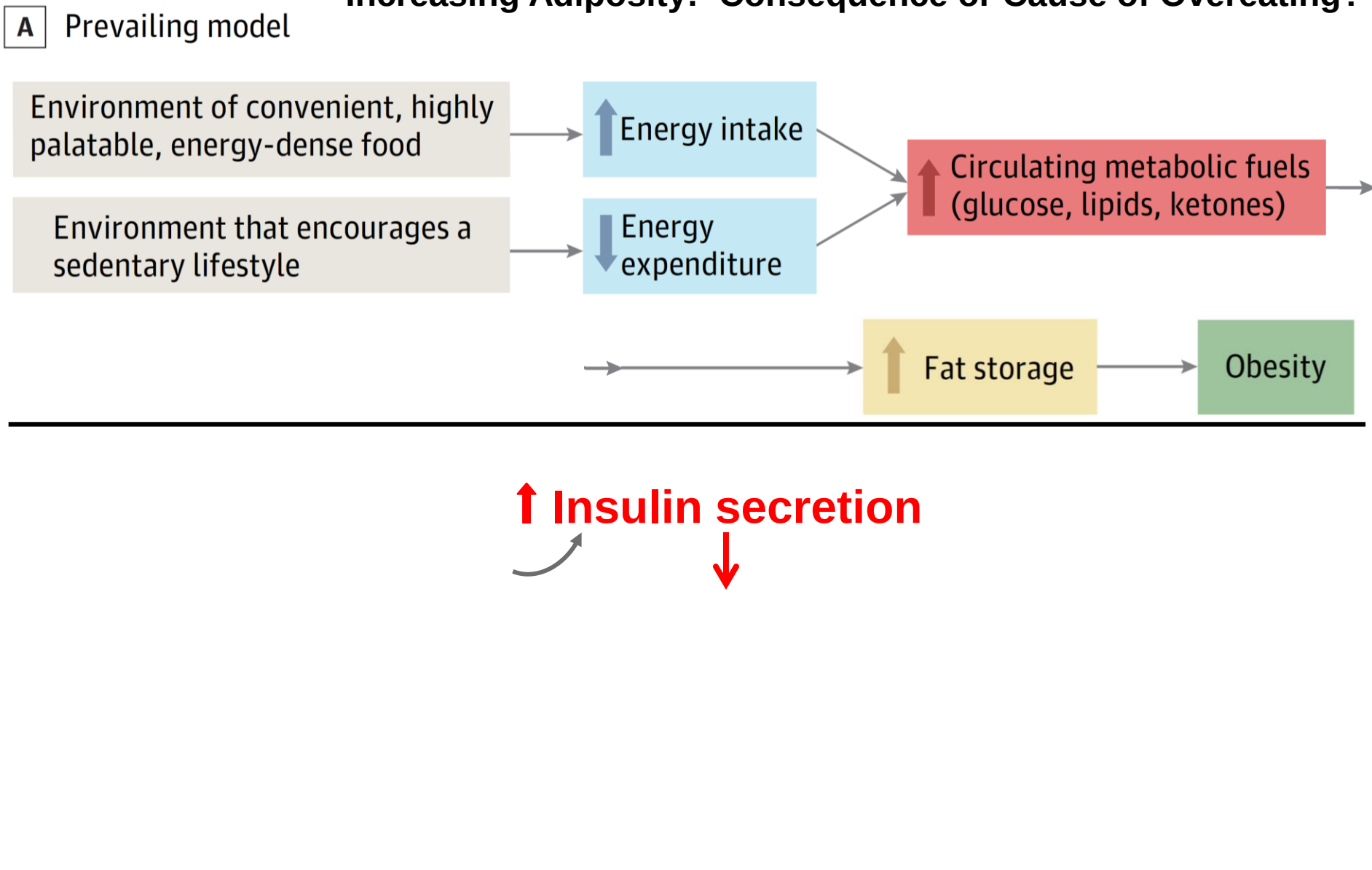
GI & Regulation of Food Intake



Ludwig et al. Pediatrics, 103:e261. (1999)

Time to put eggs back on the menu (Deb Lindsey for The Washington Post)

Increasing Adiposity: Consequence or Cause of Overeating?



Ludwig et al. JAMA. 311:2167. (2014)

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.

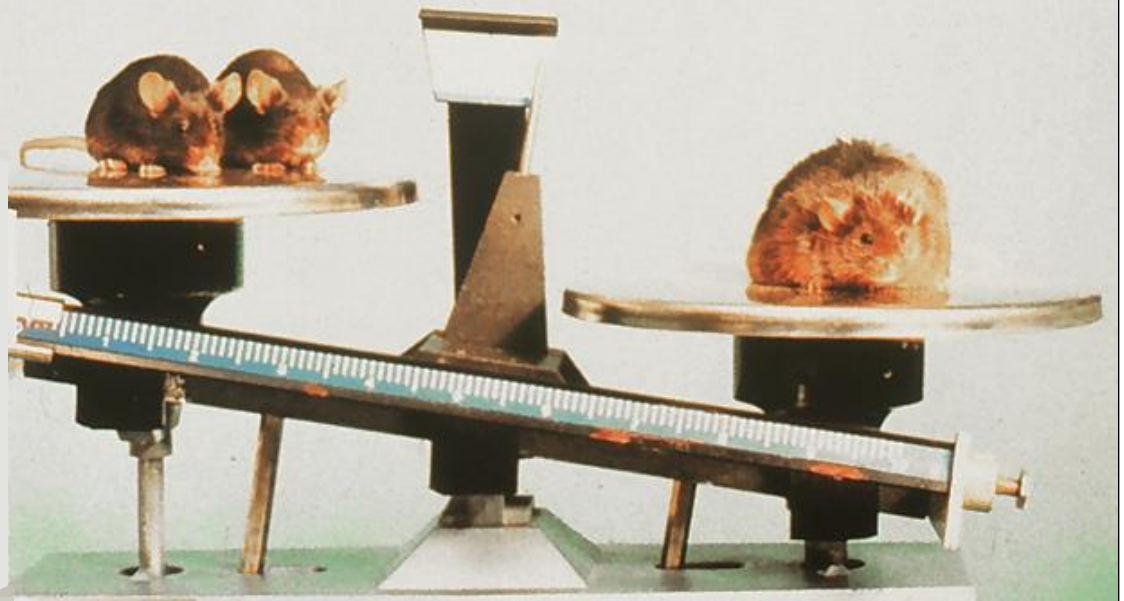
Ebbeling et al. NEJM 367:1407 (2012)

Ludwig et al. JAMA 311:2167 (2014)

nature

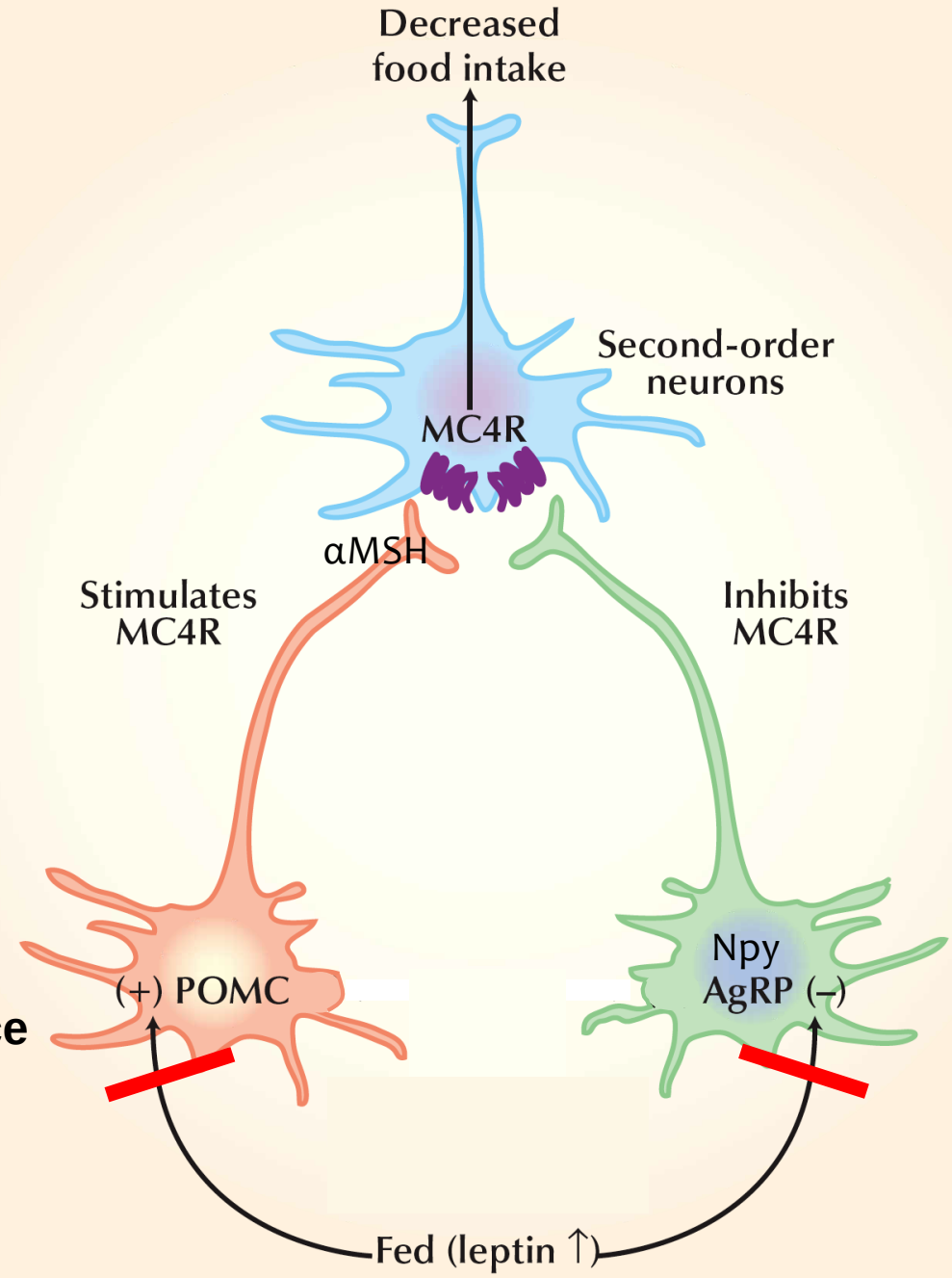
INTERNATIONAL WEEKLY JOURNAL OF SCIENCE

Volume 372 No. 6505 1 December 1994 $8.50

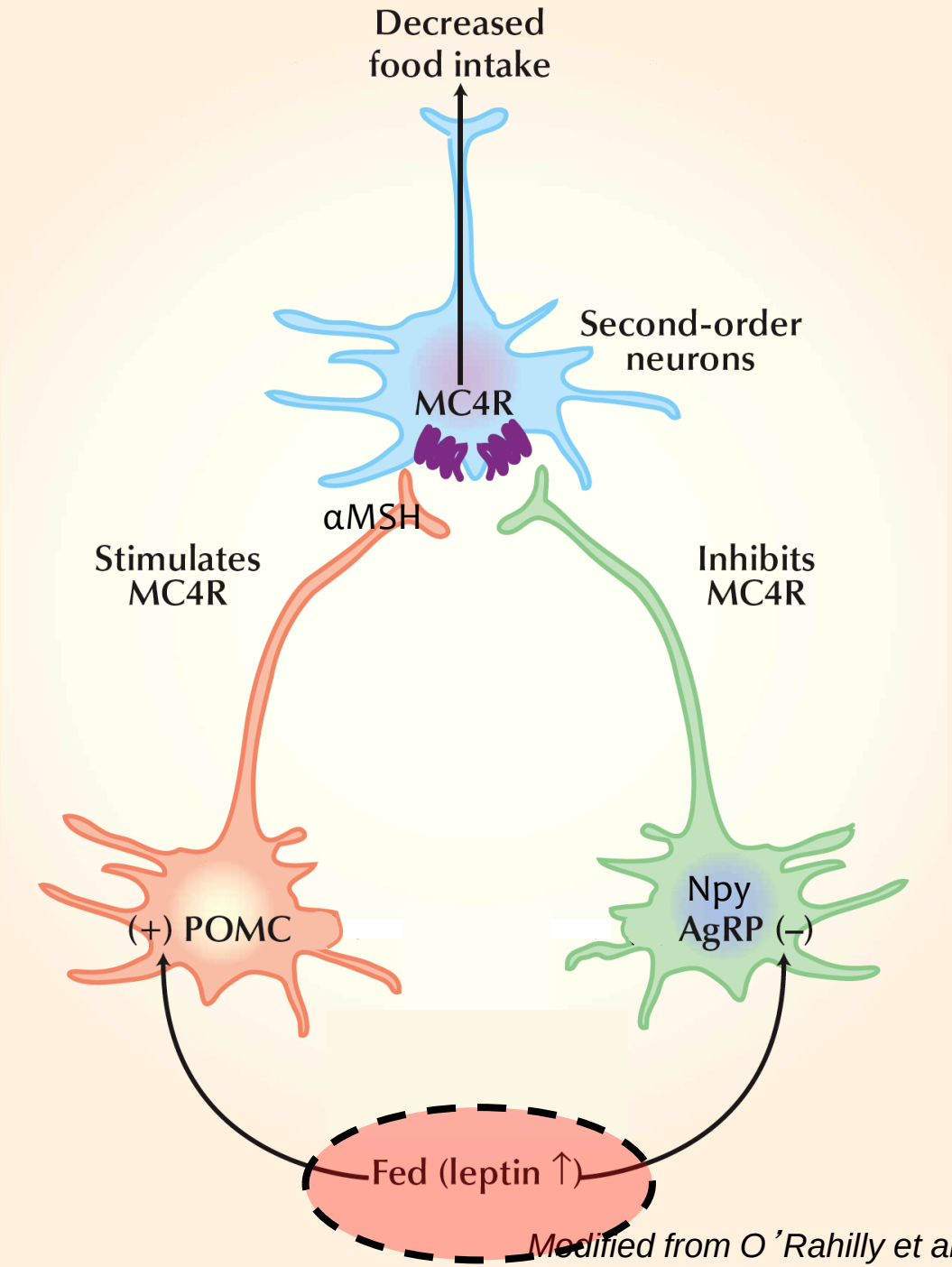


Mouse weighed down by genetics

Leptin Resistance in Obesity

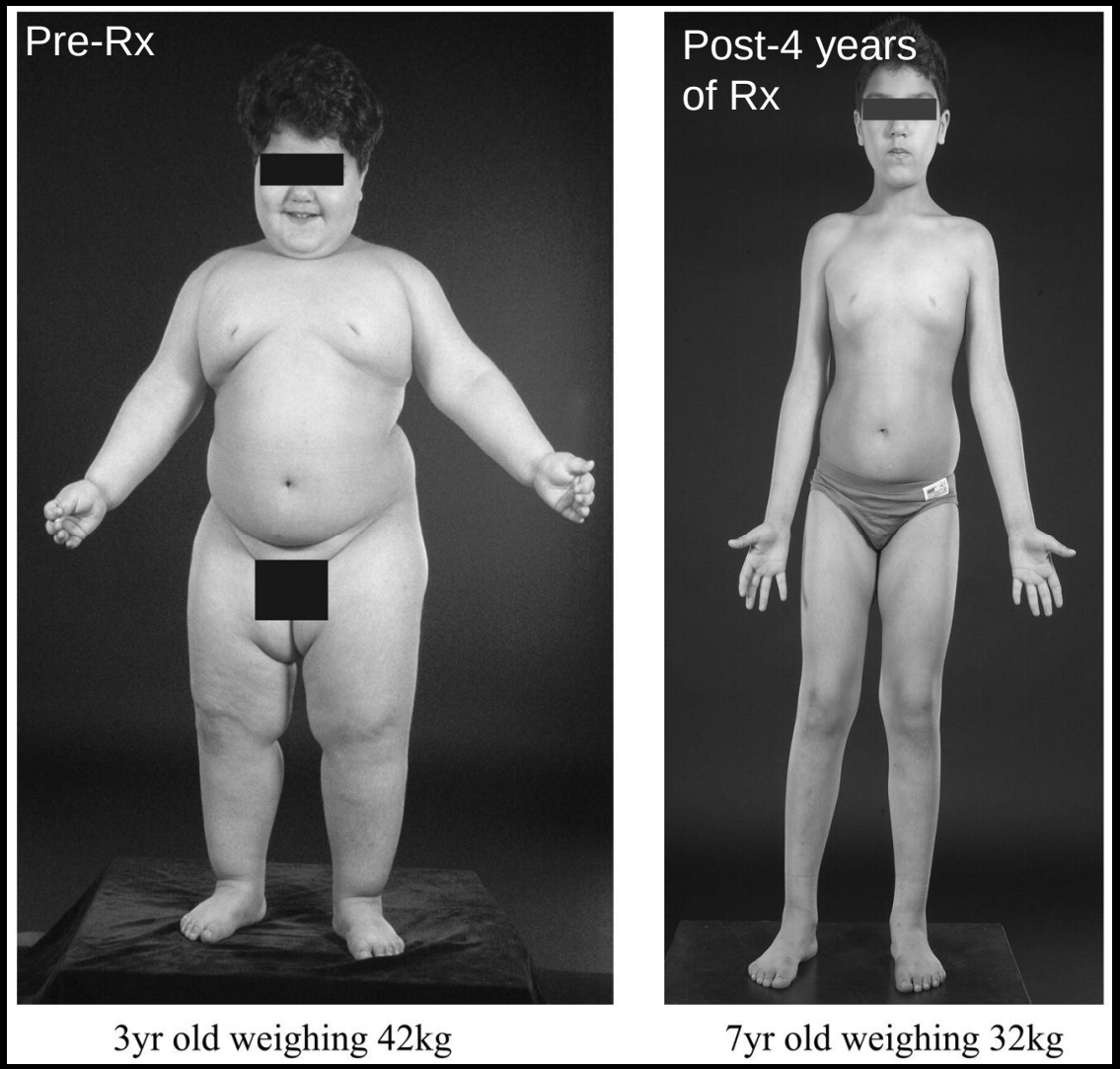


Modified from O'Rahilly et al. Nat Med, 10:351, 2004



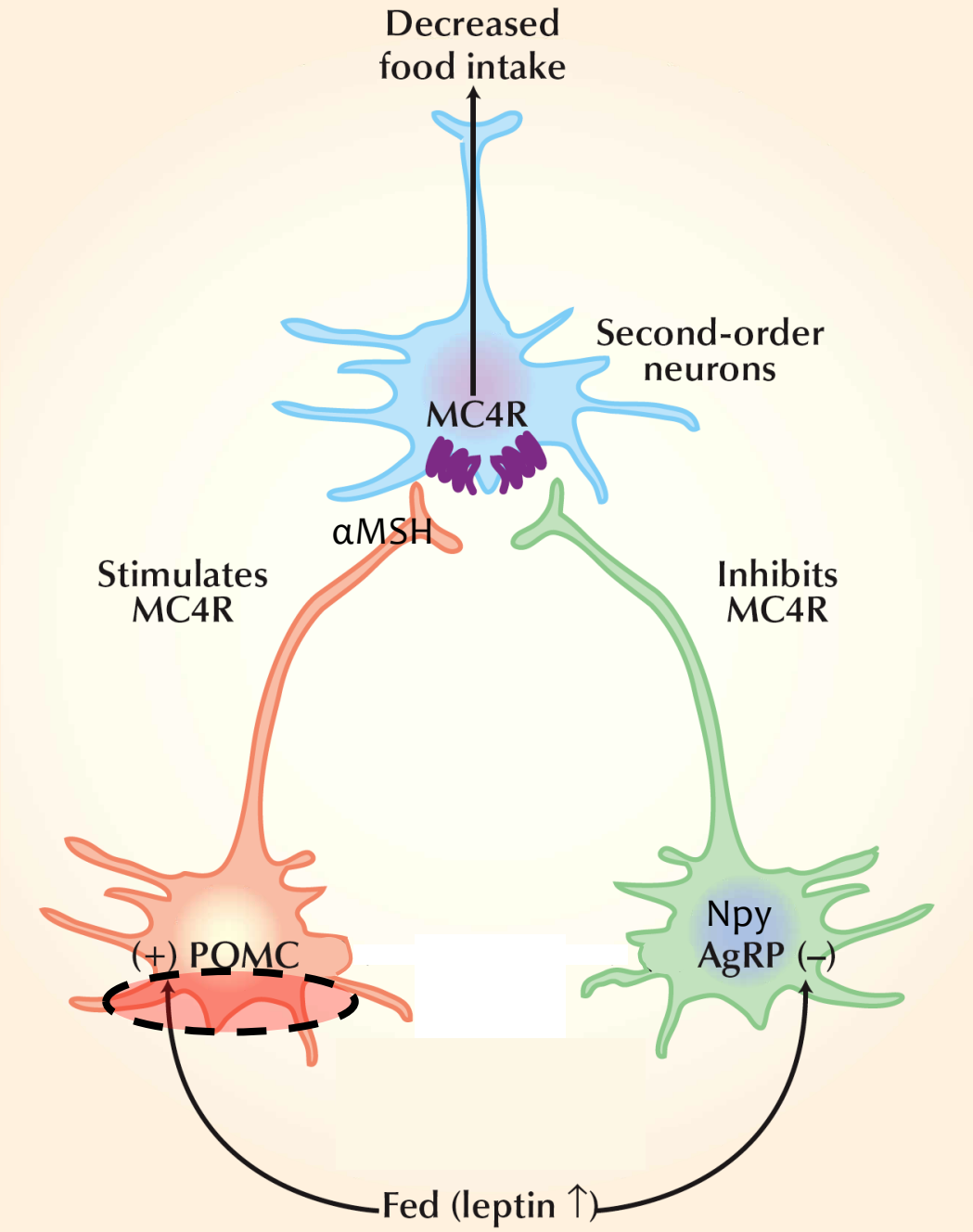
Modified from O'Rahilly et al. Nat Med, 10:351, 2004

Human *LEP* Mutation



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

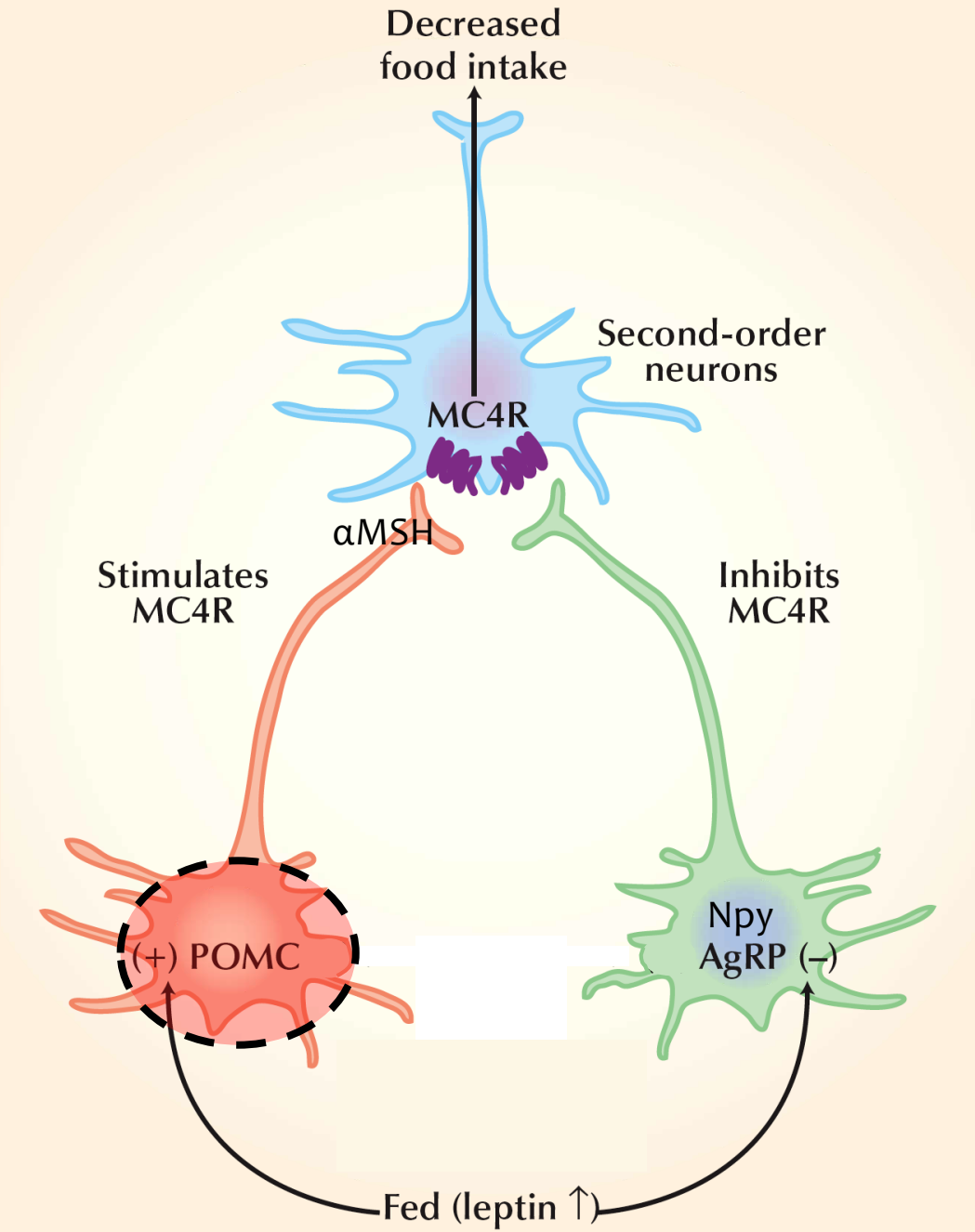
Farooqi and O'Rahilly, Rec Prog Horm Res 59:409, 2004


Decreased
food intake
Second-order
neurons
MC4R
αMSH
Stimulates
MC4R
Inhibits
MC4R
(+) POMC
Npy
AgRP (–)
Fed (leptin ↑)

Human *LEPR* Mutation

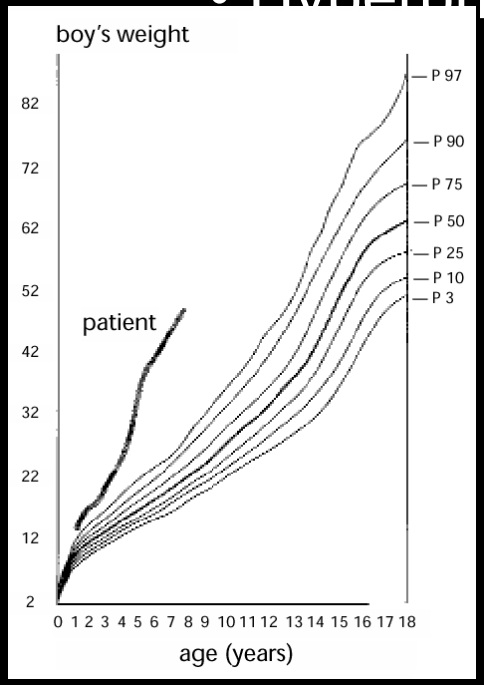
- Autosomal recessive, high penetrance
- Very rare monogenic cause of obesity
- Hyperphagia

Mazen et al. Molecular Genetics and Metabolism 102: 461–464, 2011

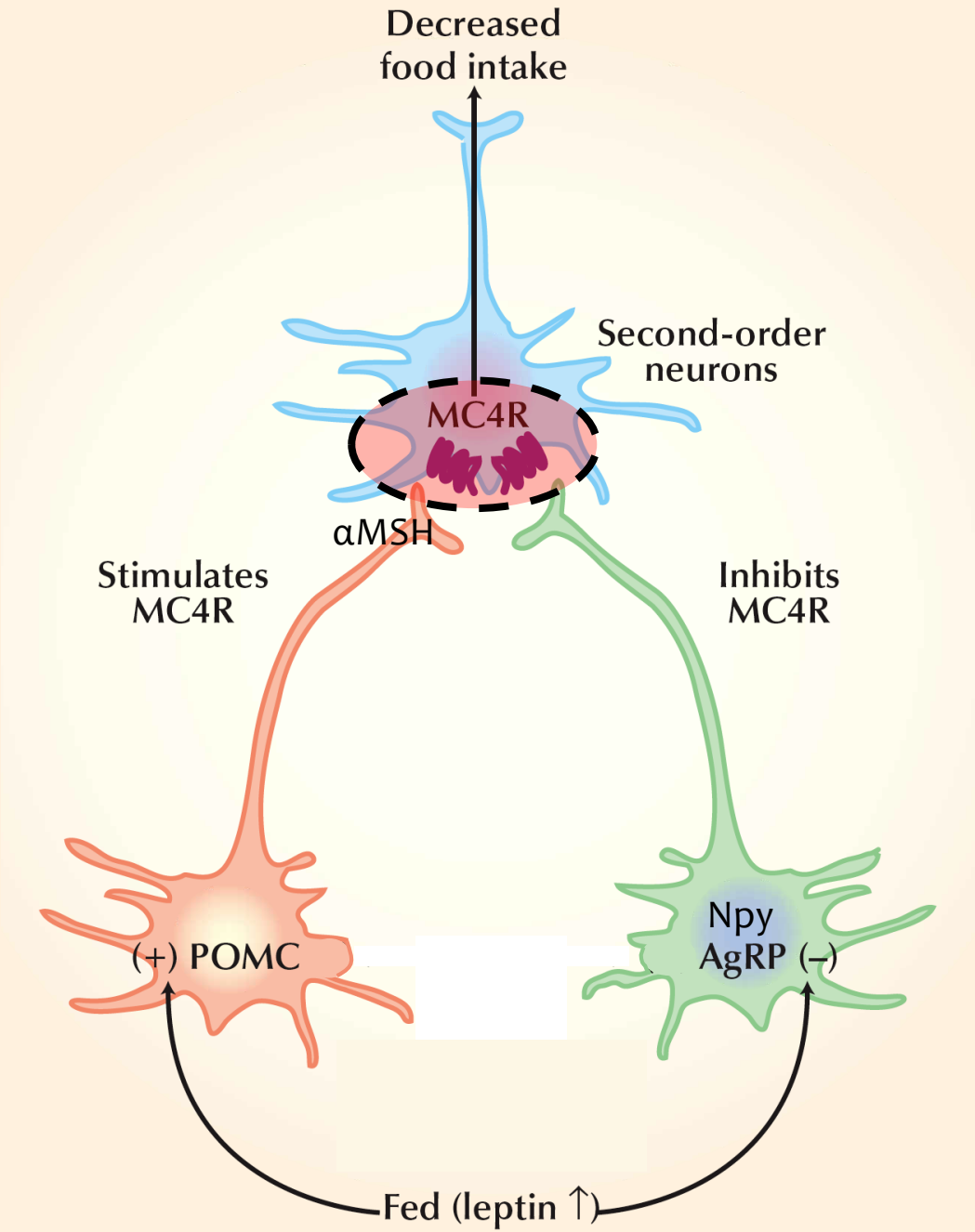

Decreased
food intake
Second-order
neurons
MC4R
αMSH
Stimulates
MC4R
Inhibits
MC4R
(+) POMC
Npy
AgRP (–)
Fed (leptin ↑)

Human *POMC* Mutation

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



Krude and Gruters Nat Genetics 19:155, 1998


Decreased
food intake
Second-order
neurons
MC4R
αMSH
Stimulates
MC4R
Inhibits
MC4R
(+) POMC
Npy
AgRP (–)
Fed (leptin ↑)

Human *MC4R* Mutation

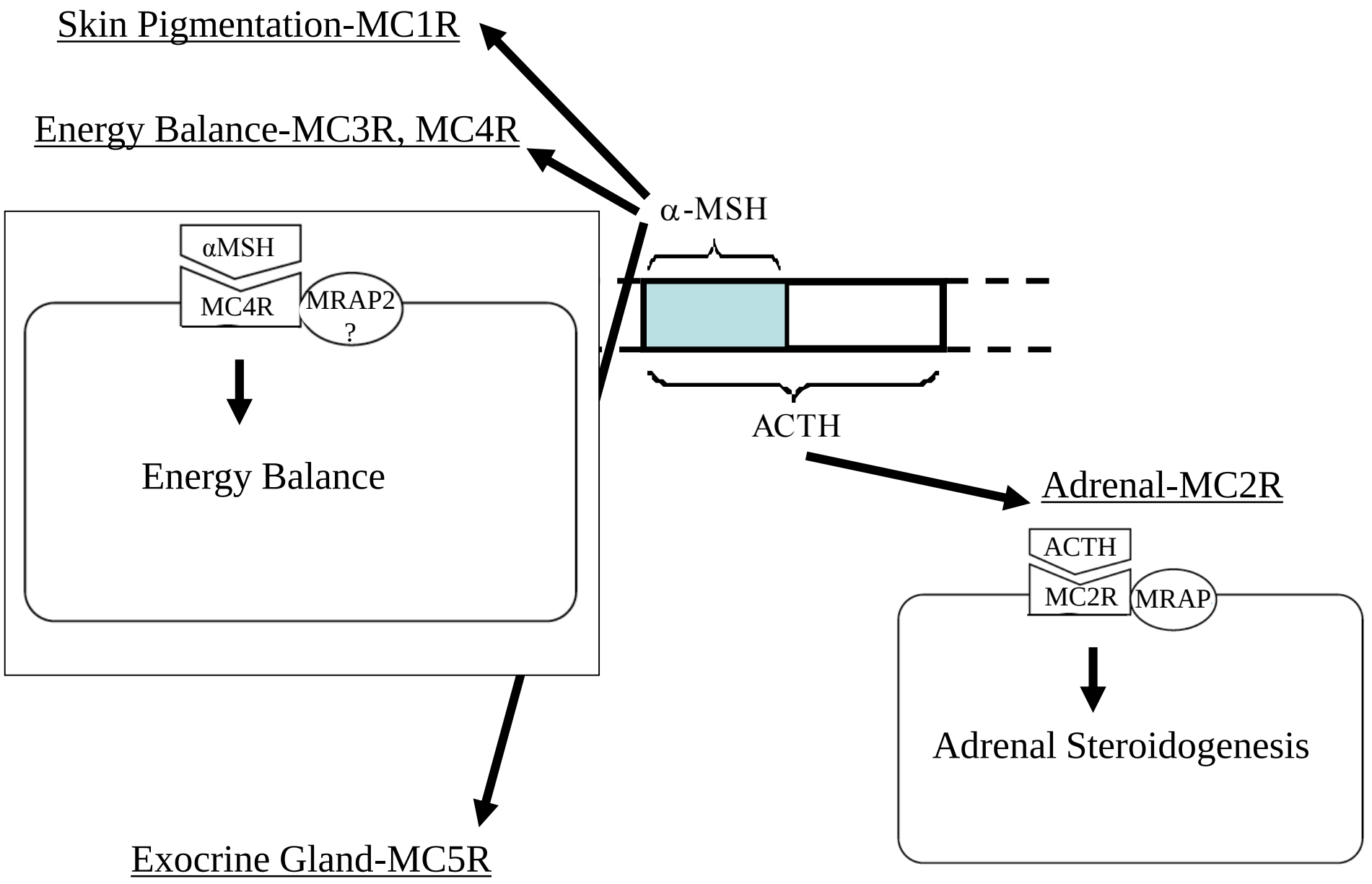
- Autosomal dominant, high penetrance
- Most common (3-5%) monogenic cause of obesity
- Hyperphagia

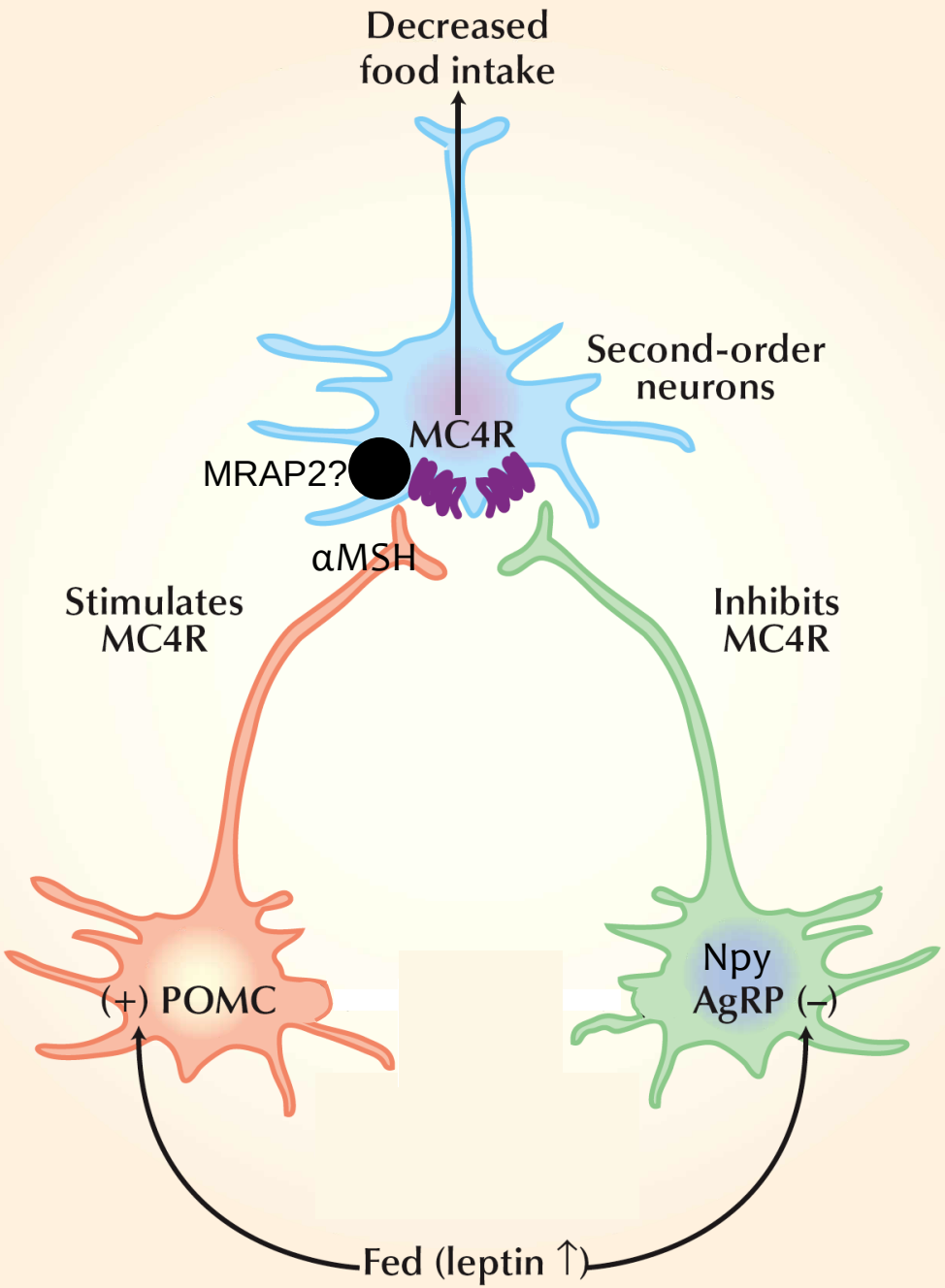
O'Rahilly et al. Nat Med, 10:351, 2004

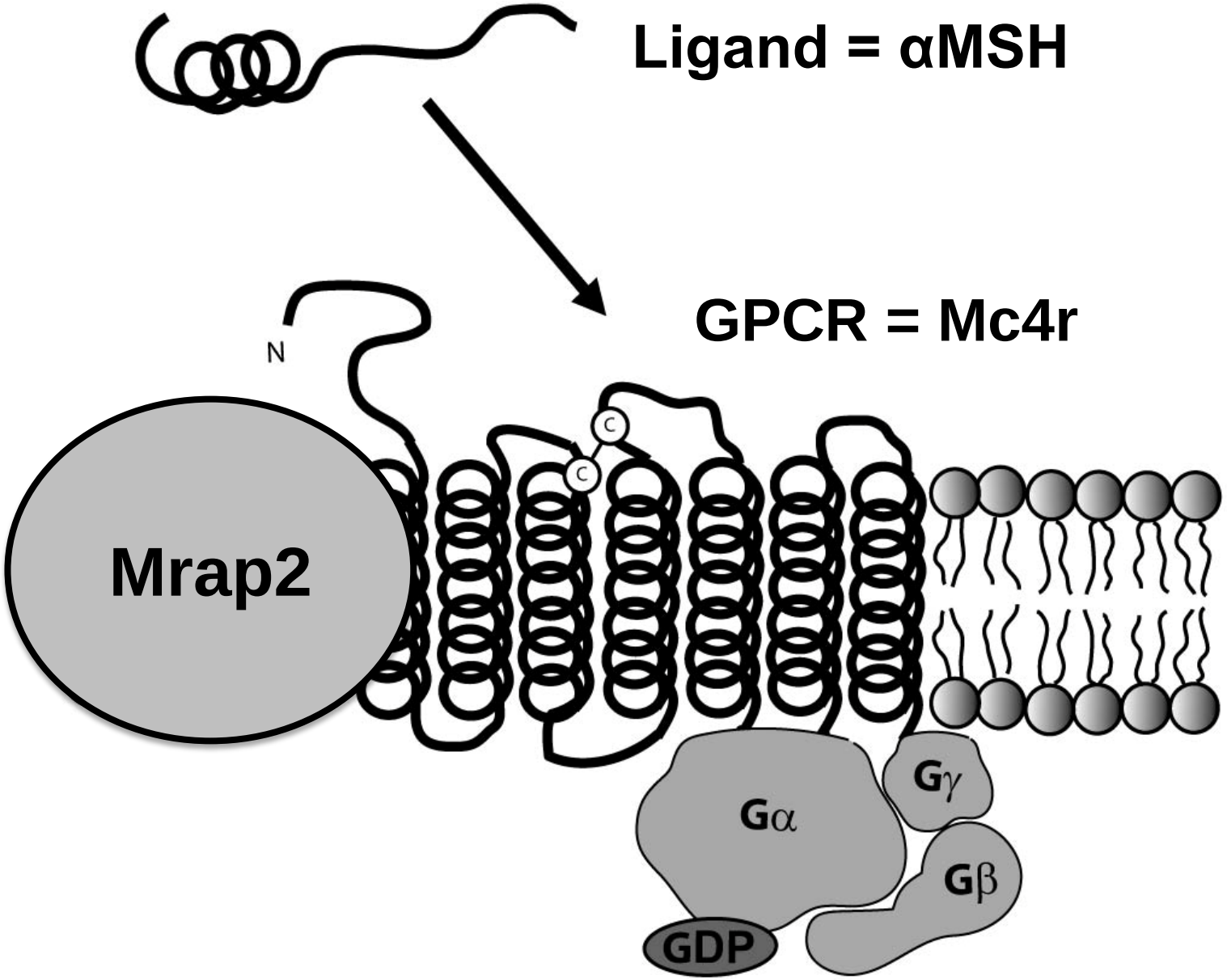
Mutations in *MRAP*, encoding a new interacting partner of the ACTH receptor, cause familial glucocorticoid deficiency type 2

Louise A Metherell[1], J Paul Chapple[2], Sadani Cooray[1], Alessia David[1], Christian Becker[3], Franz Rüschendorf[3], Danielle Naville[4], Martine Begeot[4], Bernard Khoo[1], Peter Nürnberg[3,5], Angela Huebner[6], Michael E Cheetham[2] & Adrian J L Clark[1]

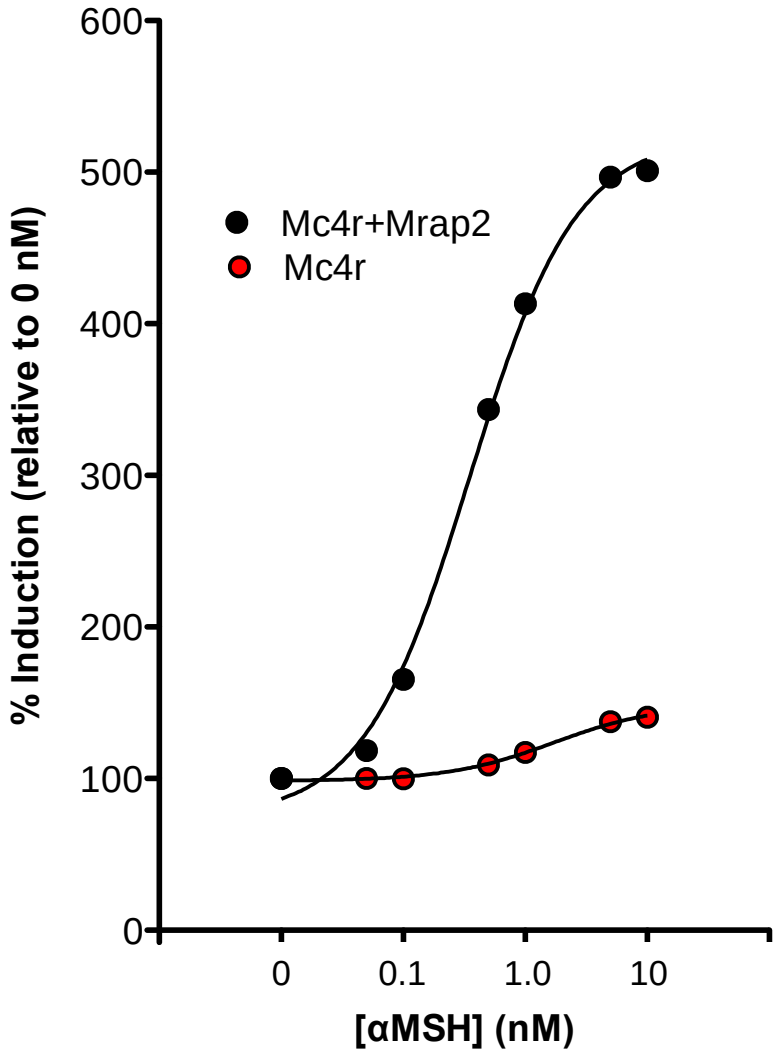
Melanocortin Receptor Family Leads to MRAP2



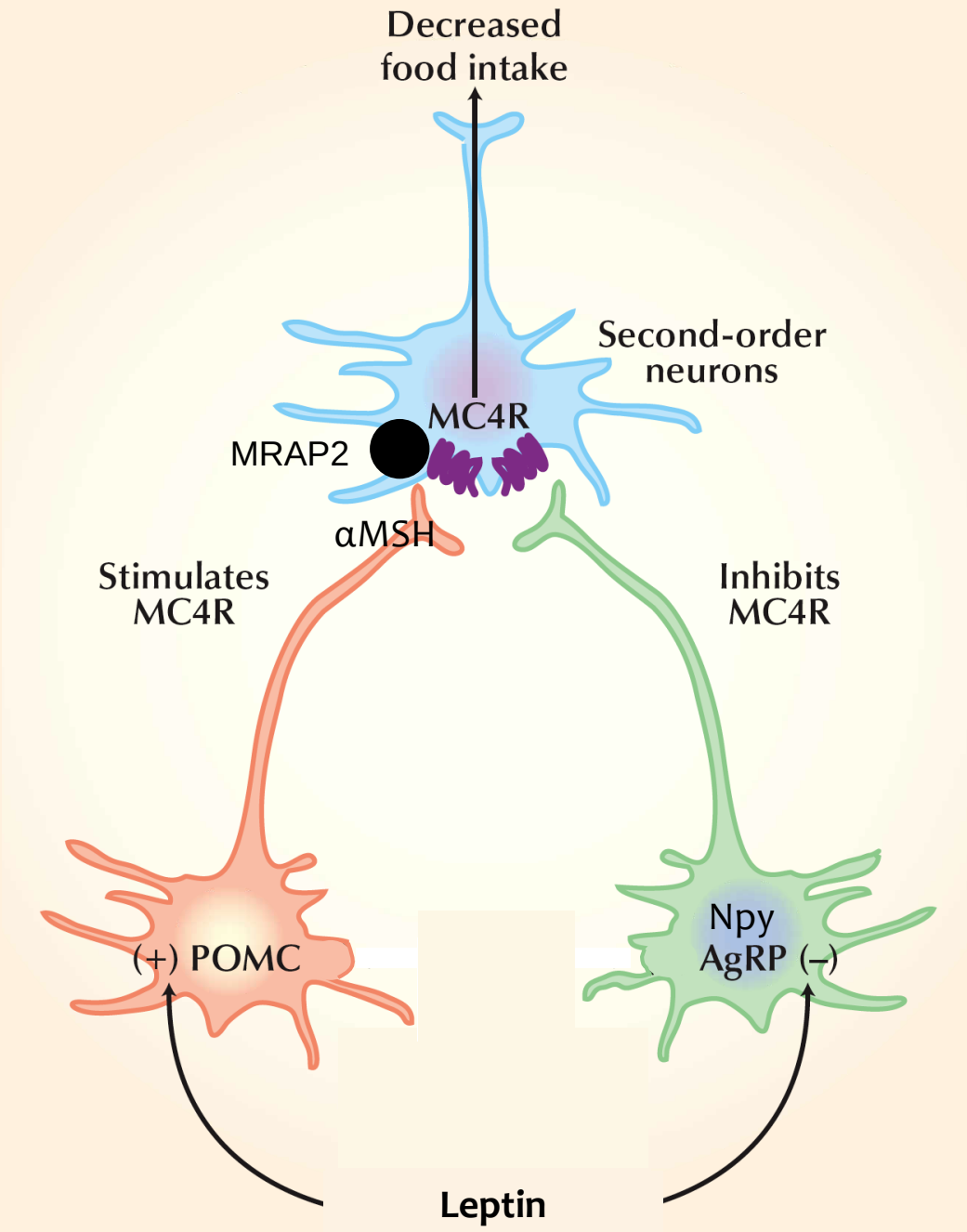

Decreased
food intake
Second-order
neurons
MC4R
MRAP2?
αMSH
Stimulates
MC4R
Inhibits
MC4R
(+) POMC
Npy
AgRP (–)
Fed (leptin ↑)


Ligand = αMSH
GPCR = Mc4r
N
C
C
Mrap2
Gγ
Gα
Gβ
GDP

Mrap2 enhances αMSH signaling via Mc4r



Asai et al. Science 341, 275, 2013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MC4R
MRAP2
αMSH
Stimulates
MC4R
Inhibits
MC4R
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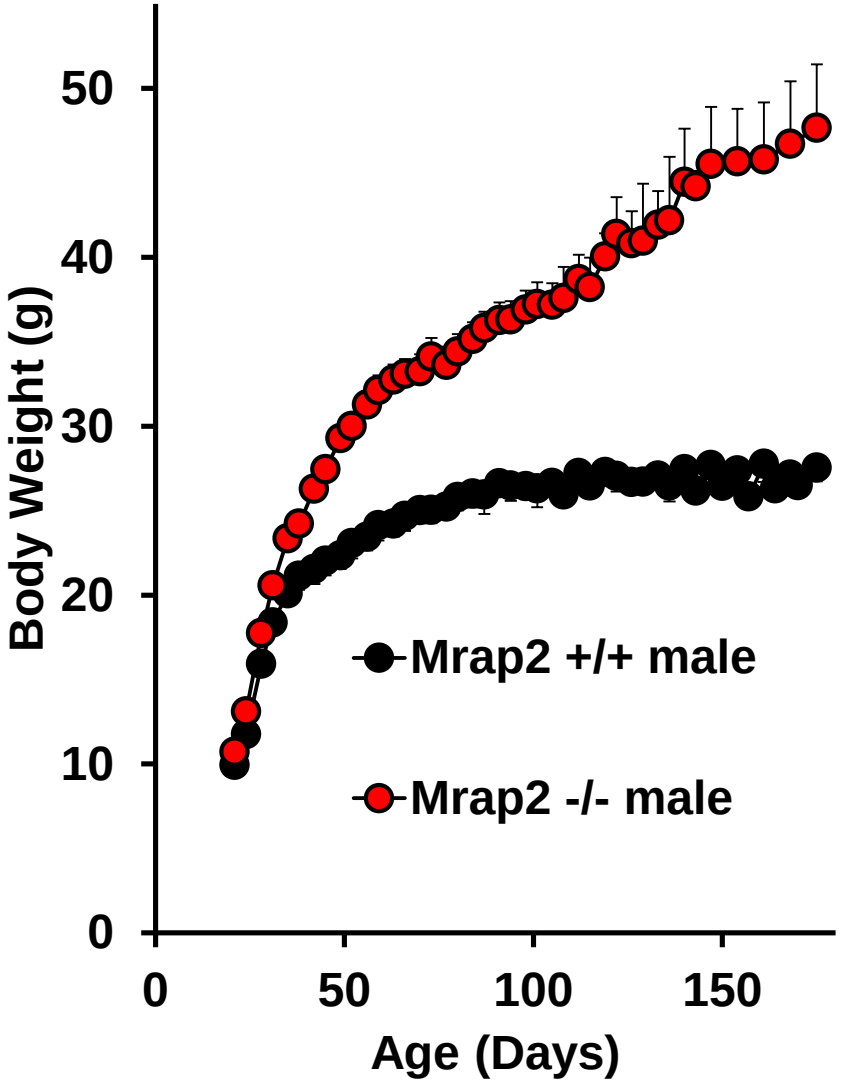
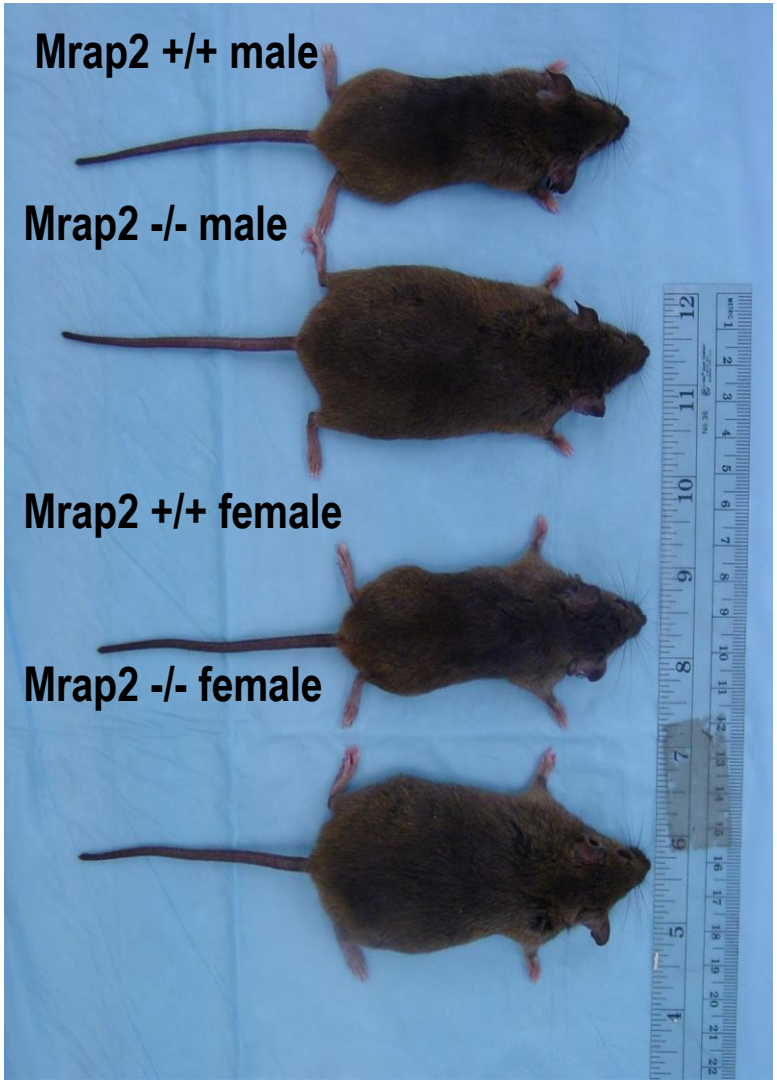
Npy
AgRP (–)
Leptin

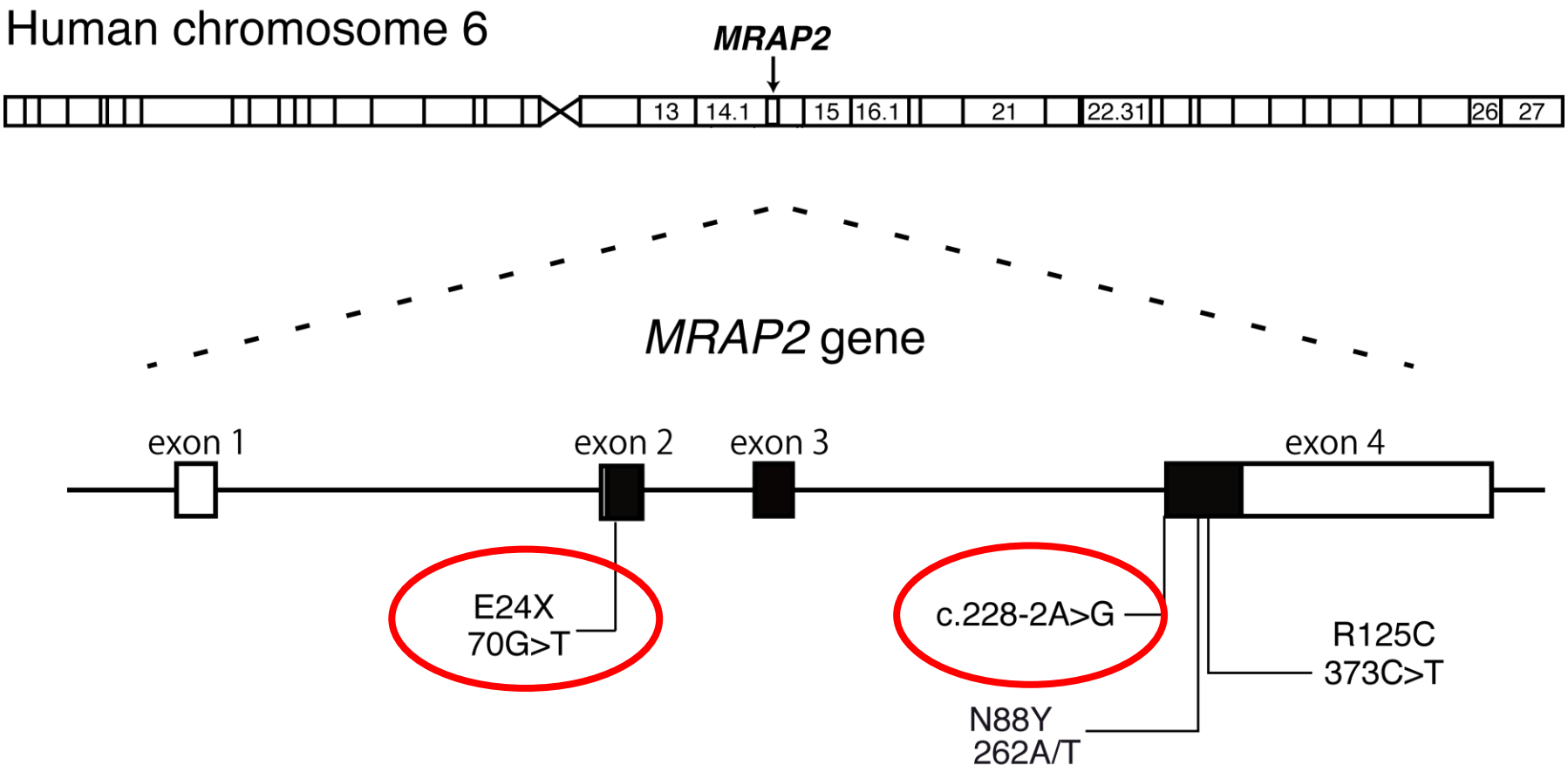
*Mrap2*KO Mice are Obese





Asai et al. Science 341, 275, 2013

Mutations in *MRAP2* in obese humans

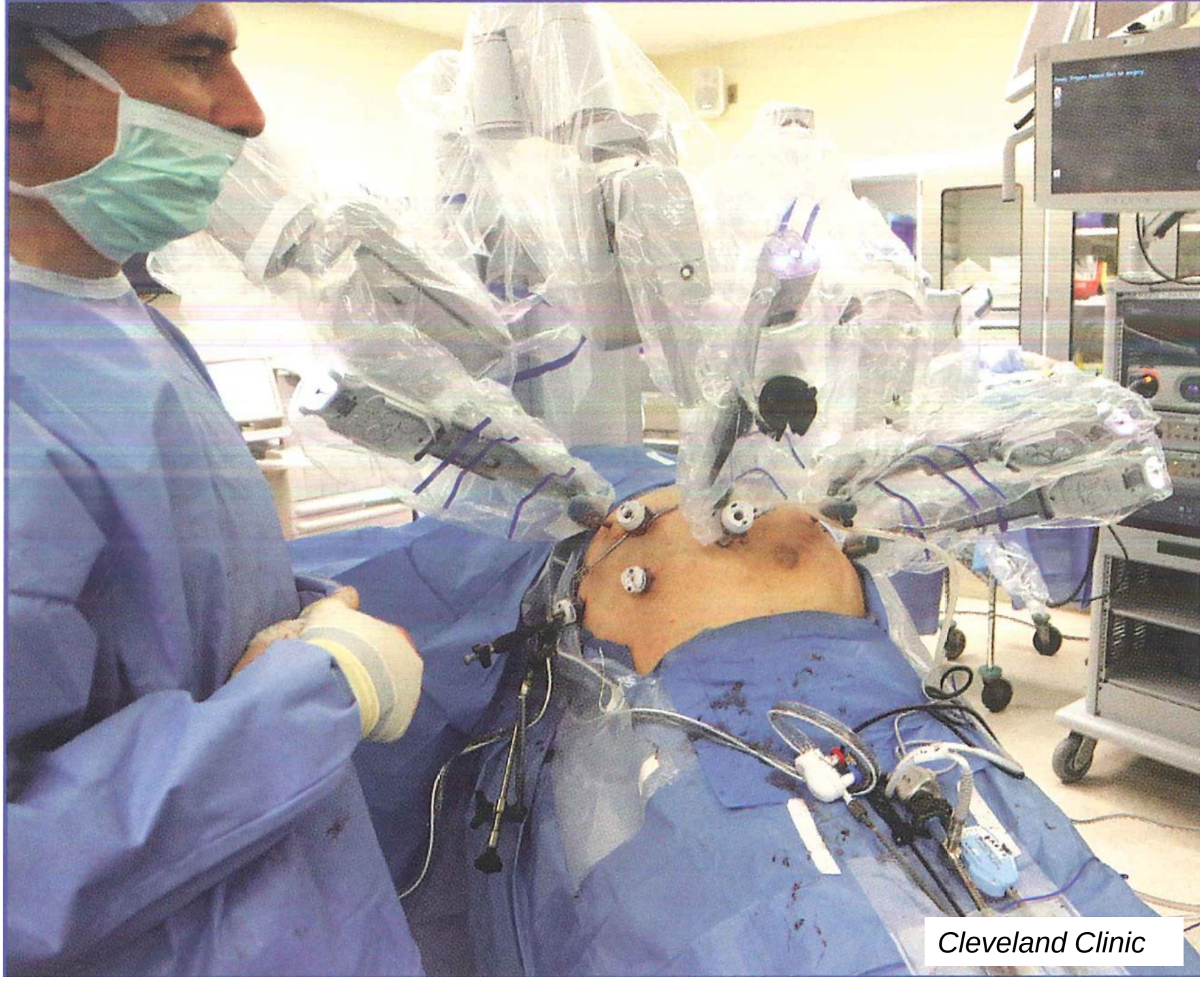


Rare (loss of function) mutations →important biology

More common mutations →important pathophysiology?

Rationale for Metabolic Surgery in Adolescents

- Curative and preventive strategy
- Most effective (but also most invasive) treatment available

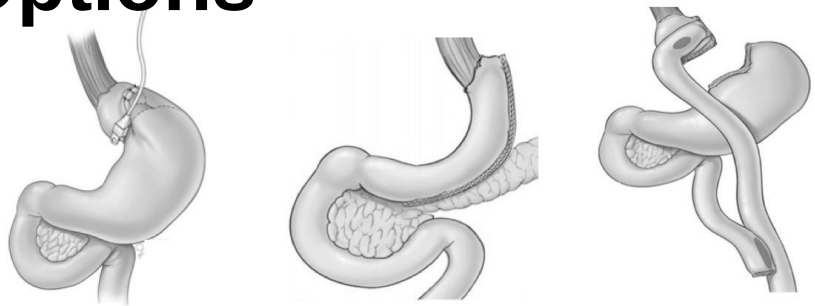

Cleveland Clinic

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

Ideal Treatment ---------->

Effectiveness

Invasiveness

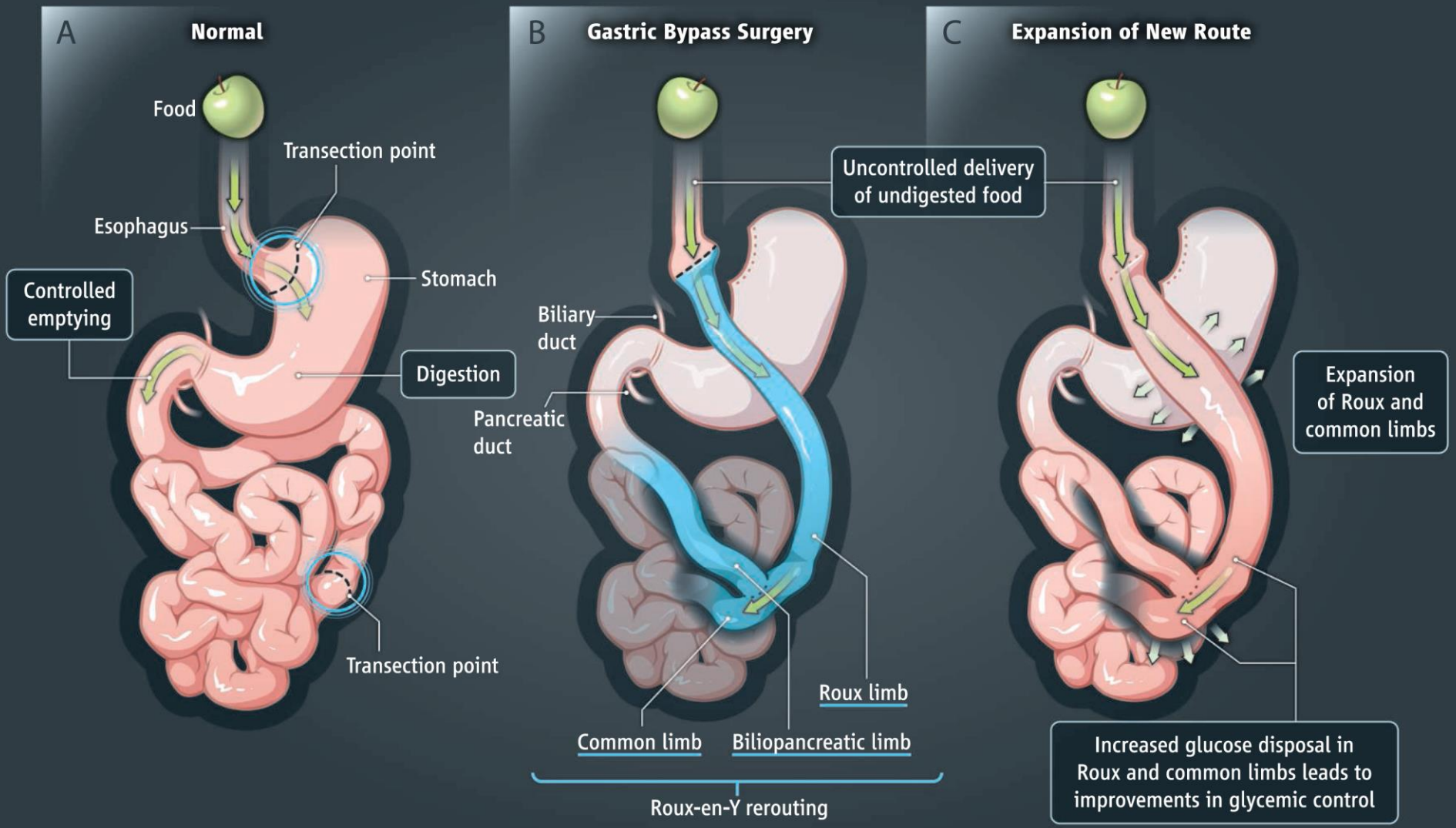
Nicholas Stylopoulos

Challenges of Bariatric Surgery in Adolescents

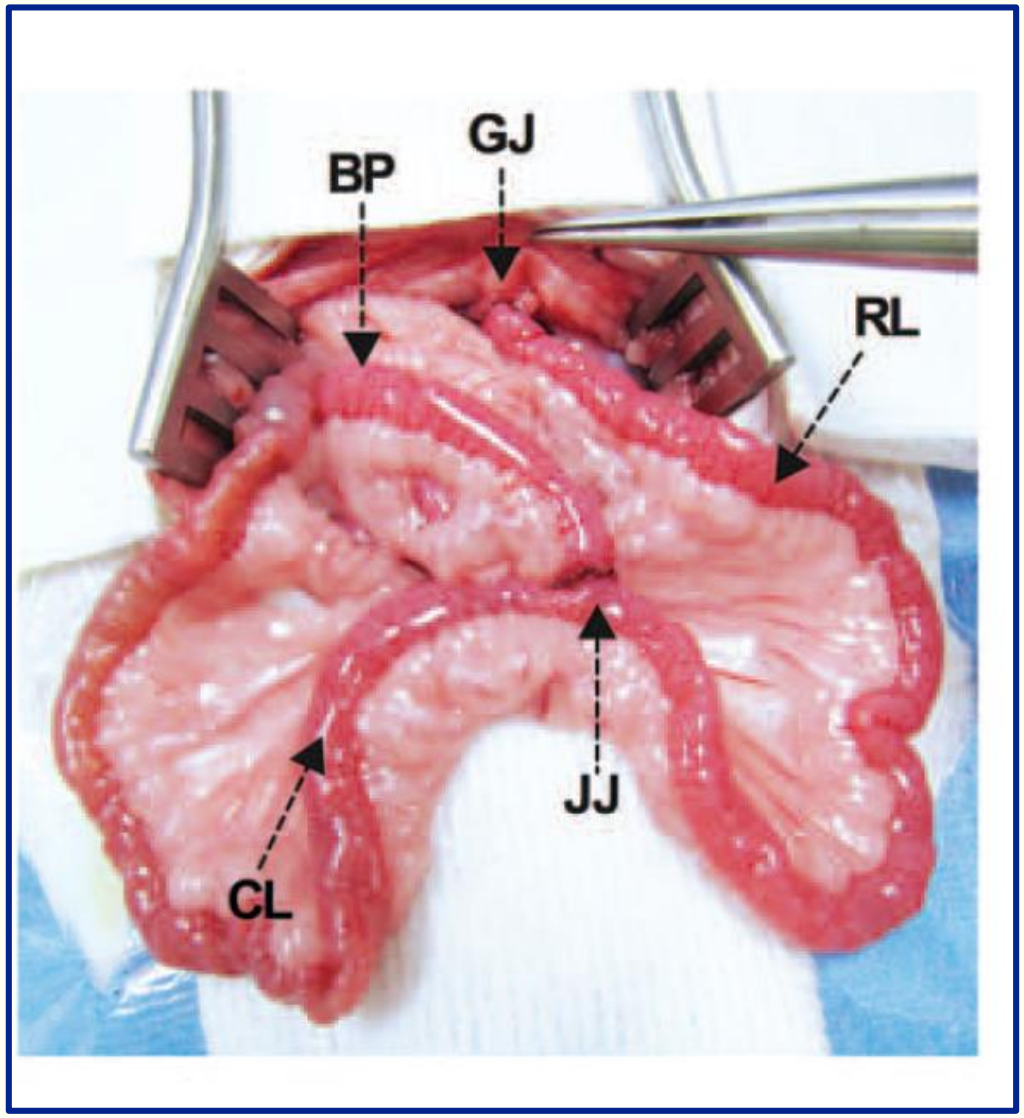
- No definitive data supporting effectiveness and safety in adolescents
- No long-term follow up
- No consensus on ideal surgical option
- Mechanisms of surgical efficacy are unknown

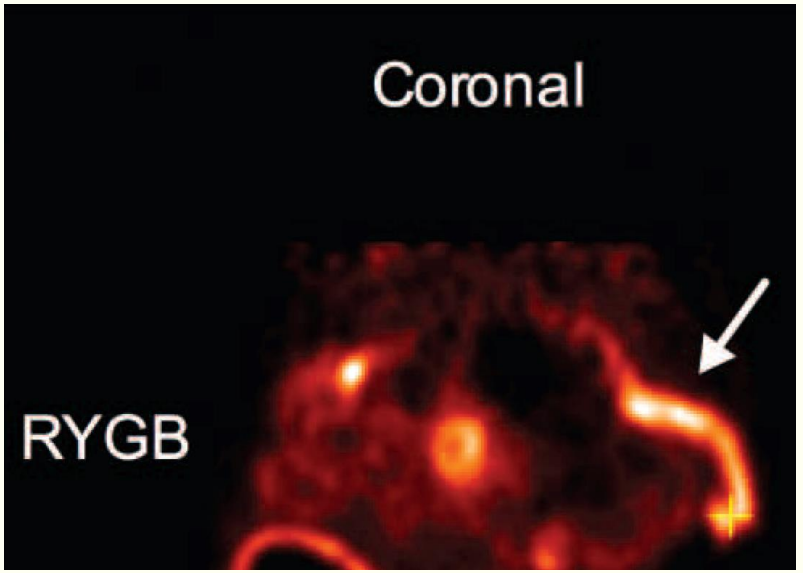
Nicholas Stylopoulos

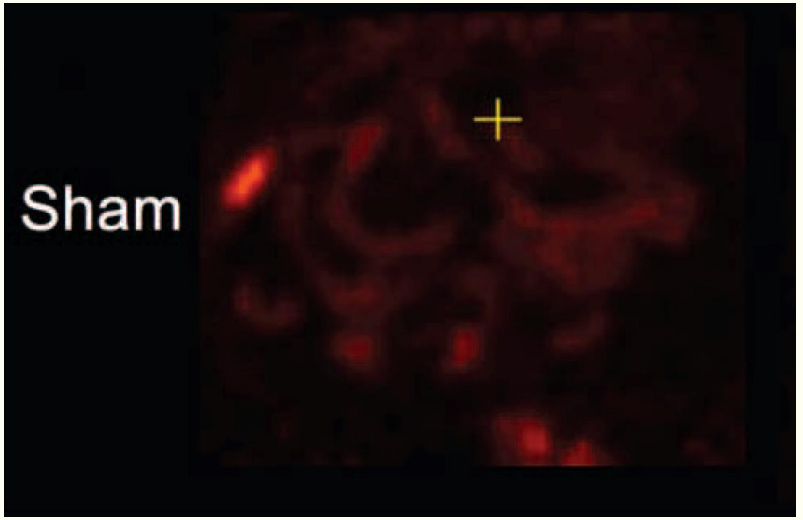
Reprogramming of Intestinal Glucose Metabolism and Glycemic Control in Rats After Gastric Bypass



Increased Glucose Uptake in the Roux Limb of RYGB







Saeidi, Stylopoulos et al. Science 341:406, 2013

Pharmacotherapy for Obesity

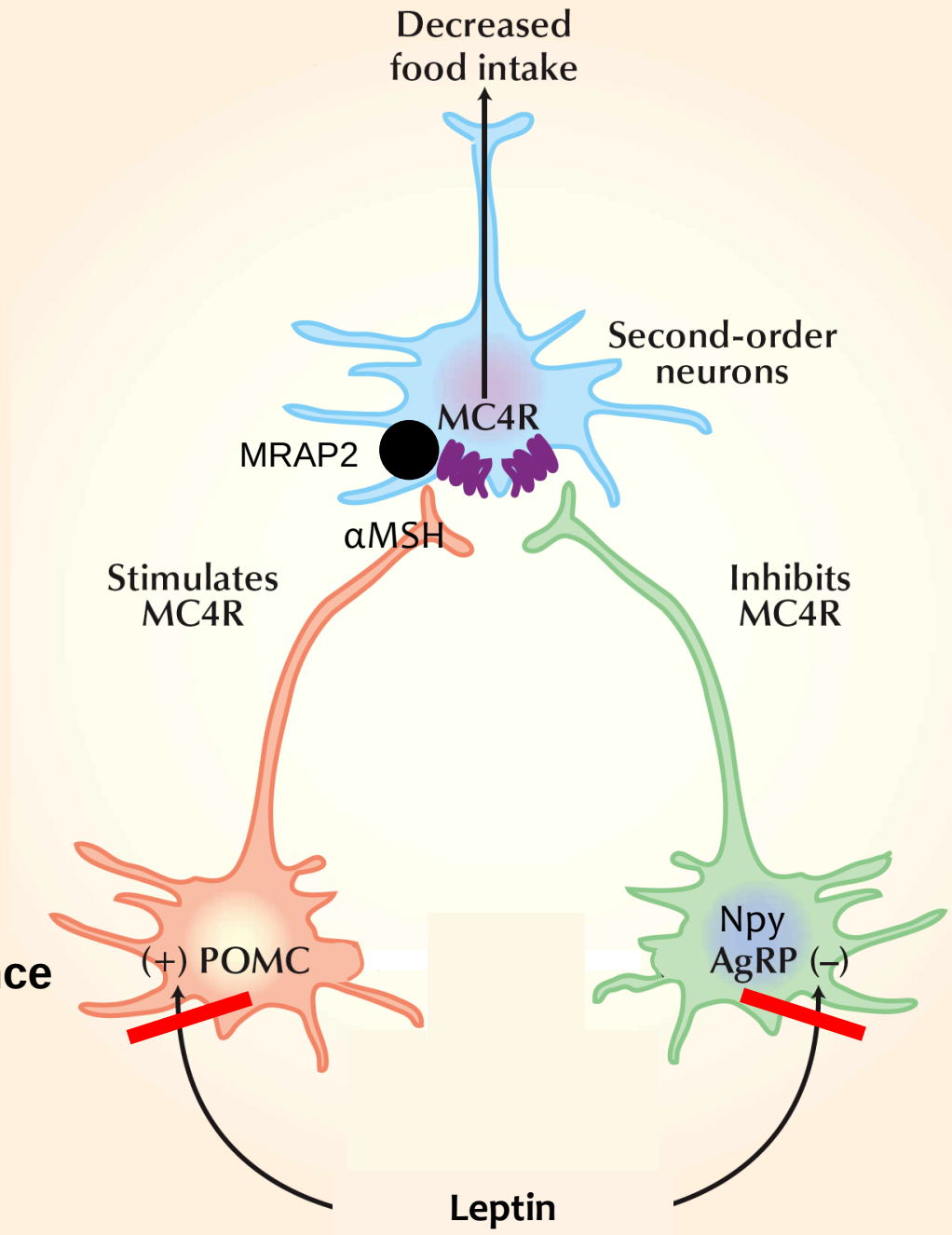
- Pharmaceuticals on market
  - Orlistat, Xenical (Roche). Pancreatic lipase inhibitor
    - Steatorrhea
  - Lorcaserin, Lorqess/Belviq (Arena). **ADULTS ONLY.** Serotonin $HT2_c$ receptor agonist. 3% weight loss over placebo.
    - Adverse events - memory, attention, language problems, depression, euphoria, 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
  - Buroprion-Naltrexone, Contrave (Orexigen). Reuptake inhibitor-opioid receptor antagonist.
    - Concern about cardiovascular toxicity. FDA requires very large outcomes study prior to approval.
  - SR01. Leptin sensitizer (ERX, Umut Ozcan, BCH).
    - Preclinical. Mice, monkeys



SR01

Leptin Resistance in Obesity

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