New Frontiers in Obesity Management: Advances in Neurobiological Treatment Strategies

Supported by an educational grant from

Takeda Pharmaceuticals International, Inc., US Region, and Orexigen Therapeutics, Inc.

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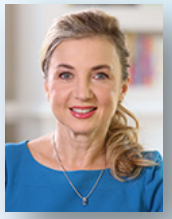
Announcements

- The session is being videotaped. Please turn off all cell phones and pagers.
- ARS keypads are provided on the table for use during the symposium.
- During the panel discussion, please use the Question Cards located on each table.
- Complete and return a CME Evaluation Form at the conclusion of the symposium.

Evolving Concepts in Obesity and Comorbid Conditions: Opening Remarks

Caroline M. Apovian, MD, FACN, FACP
Boston University School of Medicine
Boston Medical Center
Boston, Massachusetts

Agenda

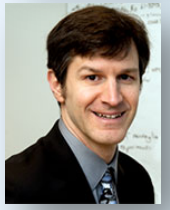


12:30-12:40PM-Caroline M. Apovian, MD

Evolving Concepts in Obesity and Comorbid Conditions: Welcome, Introductions and Opening Remarks

12:40-1:00PM-Lee M. Kaplan, MD, PhD

Weight-Centric Approaches to Cardiometabolic Disease Management



1:00-1:20PM-Joshua Thaler, MD, PhD

Food for Thought: Neurobiological Concepts to Appetite Regulation and Weight Loss: Beyond Individual Control

1:20-1:40PM-Louis J. Aronne, MD

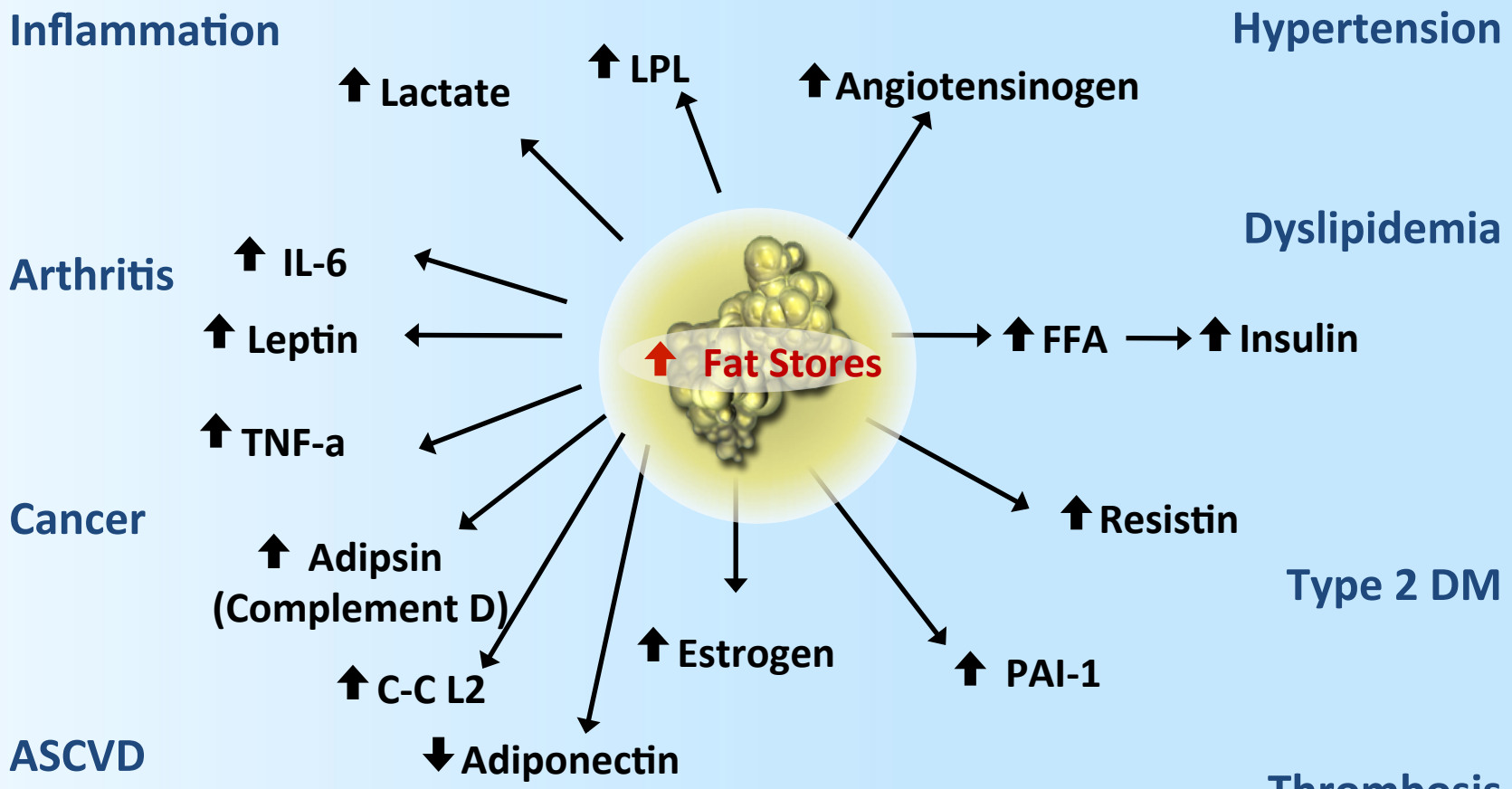
Advances in Therapeutic Interventions for Achieving and Maintaining Weight Loss

Outline

- Pathophysiology of obesity
- Link between pathophysiology of obesity and associated comorbid conditions
- Obesity as a disease

How Obesity Causes Disease

Increased Expression of Some Hormones, Suppression of Others, Leads to Inflammation and Disease



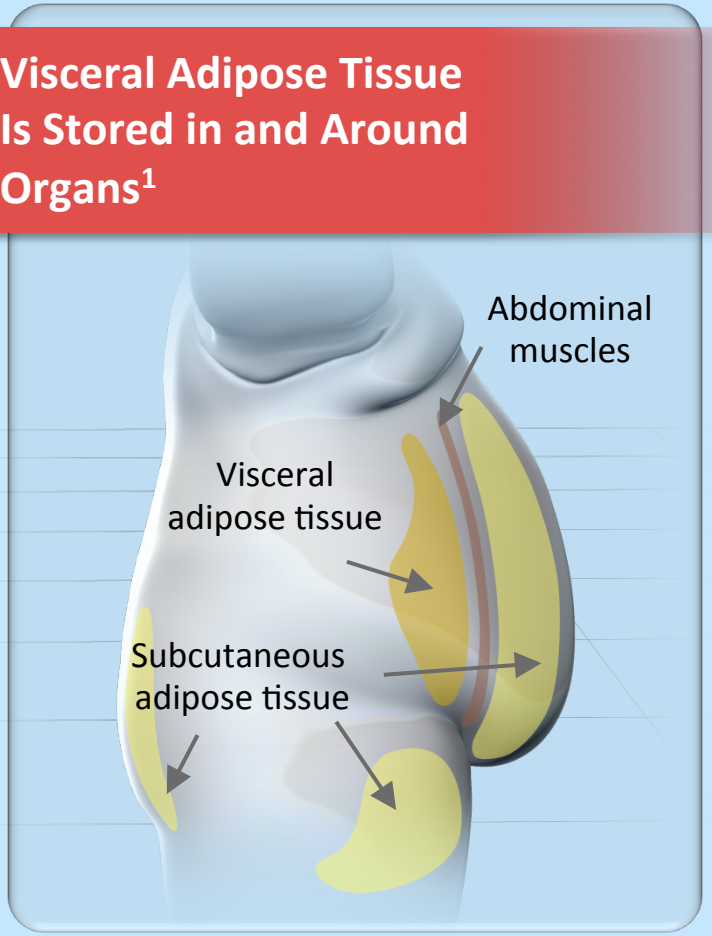
T2DM=type 2 diabetes mellitus
FFA=free fatty acid
PAI-1=plasminogen activator inhibitor-1
TNFα=tumor necrosis factor-alpha
IL-6=interleukin 6
ASCVD=atherosclerotic cardiovascular disease
C-C L2+chemokine (C-C motif) ligand2
LPL=lipoprotein lipase

Bray. Clin Endocrinol Metab. 2004;89:2583-89.
Eckel et al. Lancet. 2005;365:1415-28.
Aronne LJ, unpublished data.

Visceral Adipose Tissue May be a Greater Risk Factor for Comorbidities

- Excess adipose tissue is stored in 2 major locations[1,2]
  - Subcutaneous (under the skin; eg, buttocks and thighs)
  - Visceral (surrounding organs; eg, intra-abdominal area)
- Visceral adipose tissue has been shown in some studies to be a greater risk factor for developing obesity-related comorbidities compared with subcutaneous fat[1]
- Waist circumference is a common clinical measure of visceral adipose tissue[1]

Visceral Adipose Tissue Is Stored in and Around Organs[1]



Artist Rendition.

1. Hamdy et al. Curr Diabetes Rev. 2006;2:367-73.
2. Blüher. Exp Clin Endocrinol Diabetes. 2009;117:241-50.

Excess Adipose Tissue May Lead to Lipotoxicity and Inflammation

Lipotoxicity: A Potential Pathogenic Mechanism of Excess Adipose Tissue[1]*

- Free fatty acids released from adipose tissue may be deposited in vital organs resulting in significant damage and organ dysfunction[1,2]

Inflammation: A Potential Pathogenic Mechanism of Excess Adipose Tissue[1,3]*

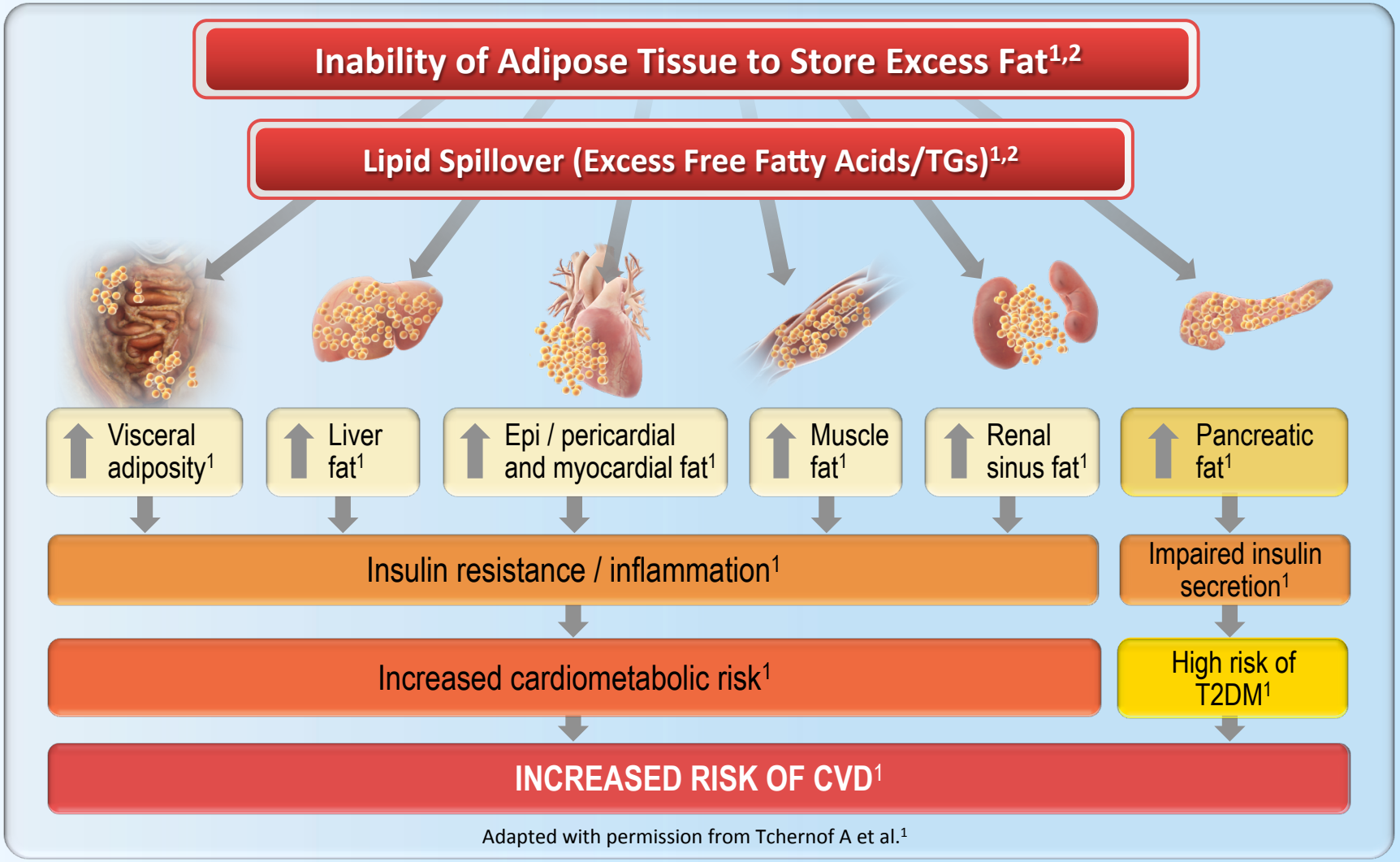
- As adipose tissue expands, production of proinflammatory cytokines increases[4]
- Clinical evidence
  - Elevations in CRP and IL-6 in obese patients[4]

What Is the Potential Clinical Relevance?

*Not completely understood in humans.
CRP, C-reactive protein; IL-6, interleukin-6.

1. Cusi. Curr Diab Rep. 2010;10:306-15.
2. Redinger. Gastroenterol Hepatol. 2007;3:856-63.
3. Tchernof et al. Physiol Rev. 2013;93:359-404.
4. Ouchi et al. Nat Rev Immunol. 2011;11:85-97.

Hypothetical Model: Lipotoxicity and Inflammation May Contribute to Development of Insulin Resistance, T2DM, and CVD

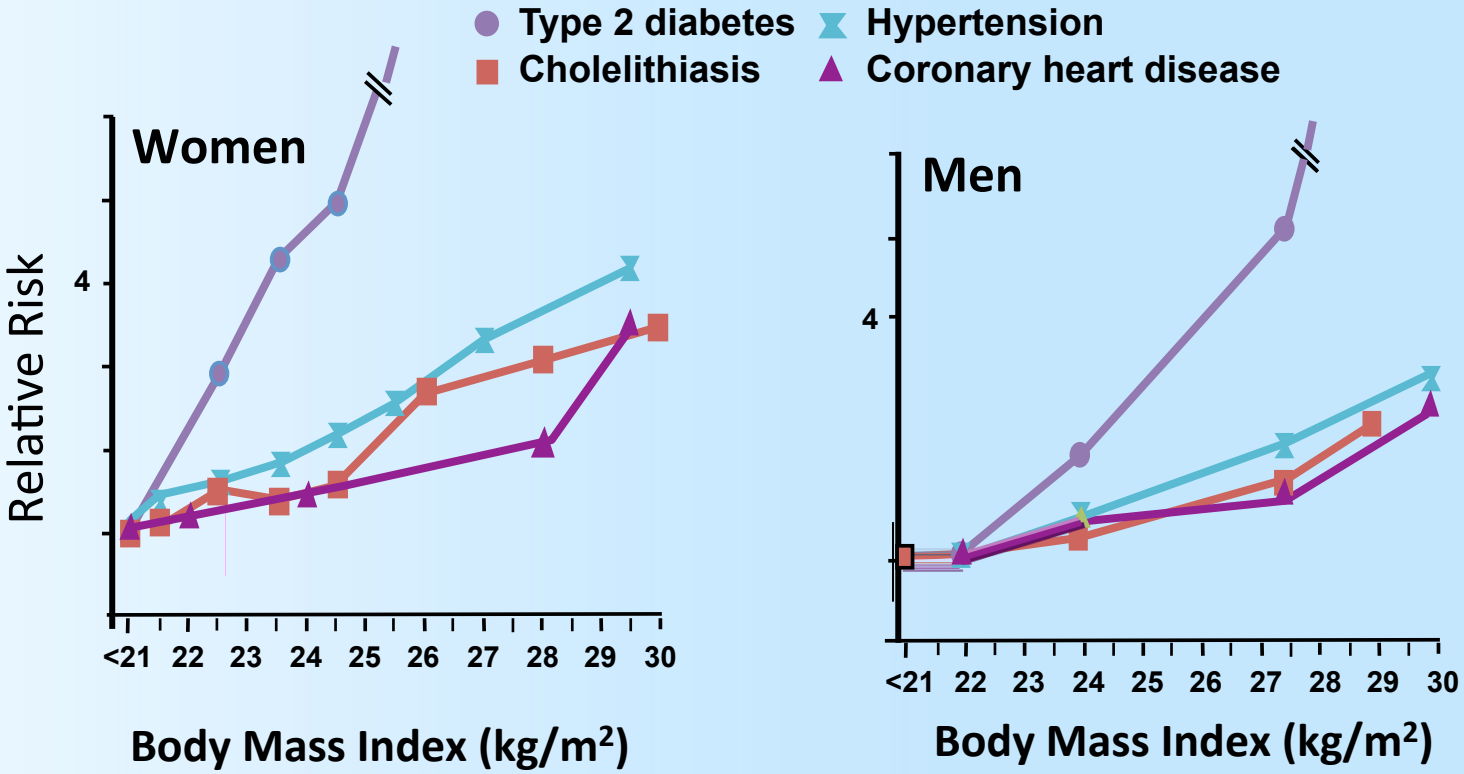


Adapted with permission from Tchernof A et al.[1]

1. Tchernof et al. Physiol Rev. 2013;93:359-404.
2. Redinger. Gastroenterol Hepatol. 2007;3:856-63.

T2DM, type 2 diabetes mellitus
CVD, cardiovascular disease
TGs, triglycerides

Association Between Obesity Development and Progression of Comorbidities



- Being overweight increases risk for number of chronic diseases
- Risk for diabetes most pronounced

Willett et al. NEJM. 1999;341:427-34.

Obesity and CVD: Effect on Risk Factors, Events, and Outcomes

Effect on CVD Risk Factors

- In an observational cohort study (n=6814 men), obesity (BMI ≥30 kg/m^2) vs normal weight (BMI <25 kg/m^2) was associated with[1]:
  - ↑ Prevalence of diabetes and hypertension
  - ↓ Levels of HDL cholesterol

Impact on CVD Risk Factors and CHD Events and Mortality

- Based on data from a large prospective trial (n=6595 men)[2]
  - Increase in BMI category was associated with:
    - ↑ Systolic / diastolic BP
    - ↑ TGs, total cholesterol
    - ↓ HDL cholesterol
  - Obesity (BMI 30-39.9 kg/m^2) was associated with increased risk of fatal coronary heart disease events (vs BMI 25-27.4 kg/m^2)

Analyses of 57 prospective studies involving ~900,000 adults reported increased risk of CVD mortality with each 5 kg/m^2 increase in BMI[3]

CVD, cardiovascular disease; BMI, body mass index; HDL, high-density lipoprotein; CHD, coronary heart disease; BP, blood pressure; TGs, triglycerides.

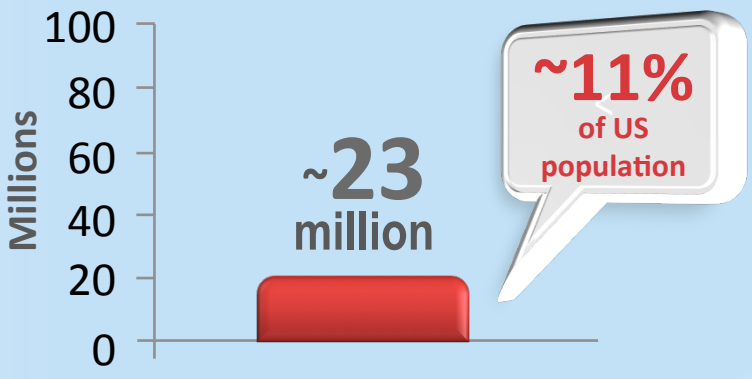
1. Burke et al. Arch Intern Med. 2008;168:928-35.
2. Logue et al. Heart. 2011;97:564-68.
3. Prospective Studies Collaboration. Lancet. 2009;373:1083-96.

Prevalence and Risk of T2DM

Per NHANES, 78 Million US Adults Were Obese in 2009-2010[1]

US Adults With Prediabetes (CDC Estimate, 2010)[2]

US Adults With T2DM (CDC Estimate, 2010)[2,3]



These CDC estimates were based on NHANES 2005-2008 data extrapolated to the 2010 US adult population (≥20 years of age) with prediabetes and diabetes.[2]

- Without lifestyle changes, 15%-30% of individuals with prediabetes will develop T2DM within 5 years[4]

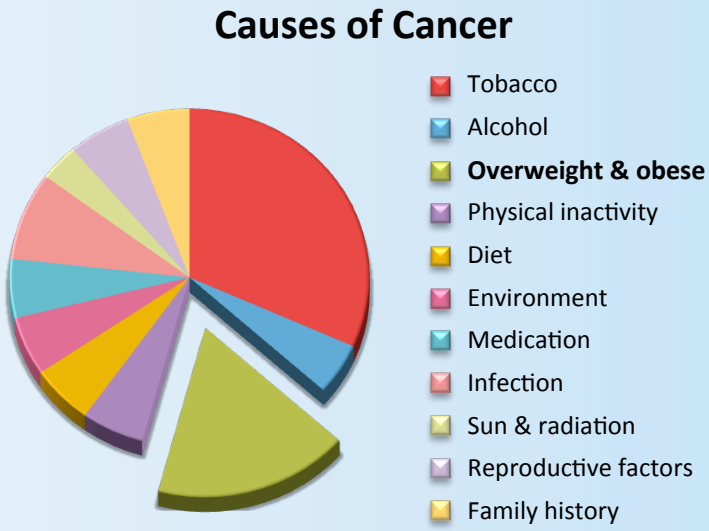
T2DM, type 2 diabetes mellitus; NHANES, National Health and Nutrition Examination Survey; US, United States; CDC, Centers for Disease Control and Prevention.

1. Centers for Disease Control. http://www.cdc.gov/nchs/data/databriefs/db82.
2. Centers for Disease Control. http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf.
3. National Institutes of Health. http://diabetes.niddk.nih.gov/dm/pubs/overview/
4. Centers for Disease Control. http://www.cdc.gov/diabetes/prevention/factsheet.htm.

Obesity and Cancer: Associated Morbidity and Mortality

Obesity and Morbidity[1]

- Overweight and obesity are associated with approximately 20% of all cancer cases



Adapted with permission from Wolin KY et al.[1]

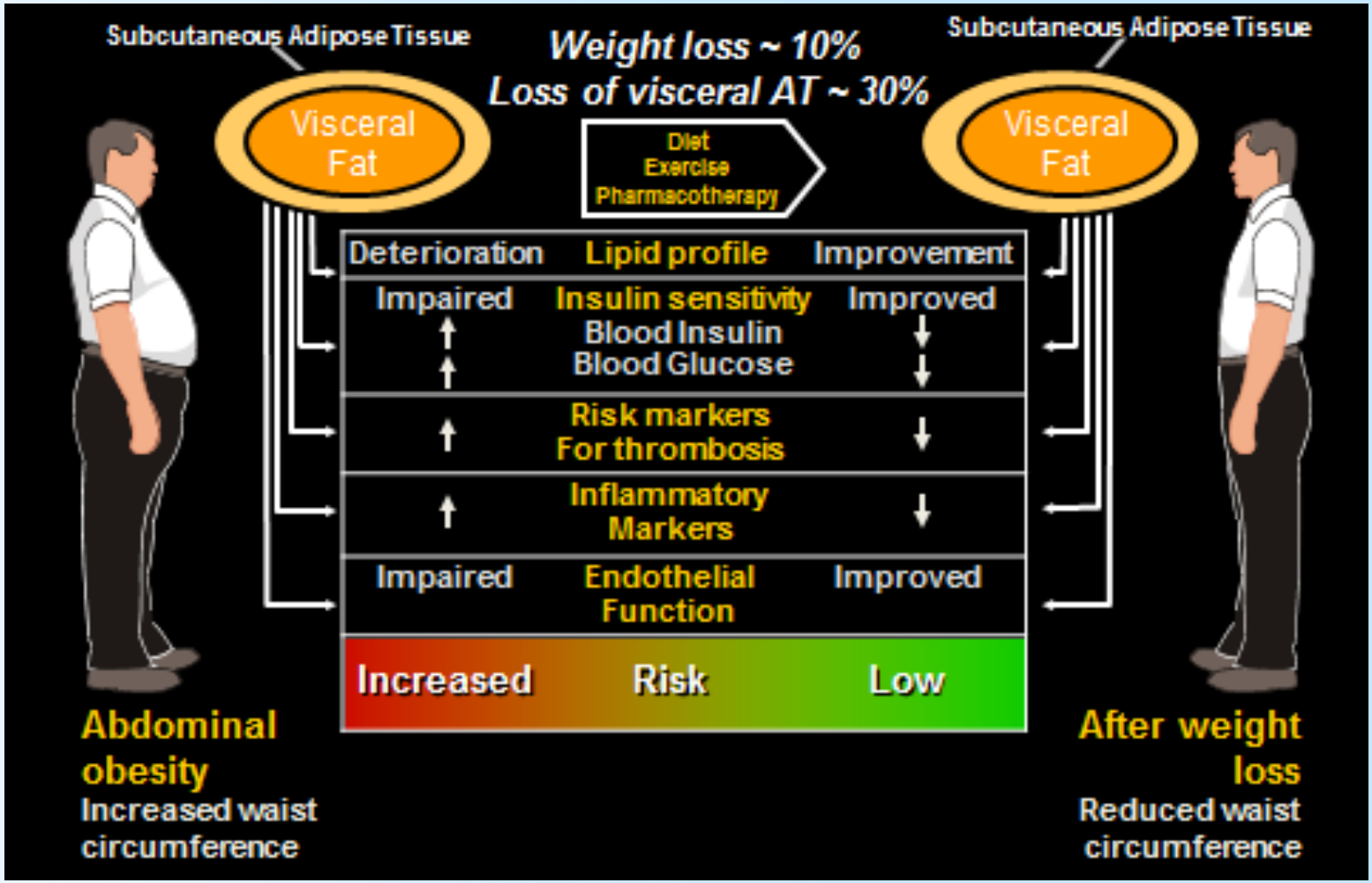
Obesity and Mortality[2]

- Overweight and obesity in the US accounted for up to ~14% and ~20% of all cancer deaths in men and women, respectively
- Increases in BMI were significantly associated with higher mortality rates for several cancers:
  - Breast, cervical, colorectal, gallbladder, kidney, liver, lung, multiple myeloma, non-Hodgkin's lymphoma, ovarian, pancreatic, prostate, corpus, and uterine

US, United States; BMI, body mass index.

1. Wolin et al. Oncologist. 2010;15:556-65.
2. Calle et al. N Engl J Med. 2003;348:1625-38.

Modest Weight Loss Produces Metabolic Benefit



Adapted from Despres et al. BMJ. 2001;322:716-20.

Designation of Obesity as a Disease

Medical Associations and Societies[1]:

- American Association of Clinical Endocrinologists
- American Academy of Family Physicians
- American College of Cardiology
- American College of Surgeons
- American Medical Association
- American Society for Reproductive Medicine
- American Urological Association
- The Endocrine Society
- The Obesity Society
- The Society for Cardiovascular Angiography and Interventions

World / National Health Organizations[1,2]:

- World Health Organization
- Food and Drug Administration
- National Institutes of Health

1. ASMBS, TOS, ASBP, AACE Joint Statement. http://asmbs.org/2013/06/obesity-is-a-disease-leading-obesity-groups-agree/
2. American Medical Association. www.ama-assn.org/assets/meeting/2013a/a13-addendum-refcomm-d.pdf.

Obesity as a Disease

Definition of a Disease per AMA[1]

- An impairment of the normal functioning of some aspect of the body
- Characteristic signs or symptoms
- Harm or morbidity

AMA Now Recognizes Obesity as a Disease[1]

- A multi-metabolic and hormonal disease state with:
- Characteristic signs and symptoms
- Increase in fat mass associated with obesity is directly related to comorbidities such as T2DM, cardiovascular disease, and cancer

AMA, American Medical Association; T2DM, type 2 diabetes mellitus.

1. American Medical Association. www.ama-assn.org/assets/meeting/2013a/a13-addendum-refcomm-d.pdf.

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Evolving Concepts in Obesity and Comorbid Conditions:
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Advances in Therapeutic Interventions for Achieving and Maintaining Weight Loss

Weight-Centric Approaches to Cardiometabolic Disease Management

Lee M. Kaplan, MD, PhD
Obesity, Metabolism & Nutrition Institute
Massachusetts General Hospital
Harvard Medical School
Boston, Massachusetts

Overall Treatment Strategy

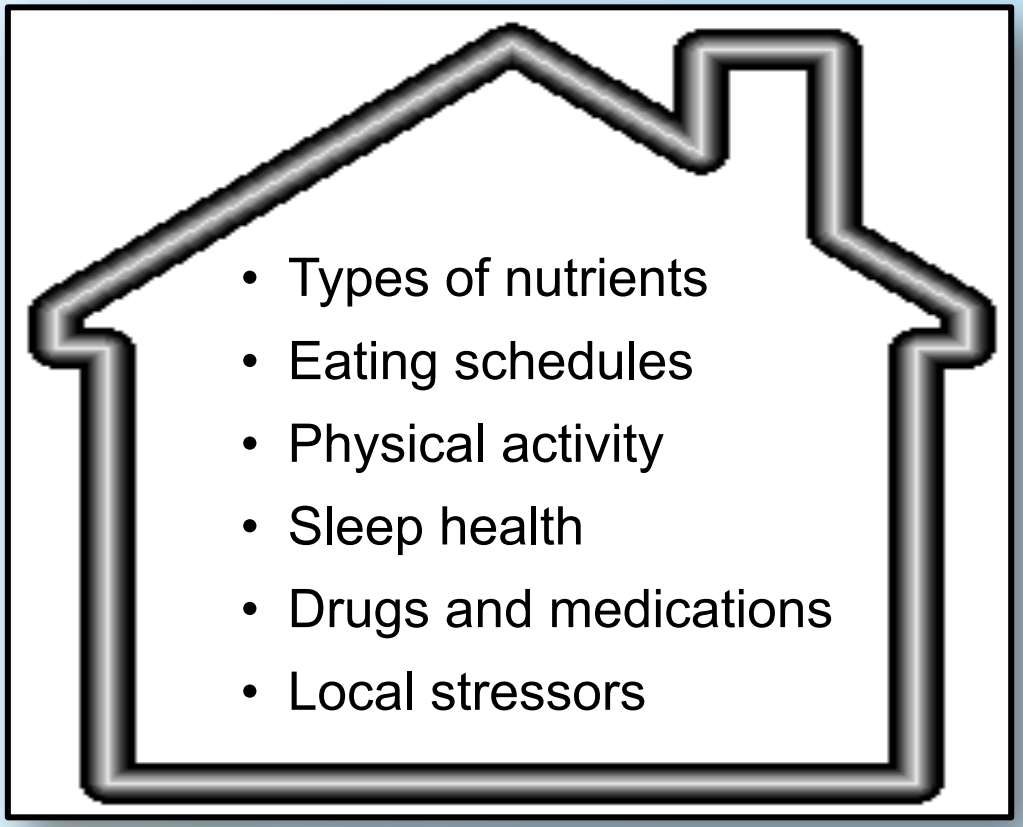
Typical Algorithm

(progress through algorithm as clinically required)

- Self-directed Lifestyle Change
- Professionally directed Lifestyle Change
- Add Medications
- Weight Loss Surgery
- Post-surgical Combination Therapies

Goal of Lifestyle Therapy

Normalize the Microenvironment

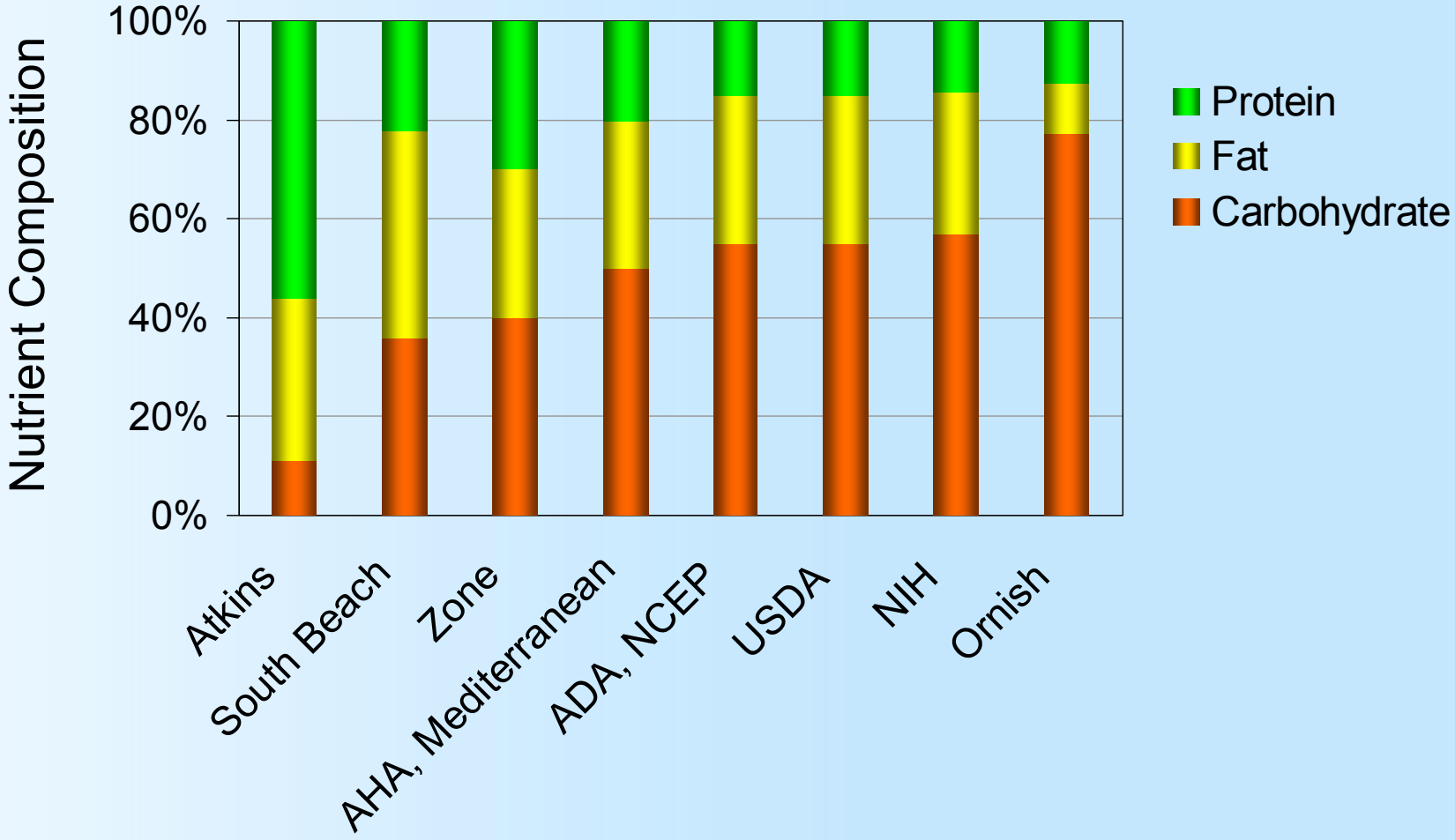


Lifestyle Treatment of the Patient with Obesity

Goal: To reverse the elevated fat mass set point, which is the cause of obesity in the first place

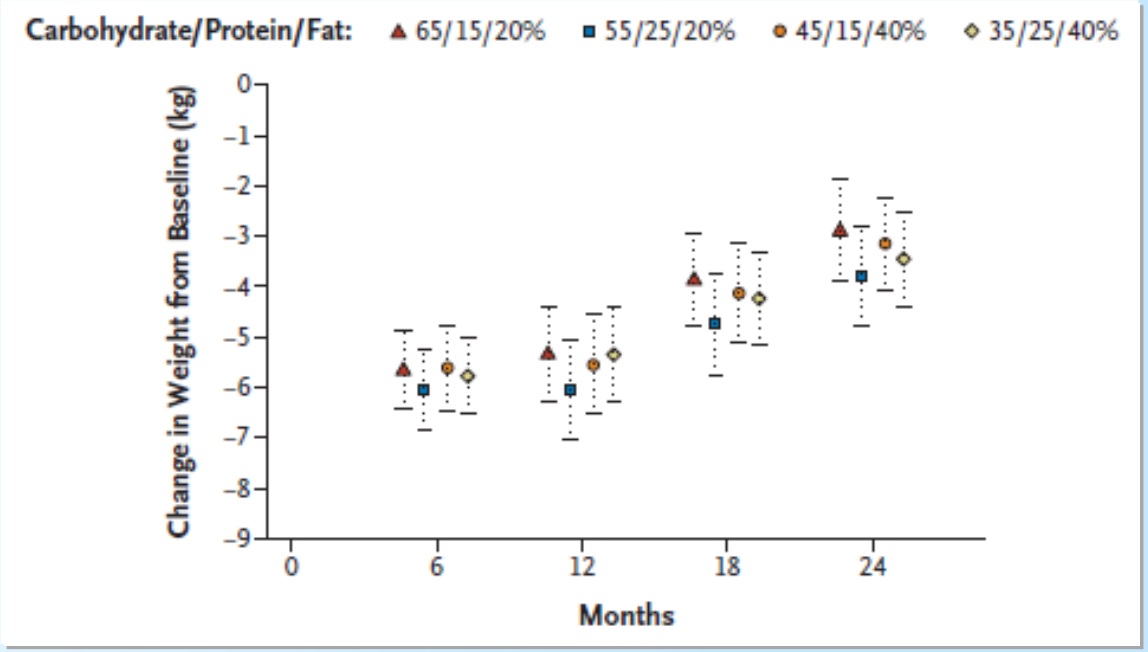
- **Healthy diet – to change nutrient *environment* by changing *chemistry***
  - Improves nutrient signaling to the brain
  - Emphasize unprocessed foods
  - Encourage complexity
  - Number of calories is MUCH less important
- **Regular exercise**
  - To improve muscle health, not to burn calories acutely
  - Long-term exercise more important than type or intensity
- **Stress reduction**
  - Reduce both perceived and "invisible" stresses
  - Restore sleep
  - Regularize circadian rhythms

Composition of Popular Diets



Macronutrient Distribution Has Minimal Effect

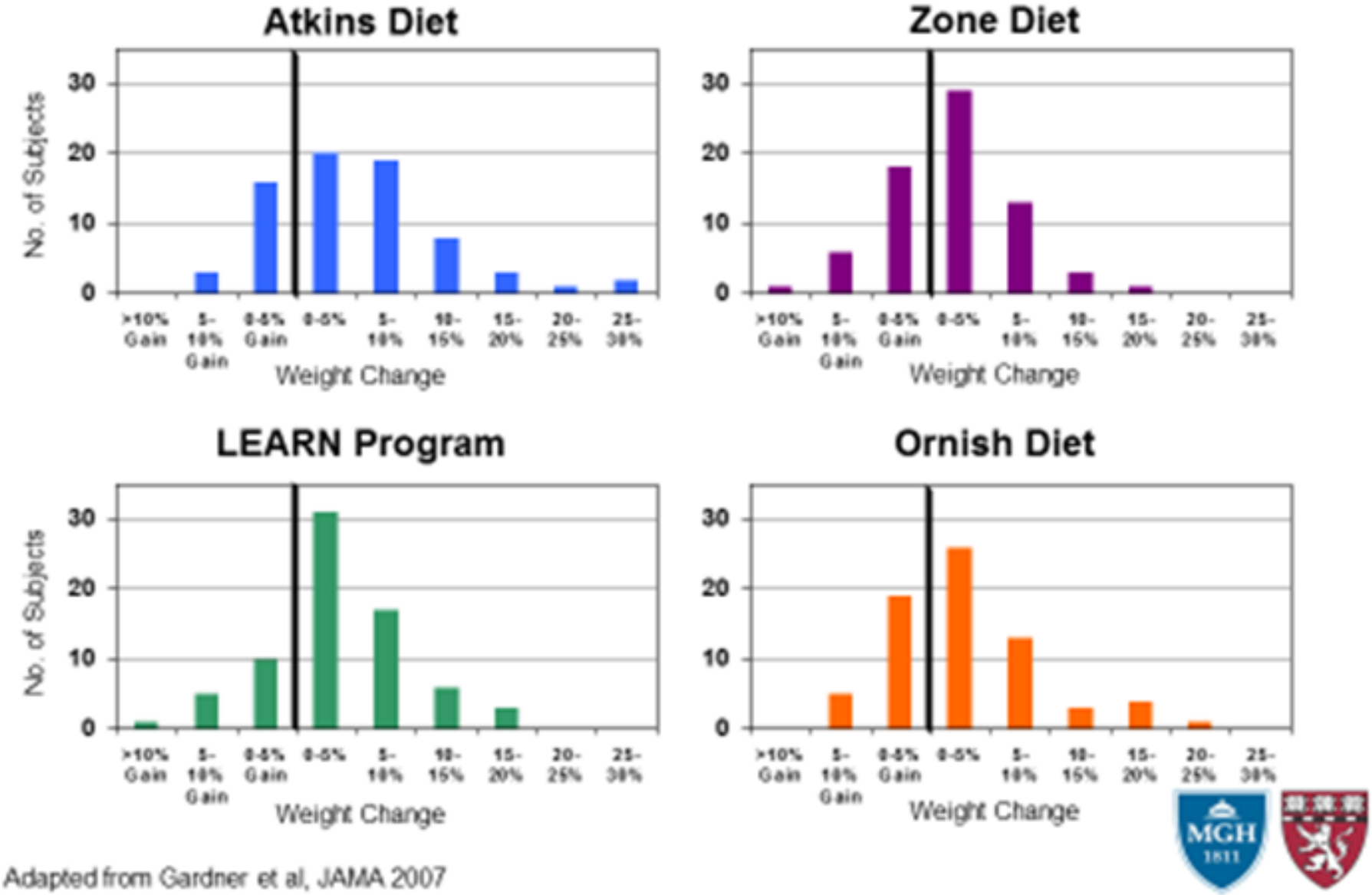
- **Fat:** Low (20%) vs. high (40%)
- **Carbohydrate:** Low (35%) to high (65%)
- **Protein:** Average (15%) vs. high (25%)



Conclusion: No difference in outcome among diets of different composition

Sacks et al. NEJM 2009;360:859.

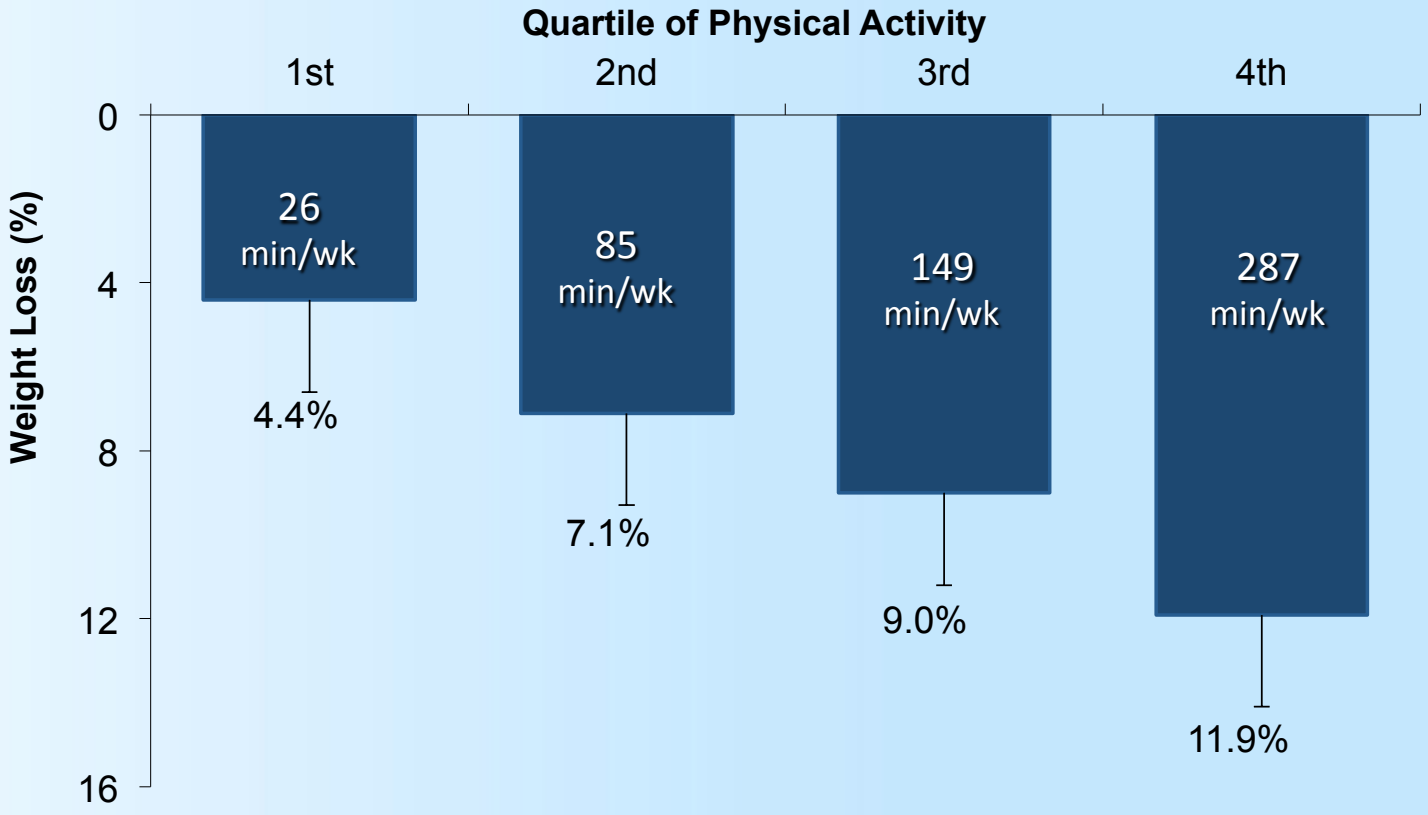
Variable Weight Loss After Diet Therapy



Adapted from Gardner et al, JAMA 2007

Physical Activity Extends Weight Loss

Look AHEAD Trial



Look AHEAD Research Group. Obesity 2009; 17:713.

Effects of Chronic Exercise

- Decreased food intake
- Altered food preferences
  - Toward healthy foods
- Increased brown fat development
- Enhanced energy expenditure
- Re-regulation of energy set point

Lifestyle Strategy

- **Keep the goal in mind:** Significant and durable weight loss

- **Assess patient's current lifestyle and habits**
  - Identify greatest opportunities for lifestyle change
  - Focus on changes that influence the obesogenic environment, *not* the cardiovascular or other risk

- **Pursue sequential application of *limited* lifestyle changes**
  - Determine effectiveness of each individual change
  - Include non-diet, non-exercise interventions (sleep, stress, circadian)
  - Use classic strategies of habit change (opportunity, cue, reinforcement)
  - Anticipate need for the additive effects of multiple lifestyle changes

- **Aim for clinically significant weight loss**
  - Be in sync with the patient

Pharmacological Therapies

Medication-induced Weight Gain

Medications account for 5-10% of obesity in the U.S.

In each relevant category, remove or substitute weight gain-promoting medications with weight neutral or weight loss-promoting alternatives

Weight Loss from Other Medications

Strategy: Aim for Double Benefits when Possible

Medication	Indicated Uses	Comments
Bupropion	**Depression**	**Avoid in bipolar disease**
Topiramate	**Seizures Migraines Mood disorders**	**May produce neurological side effects**
Zonisamide	**Seizures Mood disorders**	**Few studies**
Metformin	**Type 2 diabetes PCOS**	**Rare liver toxicity**
Liraglutide; Exenatide	**Type 2 diabetes**	**Injectable**
Pramlintide	**Type 2 diabetes**	**Injectable; nausea common**
Canagliflozin	**Type 2 diabetes**	

Medications Approved for Obesity

Medication	Average Weight Loss*	Mechanism of Action	Potential Side Effects
Phentermine	~ 5%	Adrenergic	Tachycardia, hypertension
Phentermine / Topiramate	10%	Adrenergic, CNS	Tachycardia, hypertension, cognitive dysfunction, neuropathy, teratogenicity
Bupropion / Naltrexone	4.5%	CNS; opioid antagonism	Seizures, confusion, anxiety, opiate withdrawal
Lorcaserin	3.5%	Serotonergic ($5HT_{2C}$)	Headache
Orlistat	3%	Lipase inhibitor	Steatorrhea, incontinence

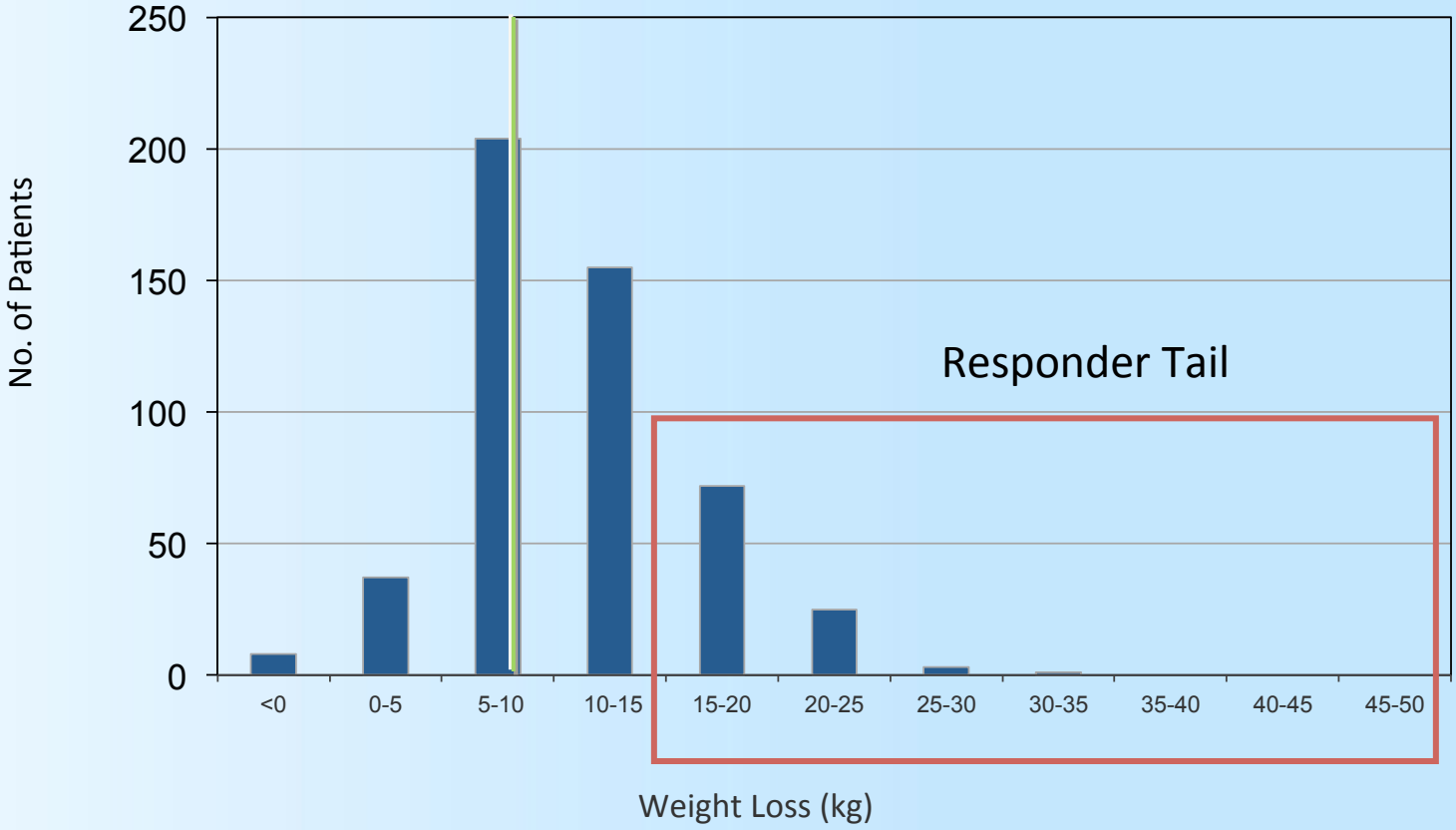
* Beyond placebo

Optimal Pharmacological Strategy

- **Optimize the patient's current medical regimen**
  - Avoid weight gain-promoting medications
  - Substitute a more weight-friendly alternative
- **Personalize the care: find the best treatment for each patient**
  - Pursue sequential trials of different medications
  - Minimum threshold for long-term use: 5% weight loss
  - Build to 2-3 drug combinations as needed
- **Aim for substantial (not minimally important) weight loss**
- **Use in conjunction with ongoing lifestyle-based therapy**
- **Anticipate life-long use of successful regimens**

Weight Loss Varies Widely Among Patients

Sibutramine*-induced Weight Loss



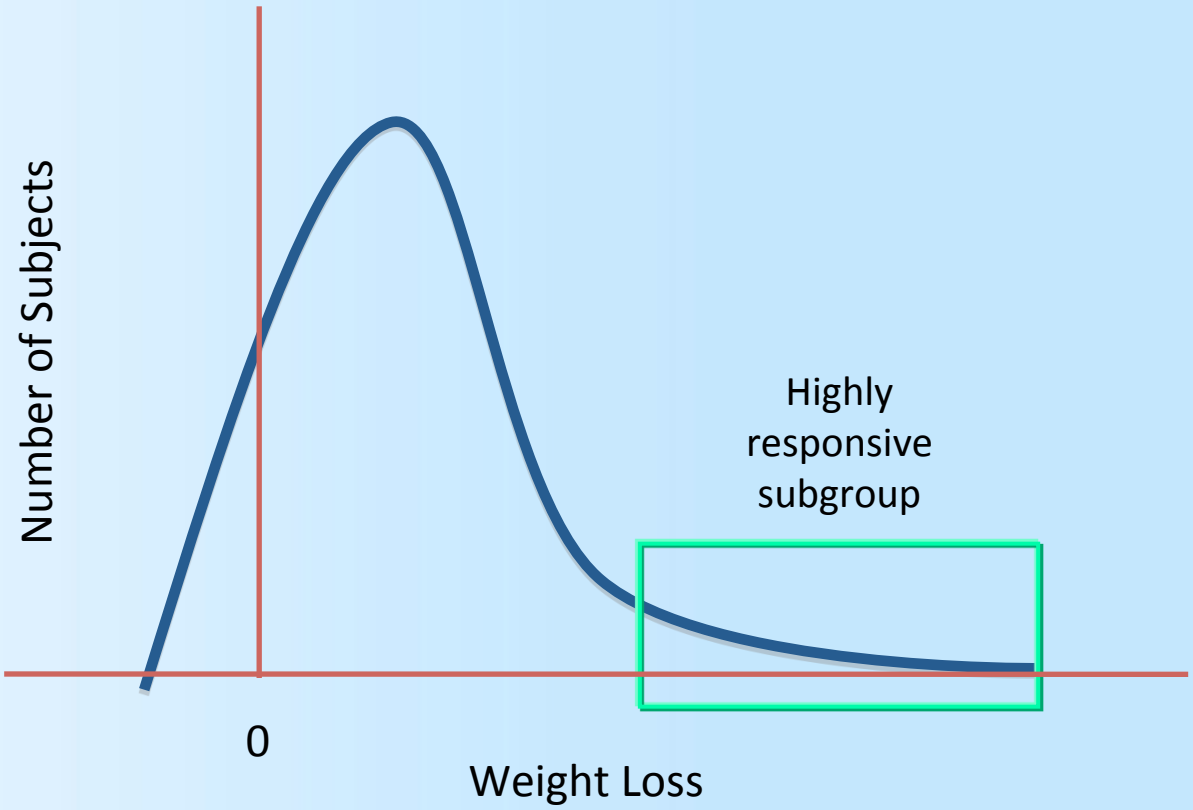
Adapted from Hansen et al. IJO 2001; 25:496.

*Withdrawn from market

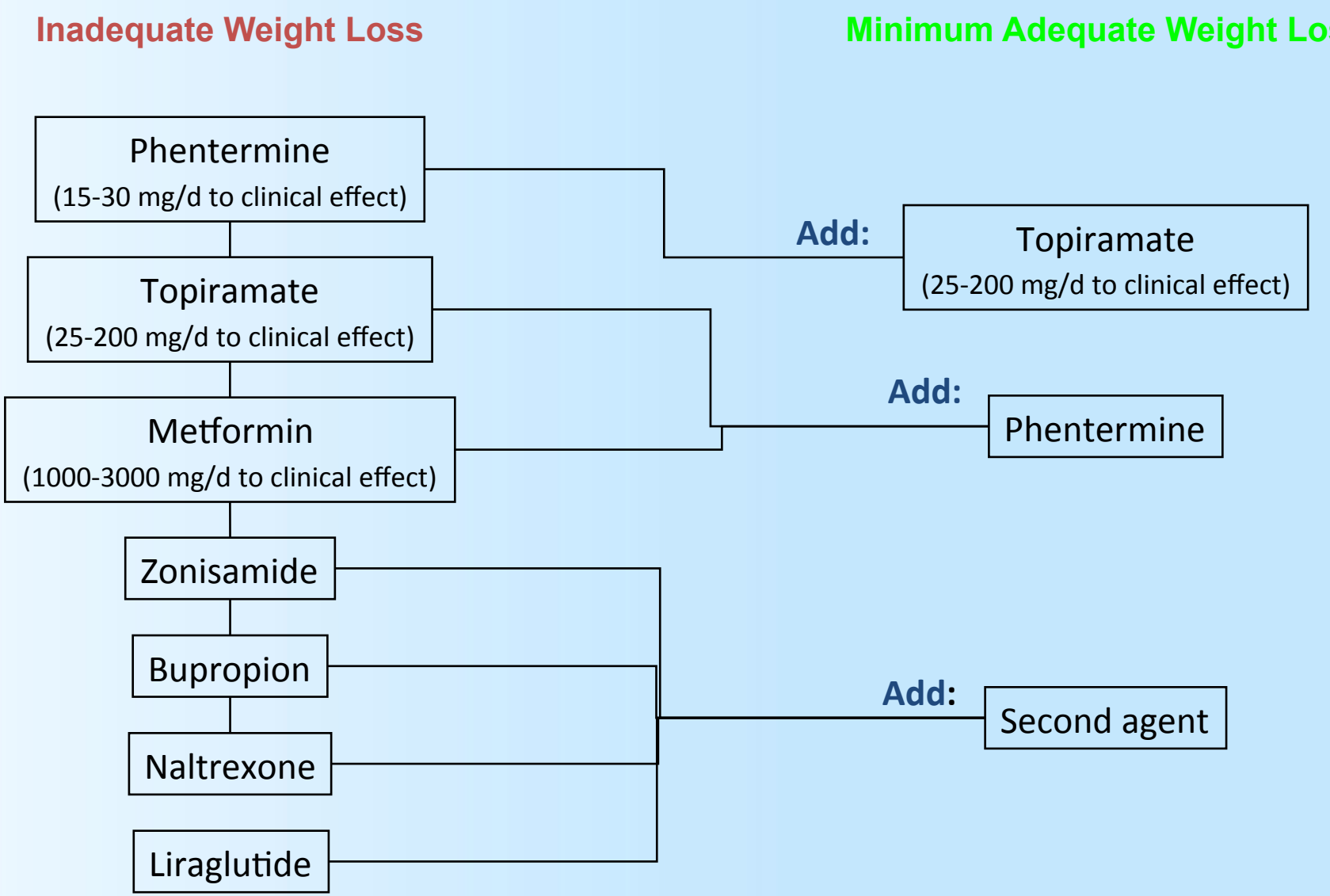
What Differs Among Different Obesity Subtypes

- **Timing of obesity onset**
- **Fat location and distribution**
- **Metabolic consequences**
- **Phenotypic differences**
  - Hunger
  - Satiety
  - Reward-based eating
  - Energy expenditure
- **Response to environmental causes**
  - Eating
  - Exercise
  - Stress
  - Sleep deprivation
  - Circadian disruption
- **Response to therapies**

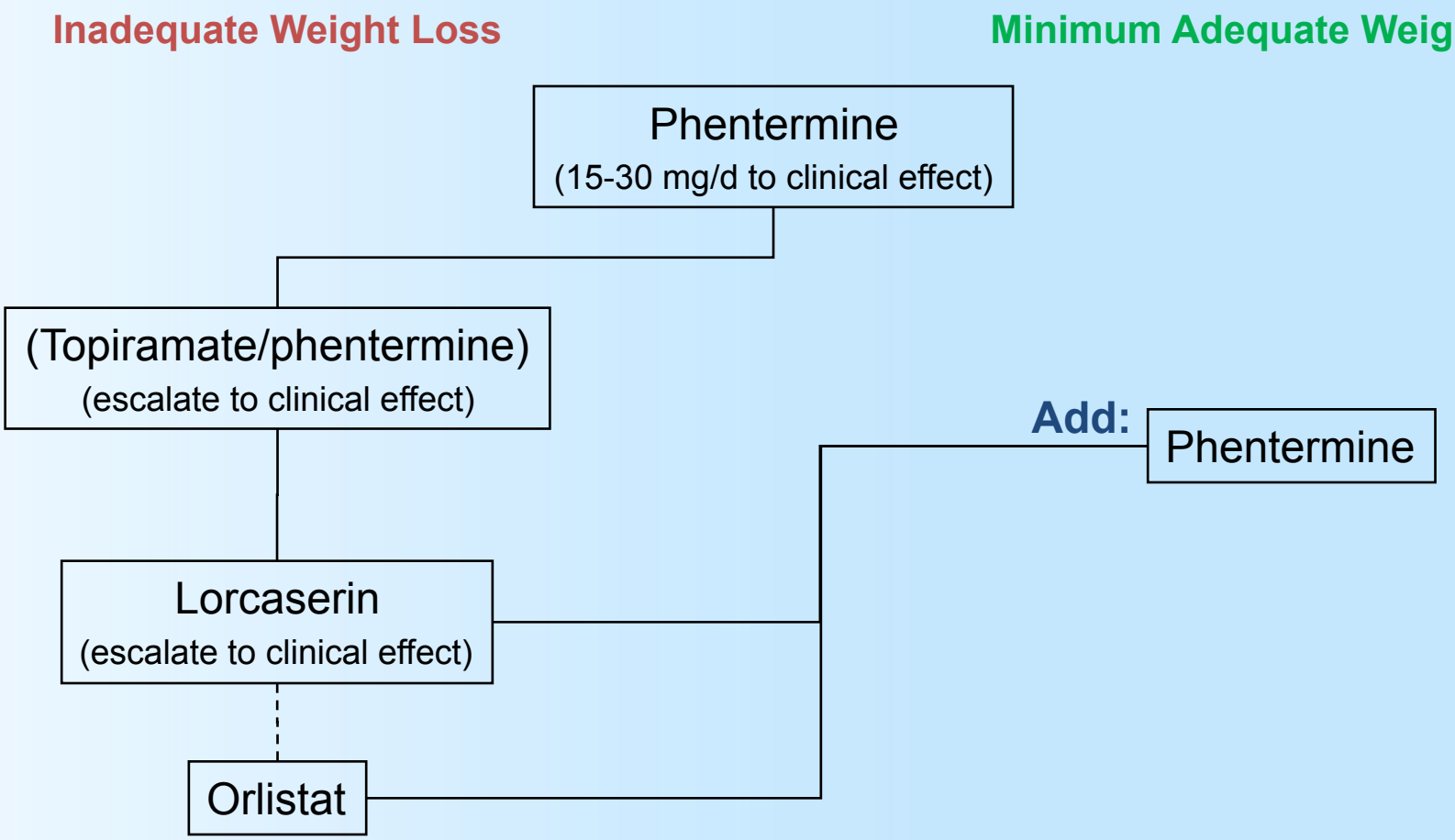
Heterogeneity of Response



Algorithm Example 1 – Off-Label Use



Algorithm Example 2 – Approved Use

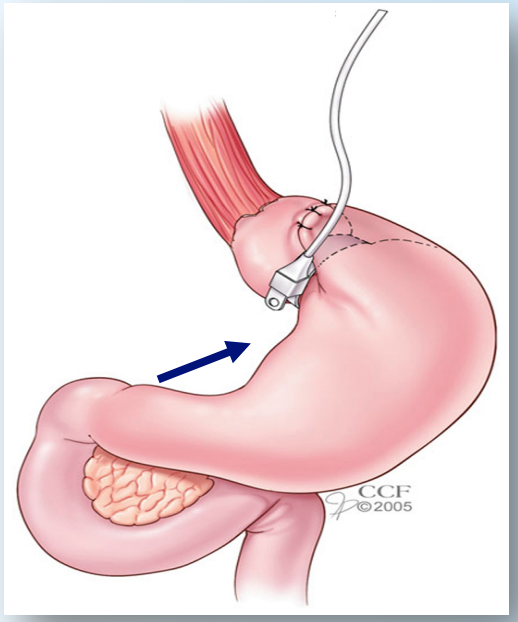


Surgical Therapies

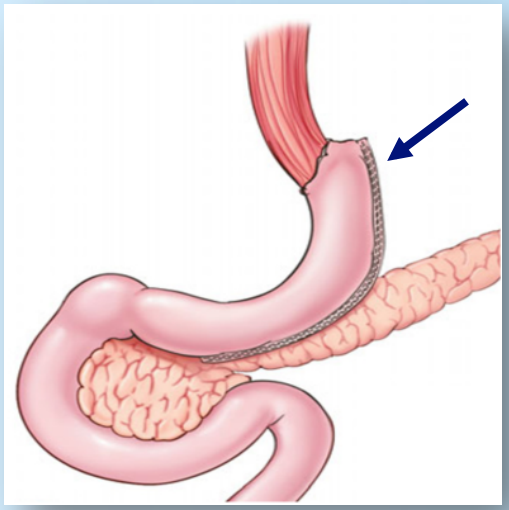
Metabolic Surgery

Weight-independent Metabolic Benefits

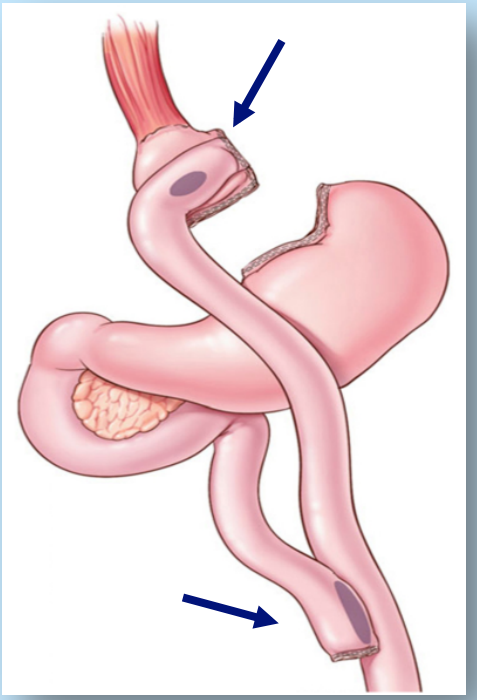
Adjustable Gastric Banding



Vertical Sleeve Gastrectomy

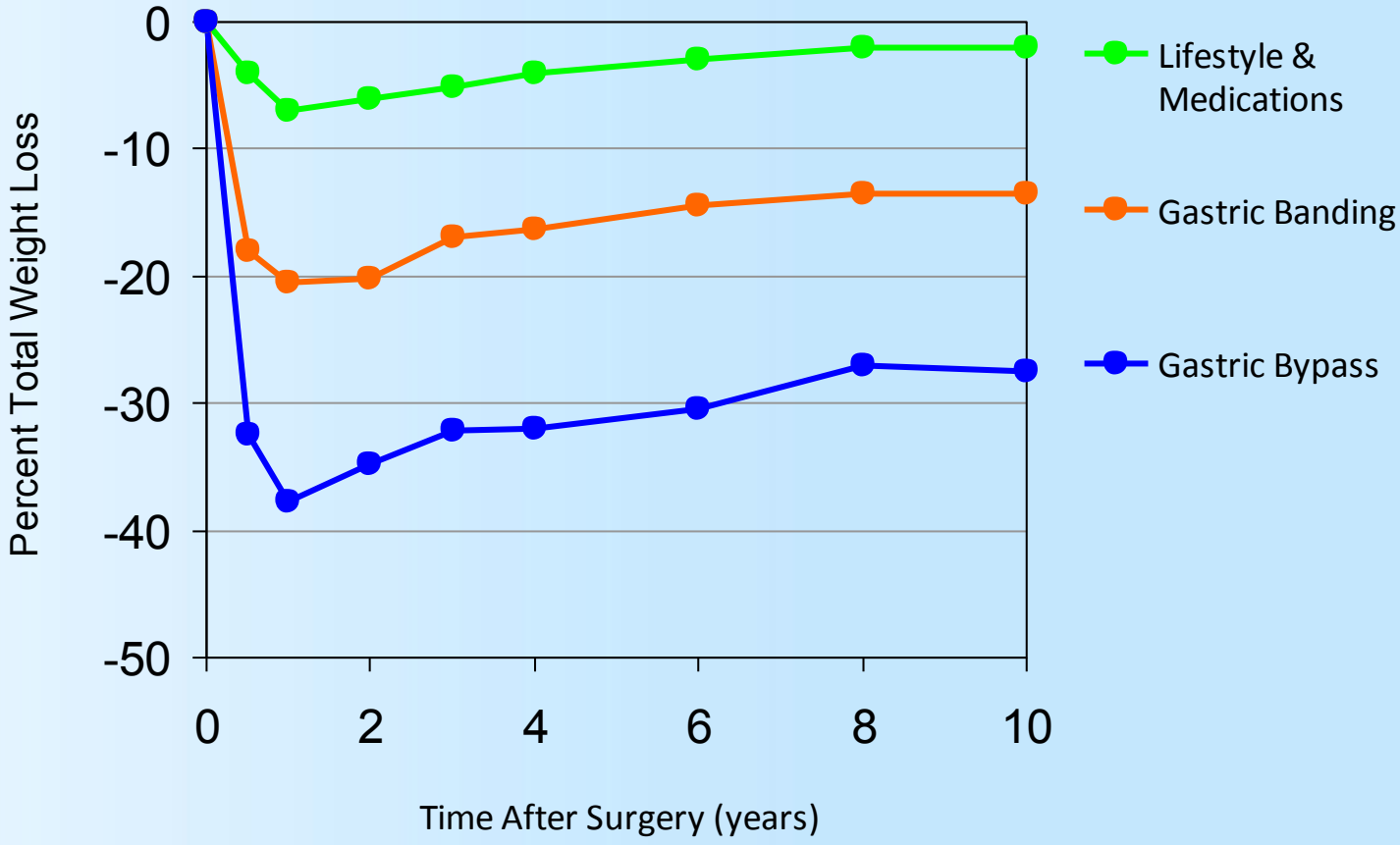


Roux-en-Y Gastric



Average Effectiveness of Obesity Treatments

Swedish Obesity Subjects Diabetes Prevention Program



Surgery Decreases Long-term Mortality

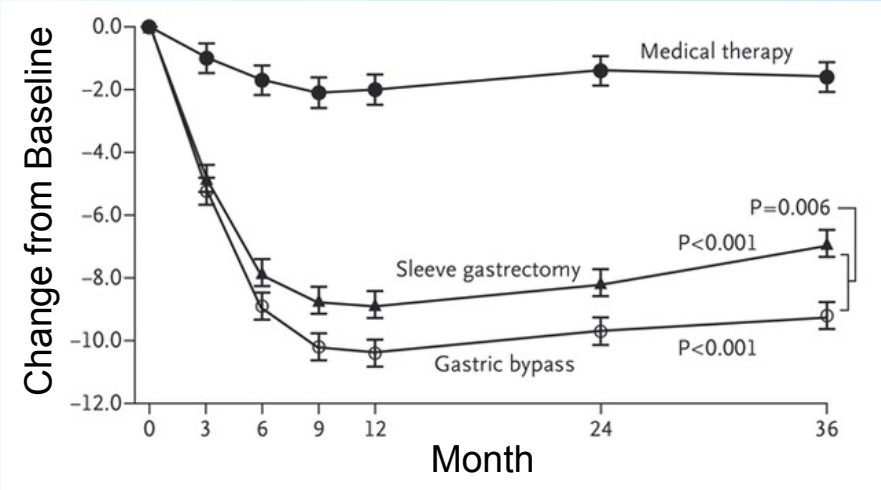
Utah Study

- 15,850 gastric bypass patients and matched controls
- 7.1 year mean follow-up
- Gastric bypass group exhibited overall 40% reduction in mortality
- Specific-cause mortality after gastric bypass
  - 56% reduction from CAD
  - 92% reduction from type 2 diabetes
  - 60% reduction from cancer

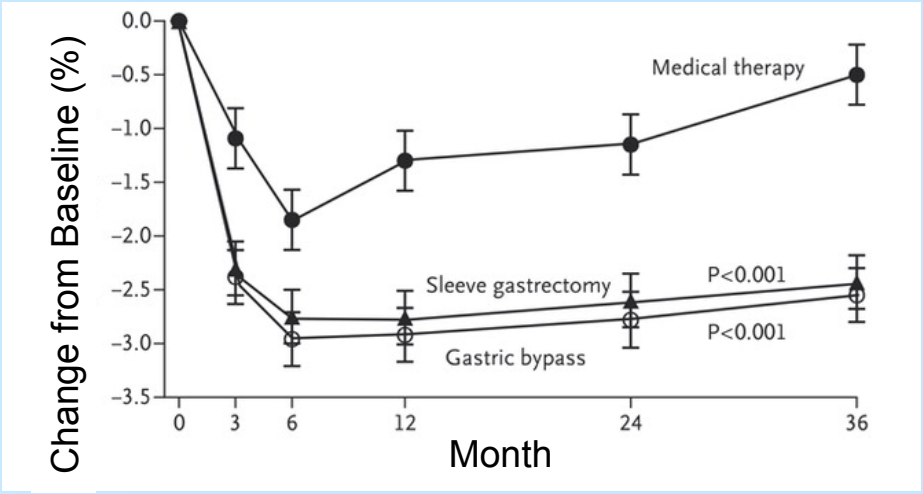
Adams et al. NEJM. 2007;357:753-61.

Weight Loss Surgery Improves T2DM

Body Mass Index



Glycated Hemoglobin



● Intensive medical therapy

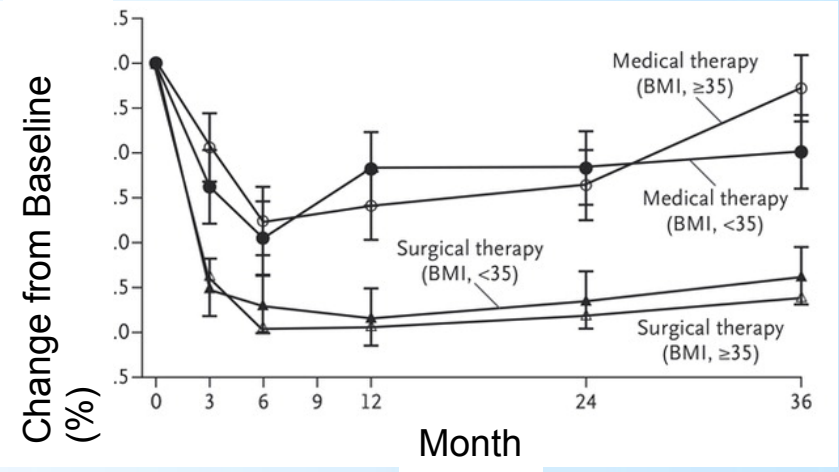
▲ Sleeve gastrectomy

■ Roux-en-Y gastric bypass

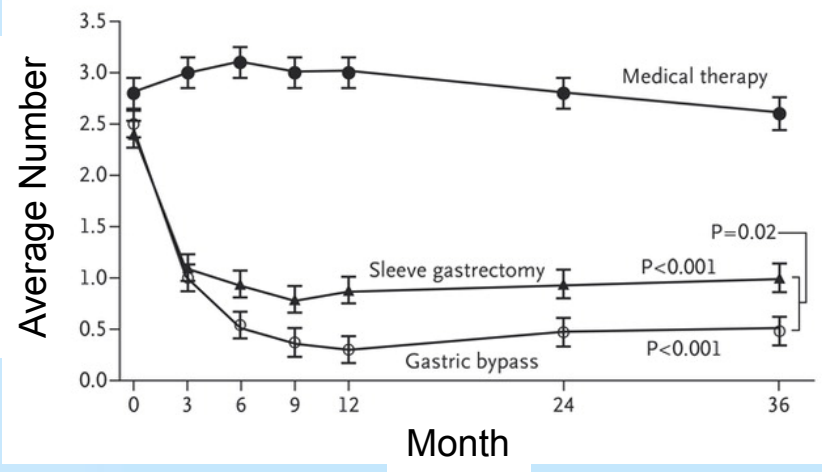
Schauer et al. NEJM 2014;370:2002-13.

Weight Loss Surgery Improves T2DM

Glycated Hemoglobin Adjusted by BMI



Use of DM Medications



● Intensive medical therapy

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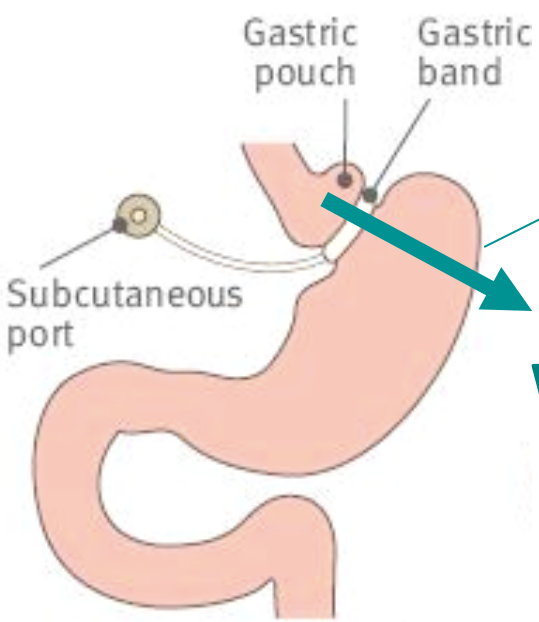
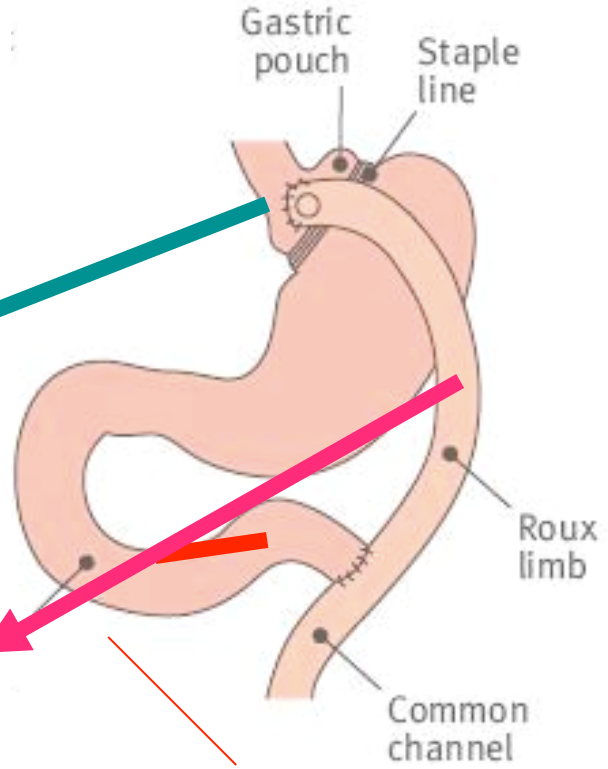
Schauer et al. NEJM 2014;370:2002-13.

Mechanisms of Diabetes Improvement

Gastric Banding



Gastric Bypass



Gradual effects

Weight Loss

Control of Diabetes

Immediate effect

Case Study – A.G.

- 51-year-old woman with BMI 43.3
  - Weight 252 lbs., height 5'4"
  - Well-controlled hypertension, hypothyroidism, Barrett's esophagus, osteoarthritis (s/p knee replacement), colonic polyps, and depression
  - Uncomplicated type 2 diabetes on pioglitazone, glimepiride and insulin (long- and short-acting to total of 65 units/day)
  - Sleep apnea well-controlled on CPAP
  - Other medications include losartan, hydrochlorthiazide, omeprazole, levothyroxine, aspirin, and sertraline

Case Study – A.G.

- **Examination**
  - Central obesity with waist circumference 41 in.
  - Benign, protuberant abdomen; no signs of chronic liver disease
  - No signs of peripheral neuropathy

- **Laboratory studies**
  - Fasting glucose 111
  - HbA1c 7.1%
  - AST 43, ALT 51, alkaline phosphatase 120
  - BUN 32; creatinine 1.2
  - TSH 5.64

Case Study – A.G.

- **Weight and lifestyle history**
  - Normal weight as a child; overweight in college and graduate school (weight 150-175; BMI 26-30)
  - Progressive weight gain in adult life; "insatiable" appetite with frequent cravings and large portions
  - Numerous unsupervised, supervised, and structured diets with variable weight loss (up to 30 lbs.); none maintained
  - Average weight stable over the past few years; currently at highest lifetime weight
  - Married with grown children; works as financial planner
  - Cooks regularly and well, and entertains often
  - Exercises three times a week with a physical trainer

Take-home Messages

Evaluation of the Patient with Obesity

- Characterize the obesity
  - Measure and follow weight and BMI
  - Use waist circumference to assess body fat distribution in patients with BMI between 25 and 35 kg/m^2
- Identify and treat comorbidities
- Aim to reduce disparities in care; respect the patient
- Develop a long-term strategy for treating the obesity itself

Take-home Messages

Obesity Treatment

- Lifestyle adjustment is the mainstay of therapy
- Medications can be effective
  - In selected patients
    - Medications work differently in different patients – requires 'trial and error' approach
  - Combination therapies look particularly promising

Take-home Messages

Surgery Works by Influencing Metabolic Physiology

- Different procedures work through distinct mechanisms
- Bypass operations and sleeve gastrectomy are particularly effective for T2DM and metabolic disorders

Practical Guidance

Embrace Modest Weight Loss

- Current non-surgical weight loss therapies are generally an *adjuvant* treatment for obesity comorbidities
- Focus on what is achievable – and sustainable
  - Understand that there are biological limits to each therapy
  - Be clear about what treatment can and cannot do
- Understand that one size does not fit all

Practical Guidance

Go Slow and Try Different Approaches

- Test therapies sequentially
- Pursue combination therapies – including combinations of specific lifestyle changes with more classical medical approaches
- Be supportive
  - Be persistent
  - Be there for the patient

Aim for "*cure*," but always provide *care*

Food for Thought
Neurobiological Concepts to Appetite Regulation and Weight Loss
Beyond Individual Control

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Div. of Metabolism, Endocrinology, and Nutrition

University of Washington Department of Medicine

Seattle, Washington

Outline

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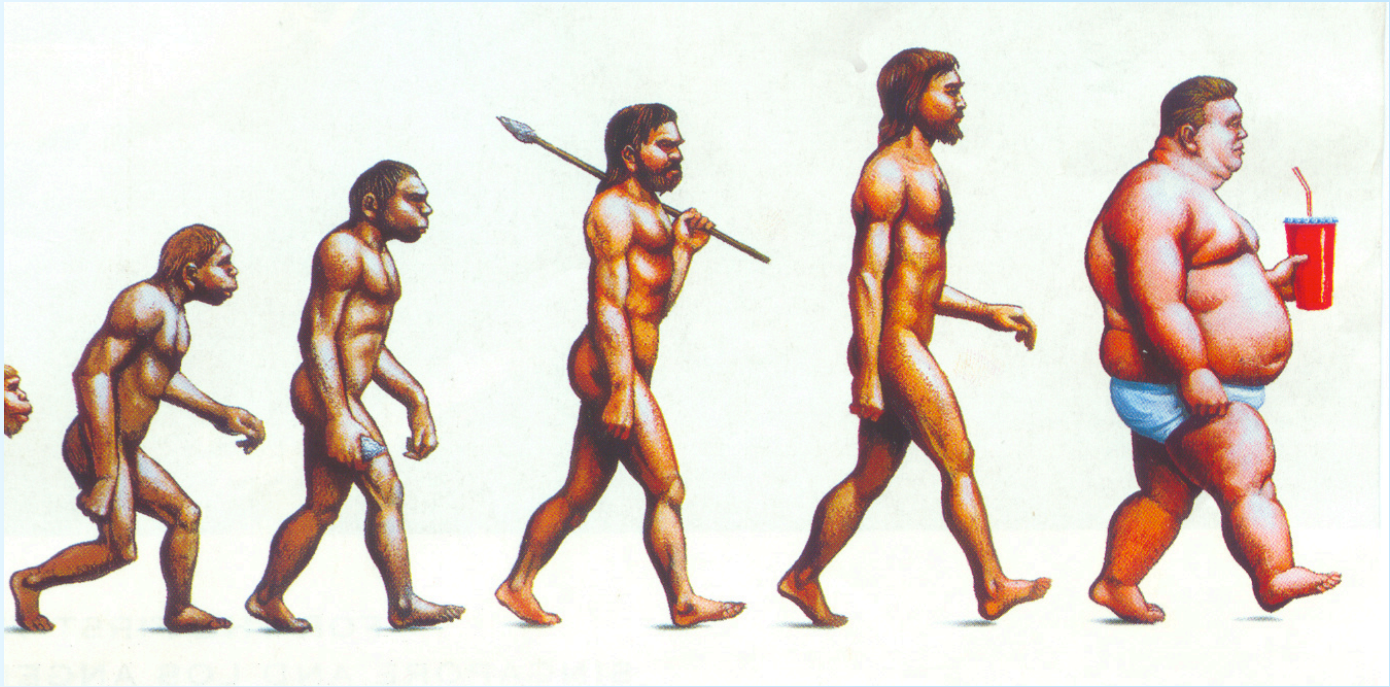
- Obesity and brain inflammation – The middle.
- Obesity and hypothalamic injury - The end?



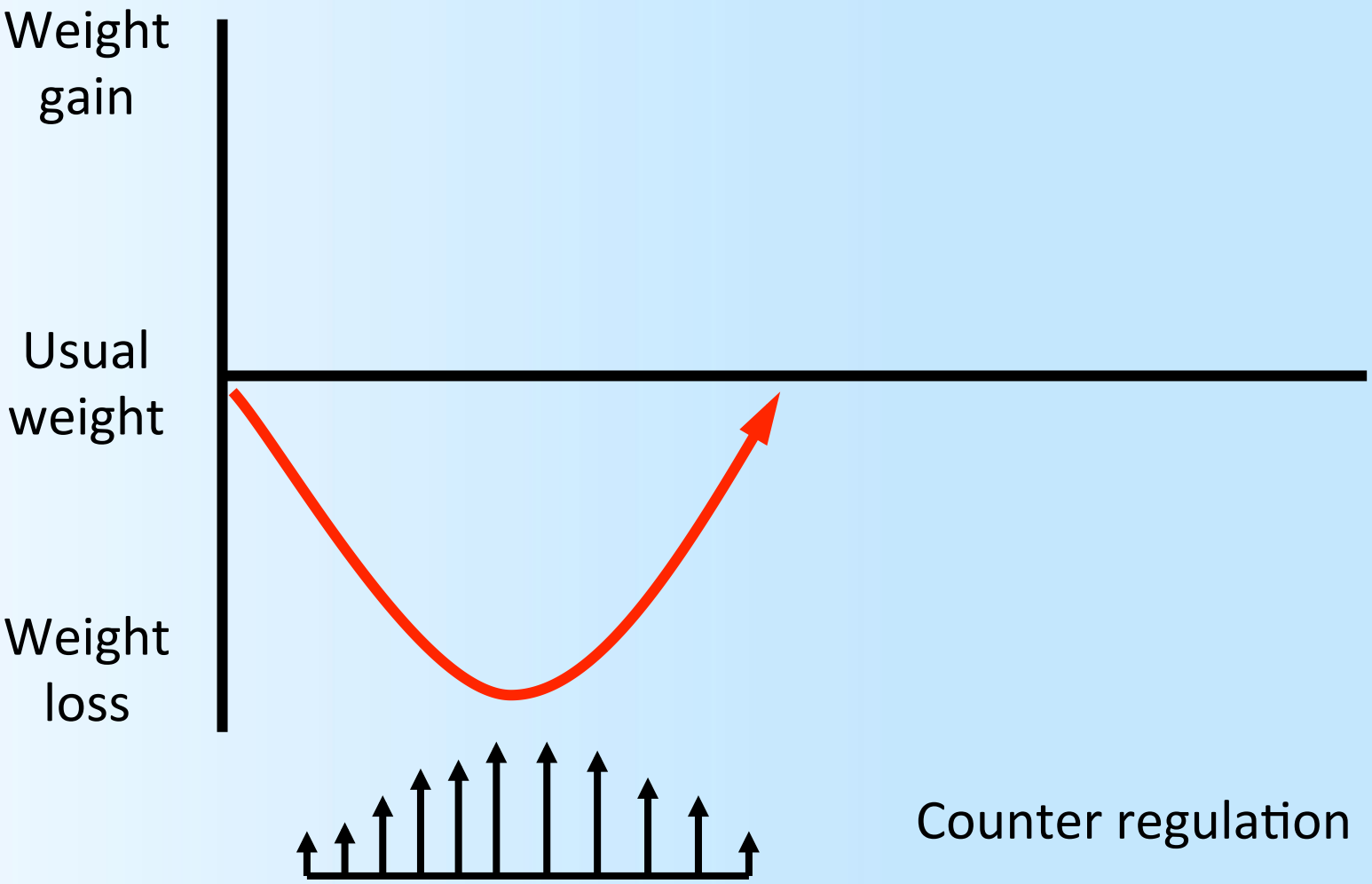
Theories on Obesity

Theories on Obesity

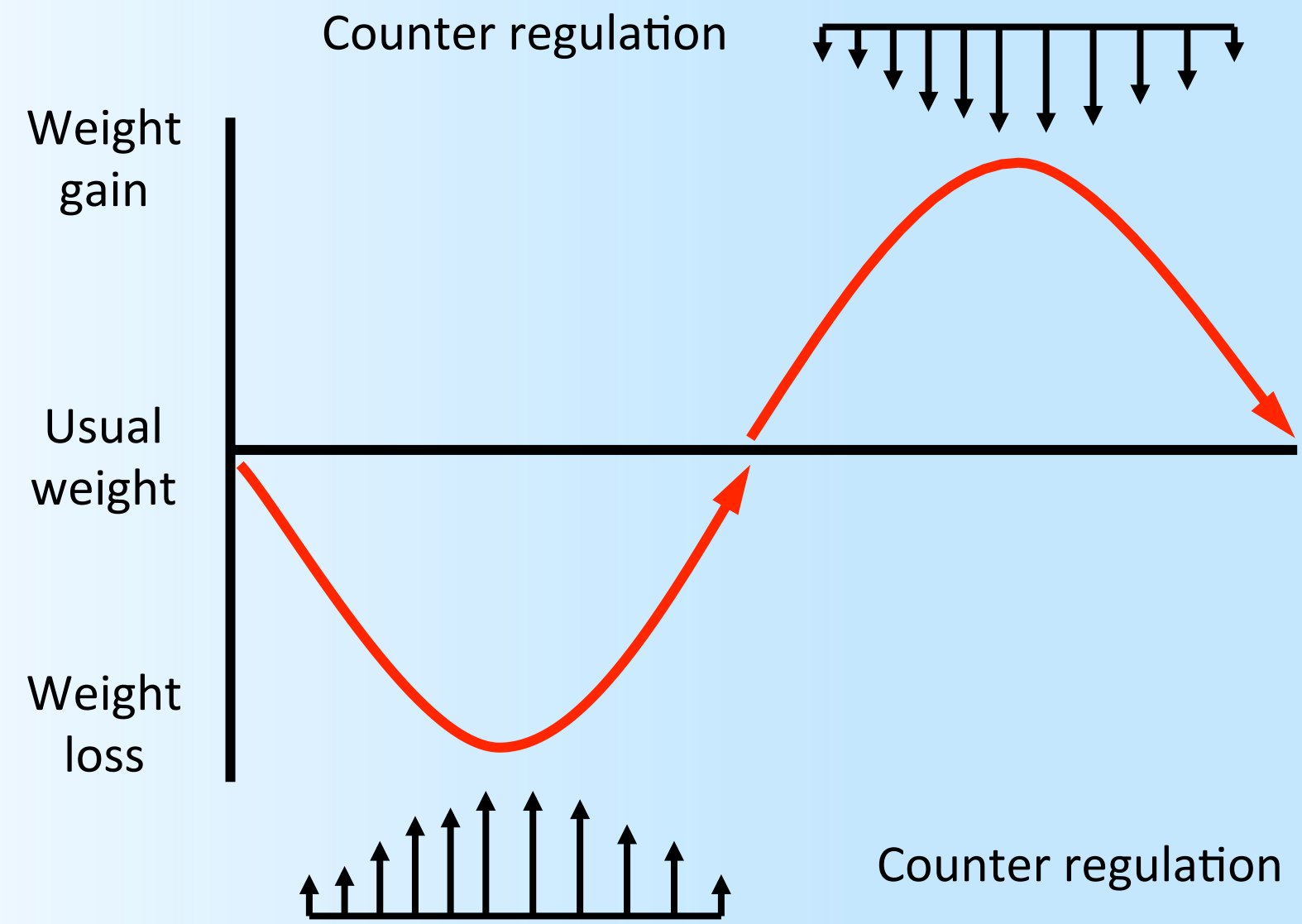
Energy Homeostasis

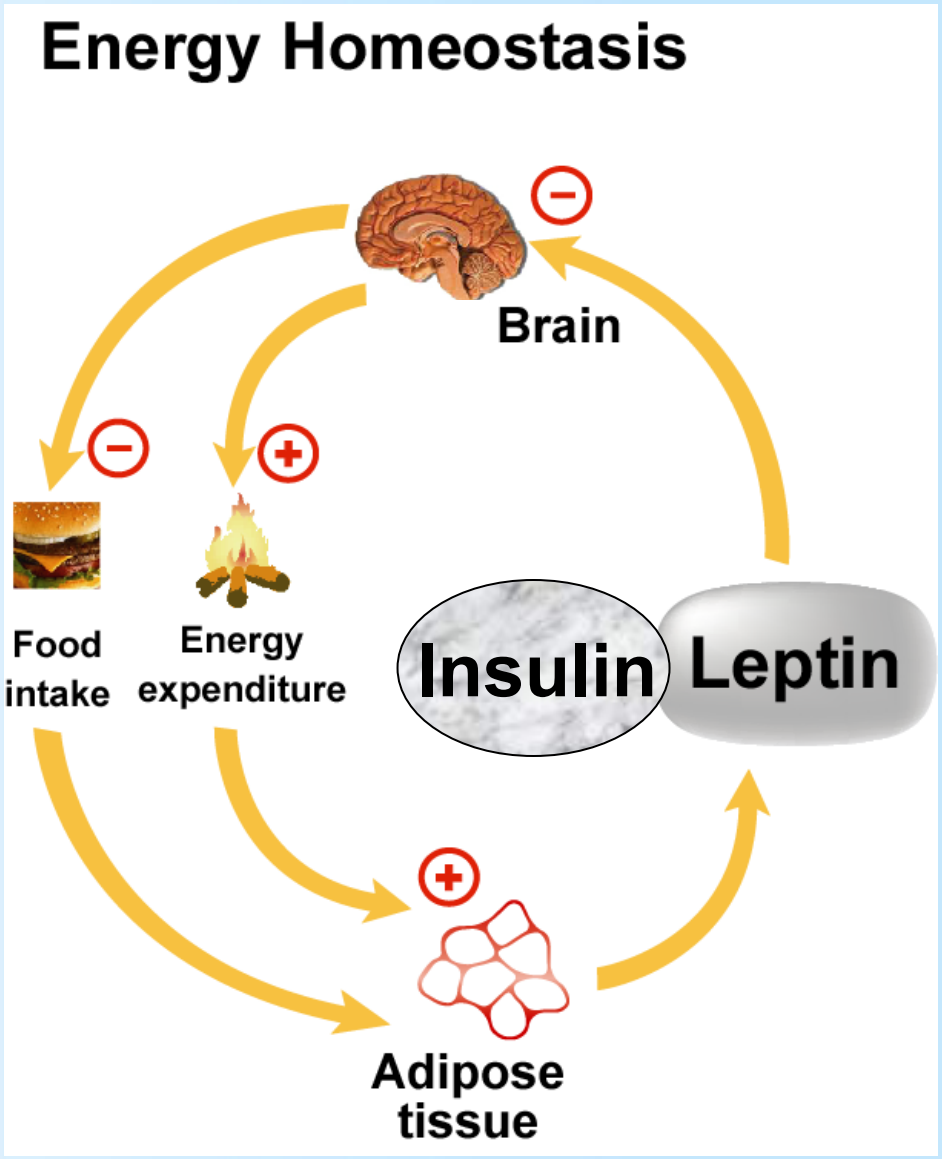
The physiological process whereby energy intake is matched to expenditure over time to promote the stability of body fuel stored in the form of fat.

"Adipostatic" Body Weight Regulation



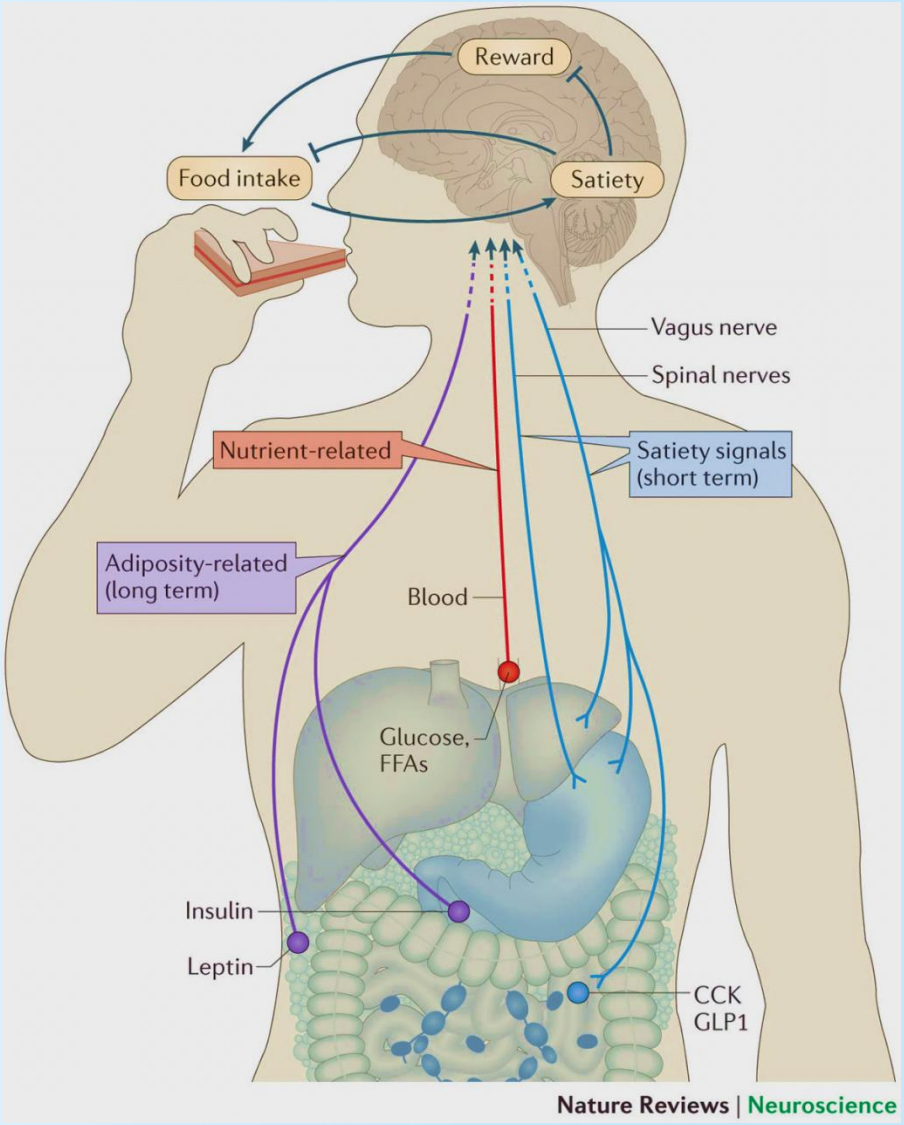
"Adipostatic" Body Weight Regulation





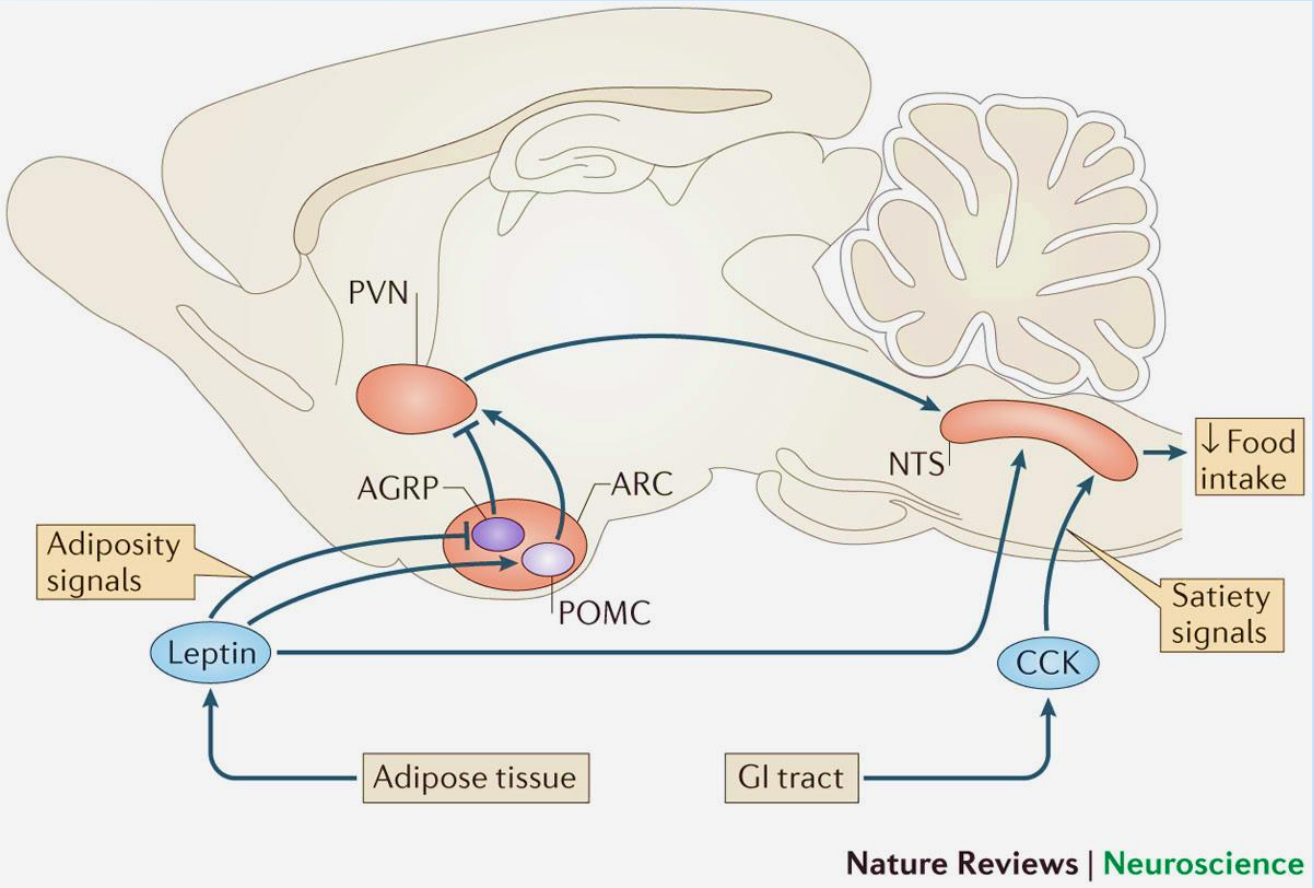
Adapted from Schwartz et al, Nature 2000;404:661-71.

Integrative View of Intake Behavior



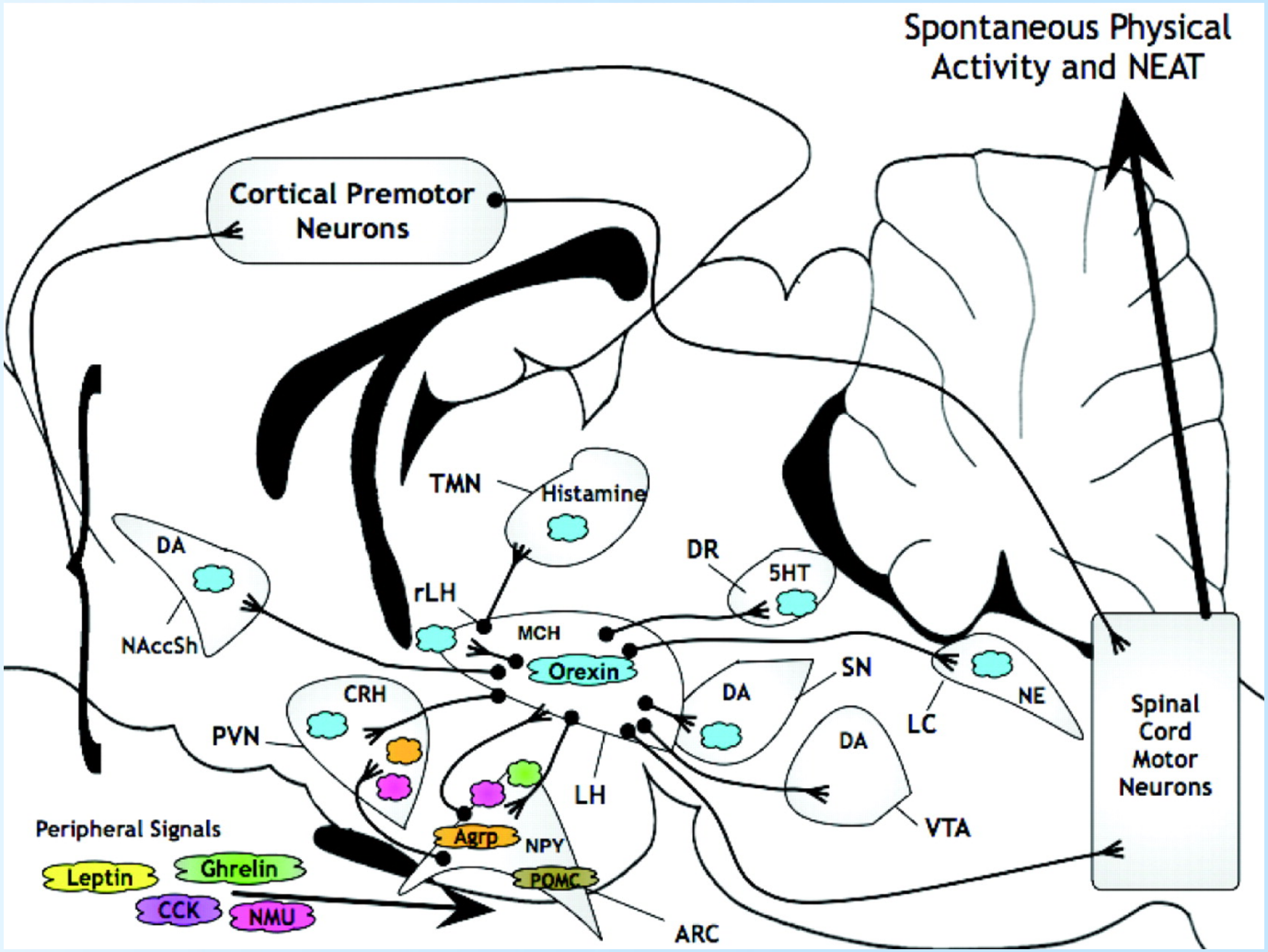
Morton et al. Nat Rev Neurosci. 2014;15:367-78.

Integrative View of Intake Behavior



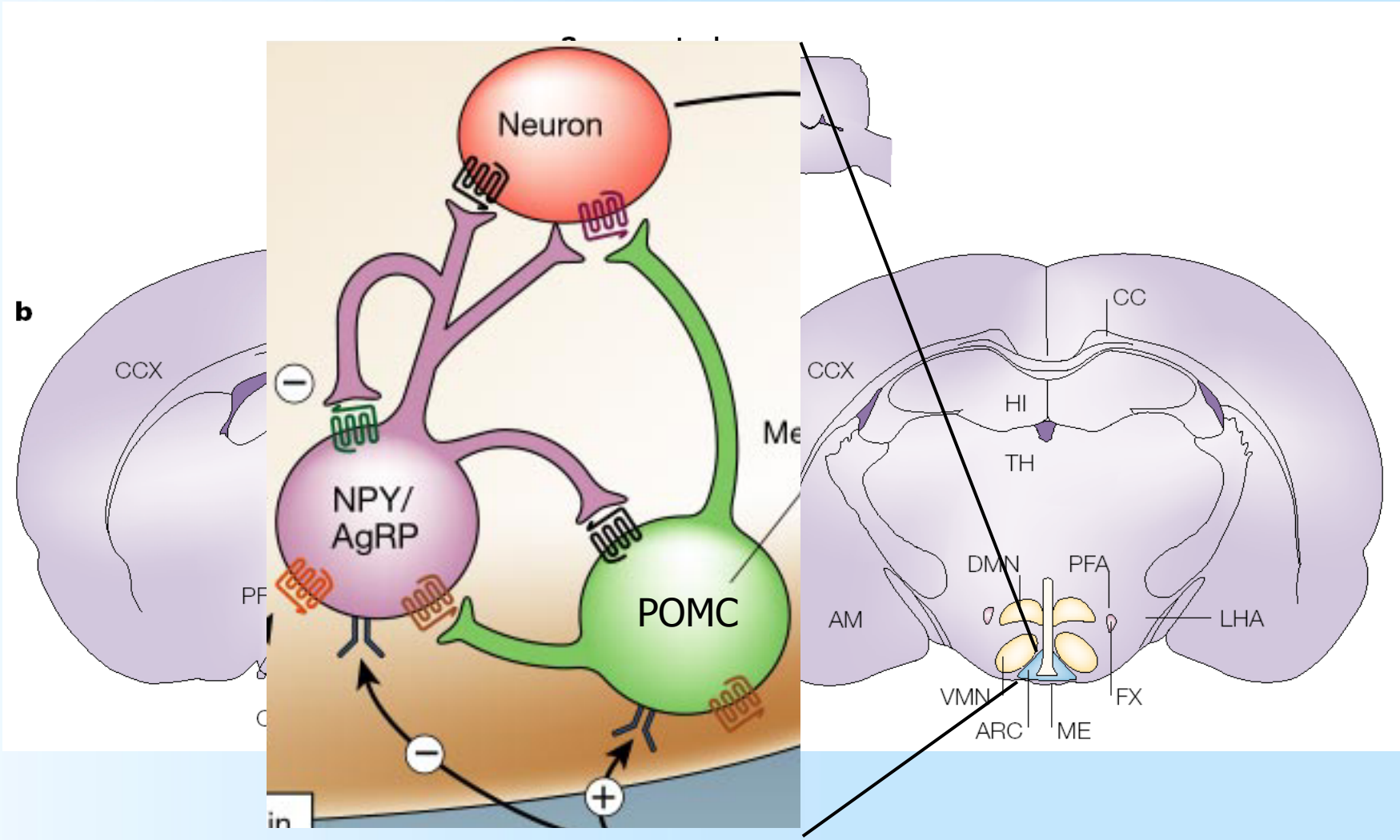
Morton et al. Nat Rev Neurosci. 2014;15:367-78.

Integrative View of Energy Expenditure



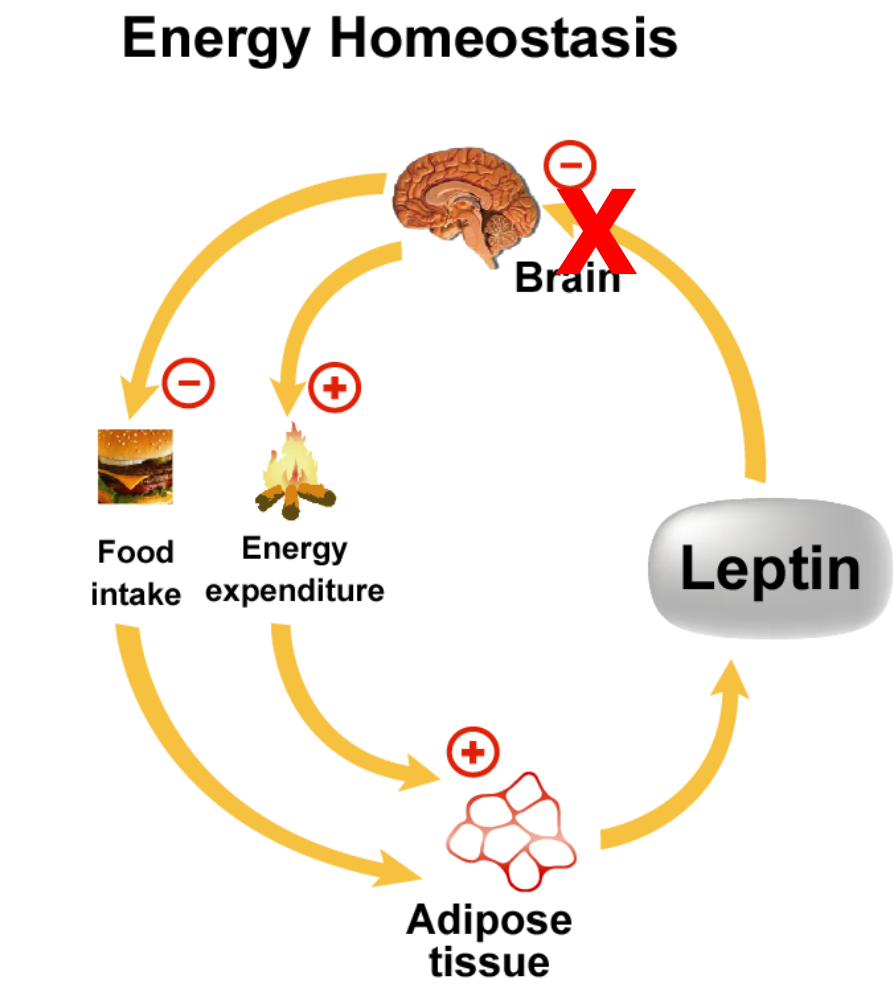
Garland et al. J Exp Biol. 2011;214:206-29.

Brain Regions Involved in Energy Balance



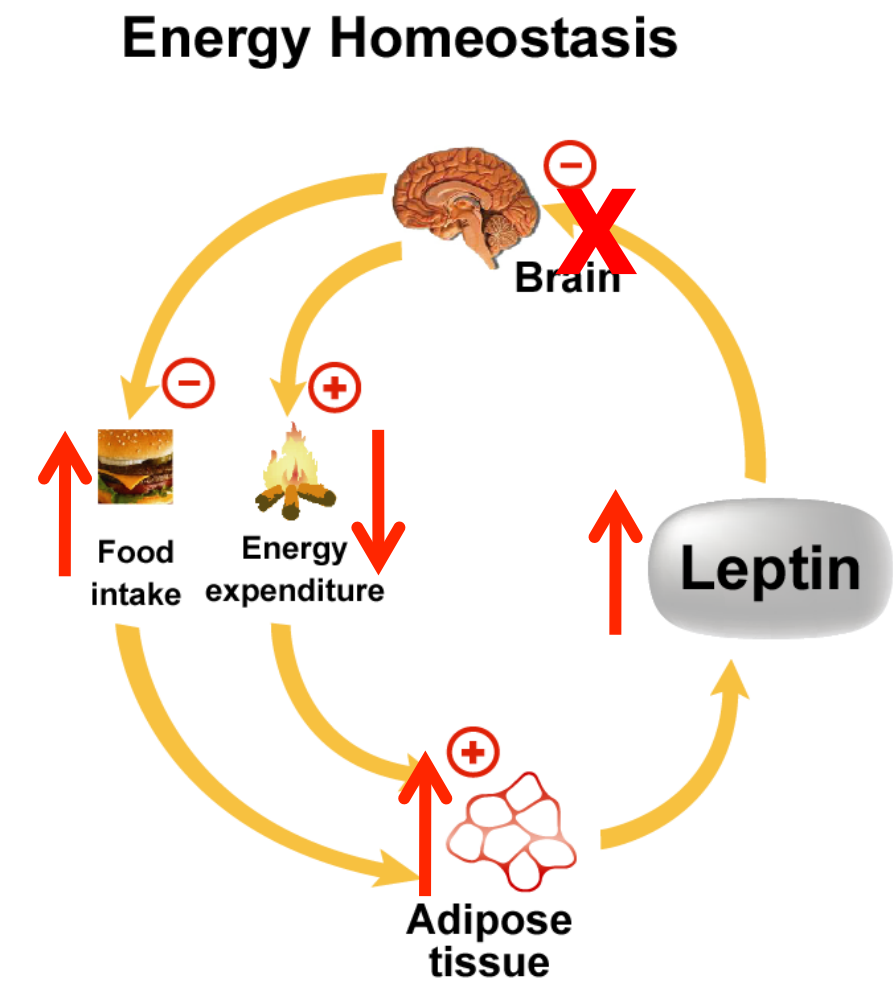
Adapted from Schwartz et al. Nature. 2000;404:661-71.

Is obesity caused by failure of homeostasis?



Adapted from Schwartz et al. Nature. 2000;404:661-71.

Obesity = Defense of elevated body adiposity

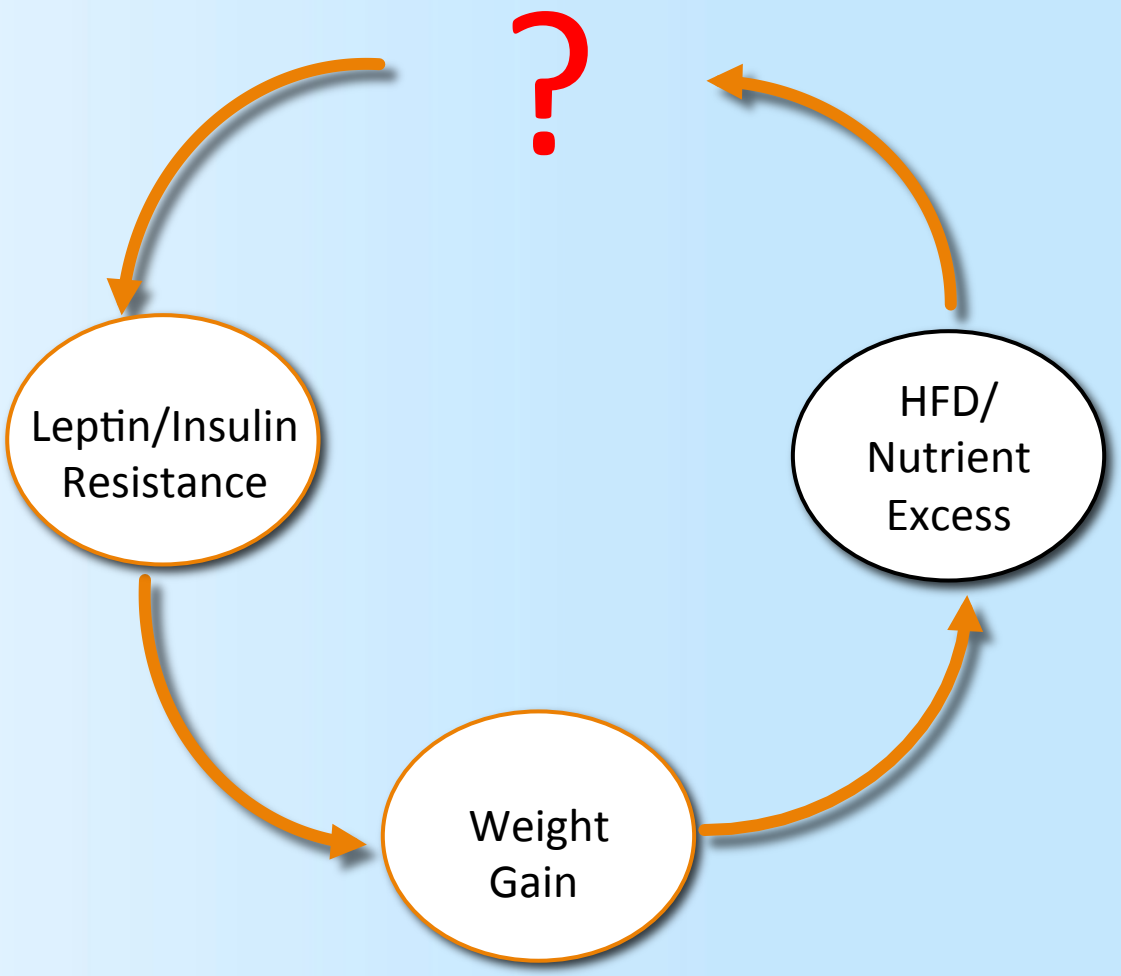


Adapted from Schwartz et al. Nature. 2000;404:661-71.

Defense of Elevated Body Weight

"I just read somewhere that 160 pounds is the new 135!"

HYPOTHALAMUS



Outline

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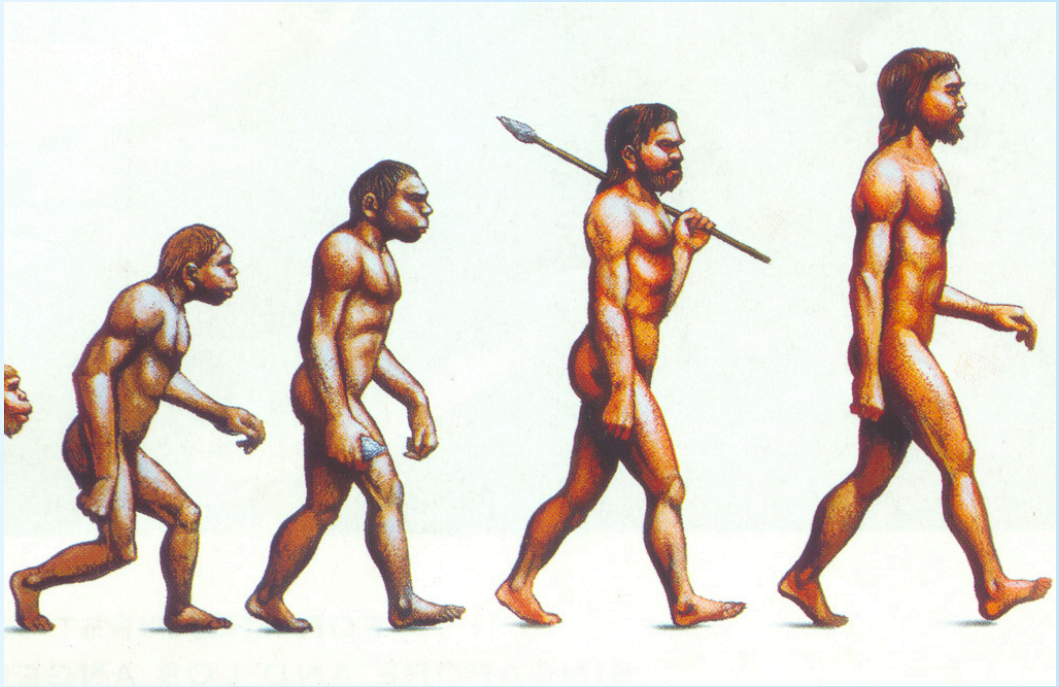
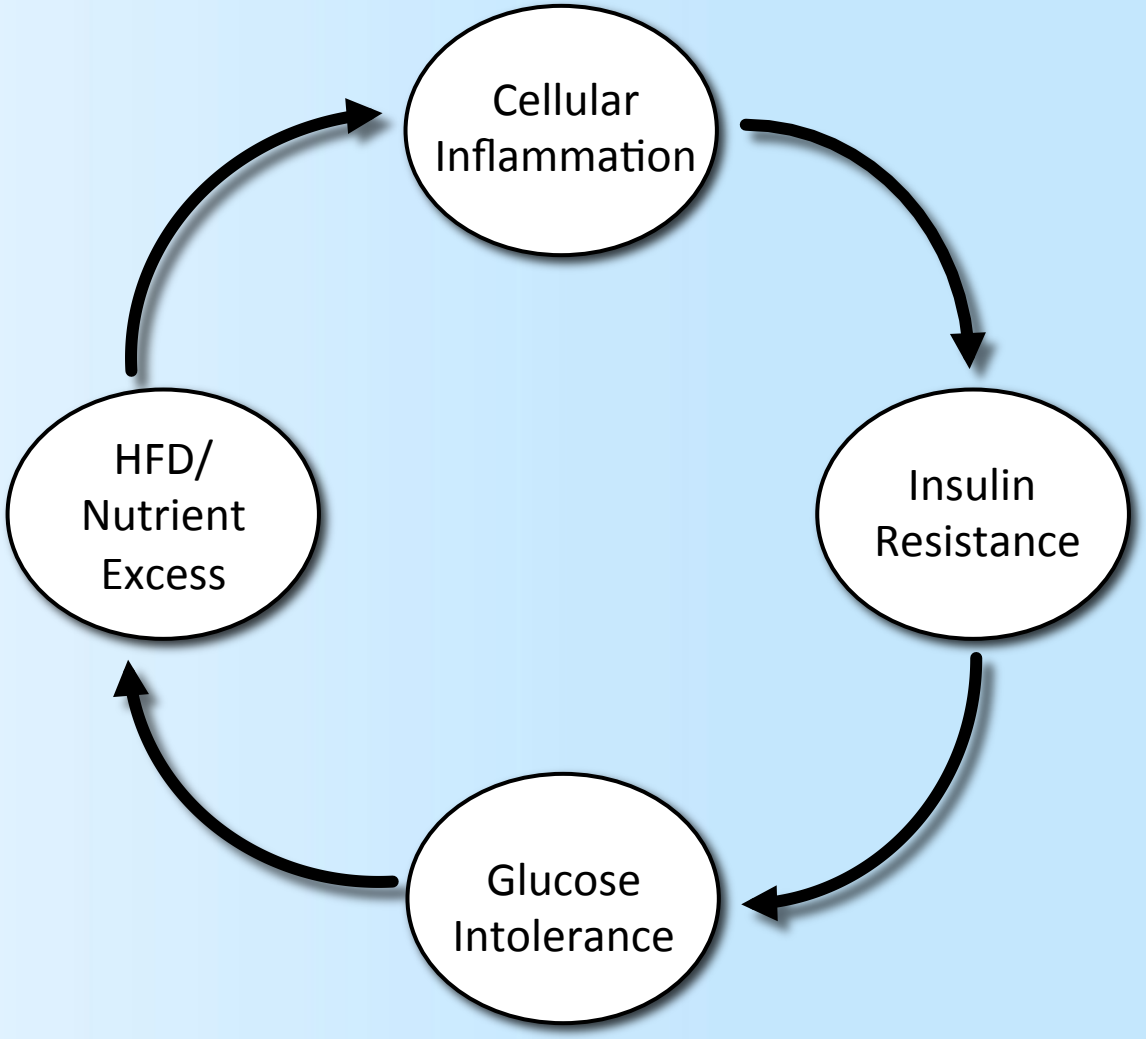
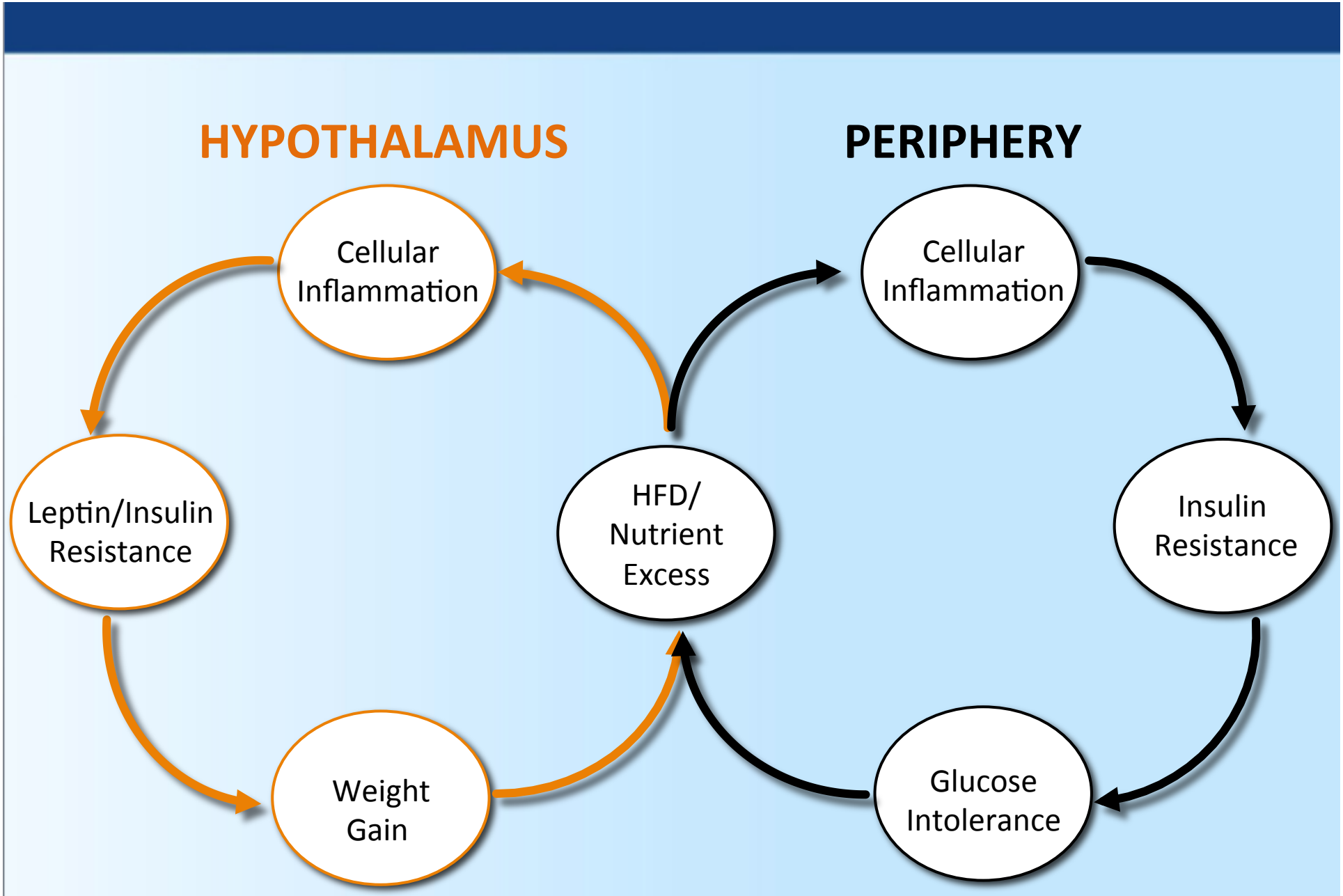


Lessons From the Periphery





Thaler and Schwartz. Endocrinology 2010;151:4109-15.

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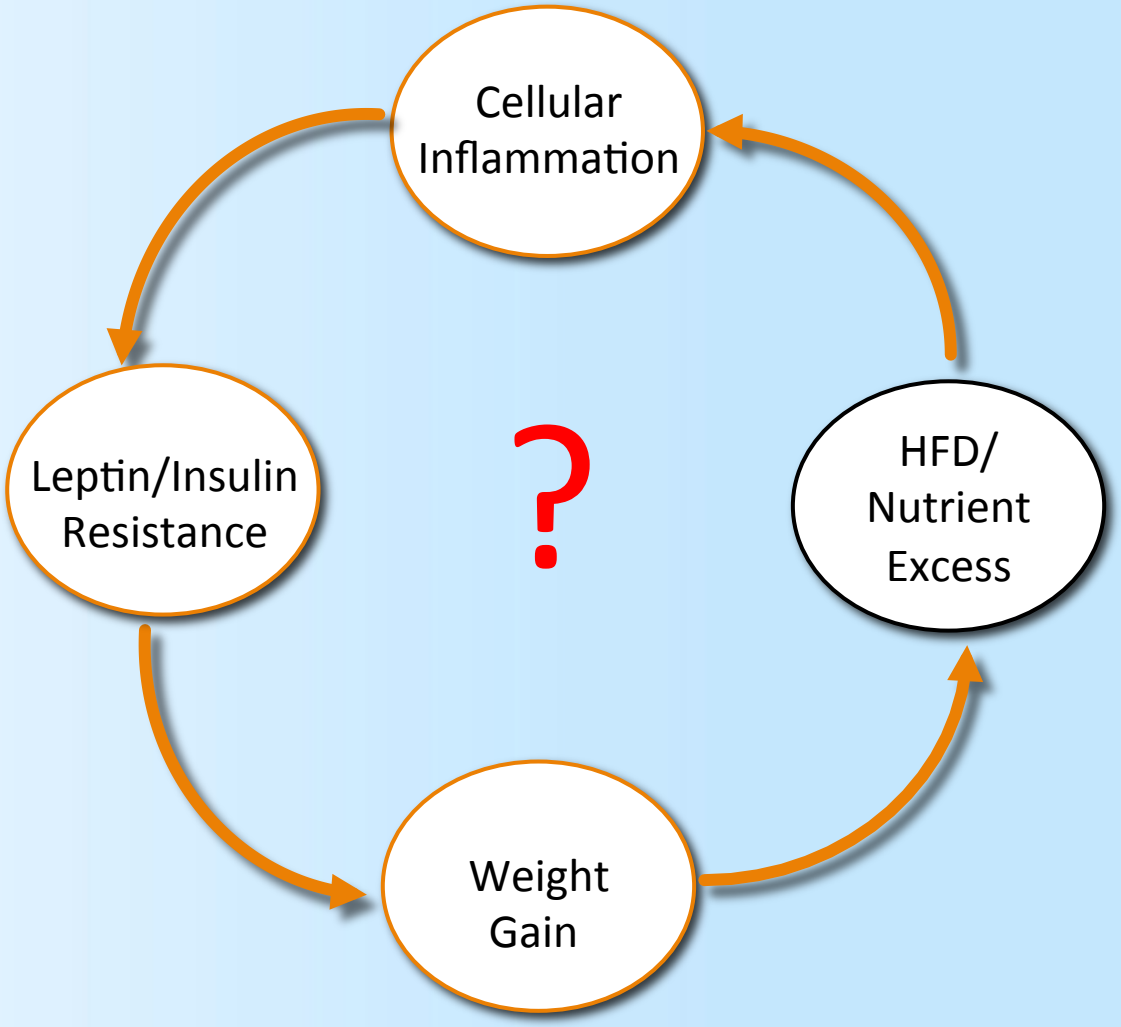

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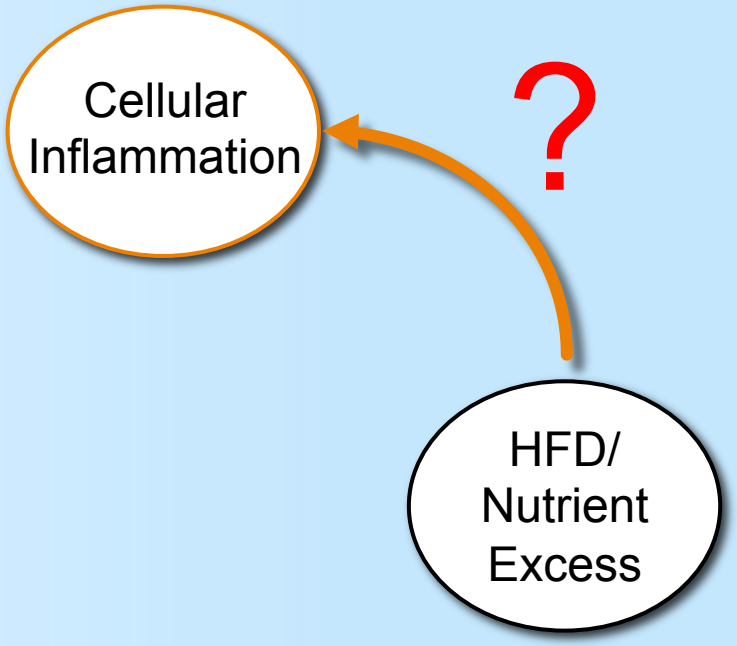
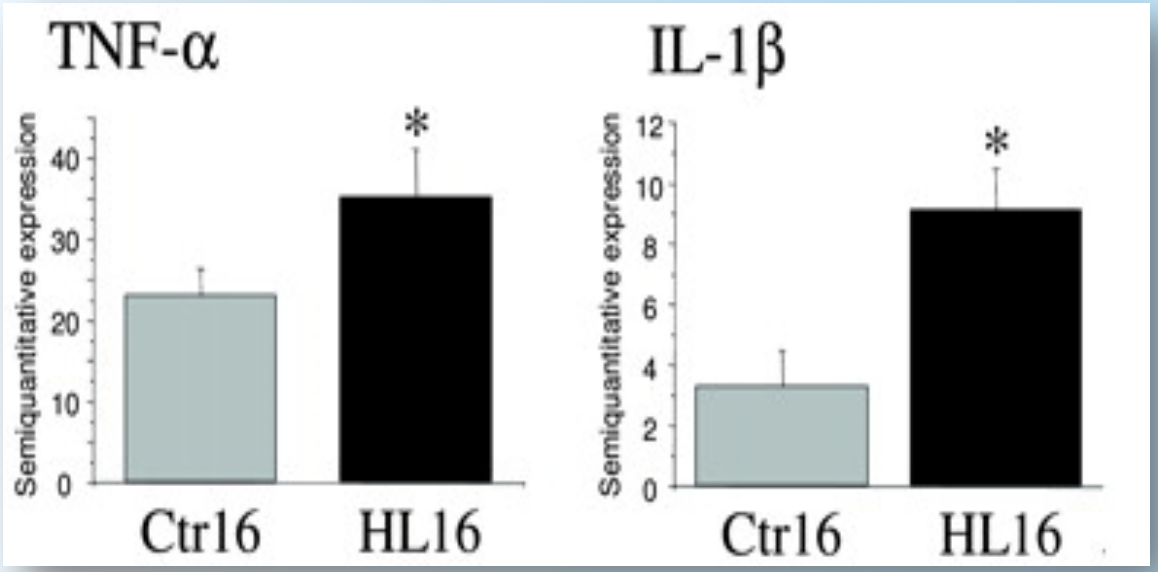
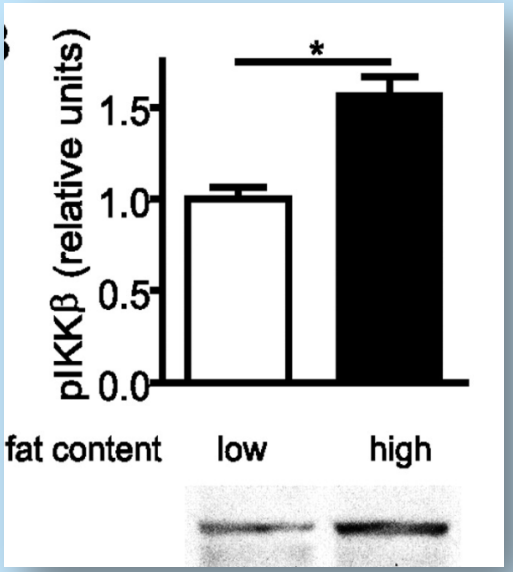


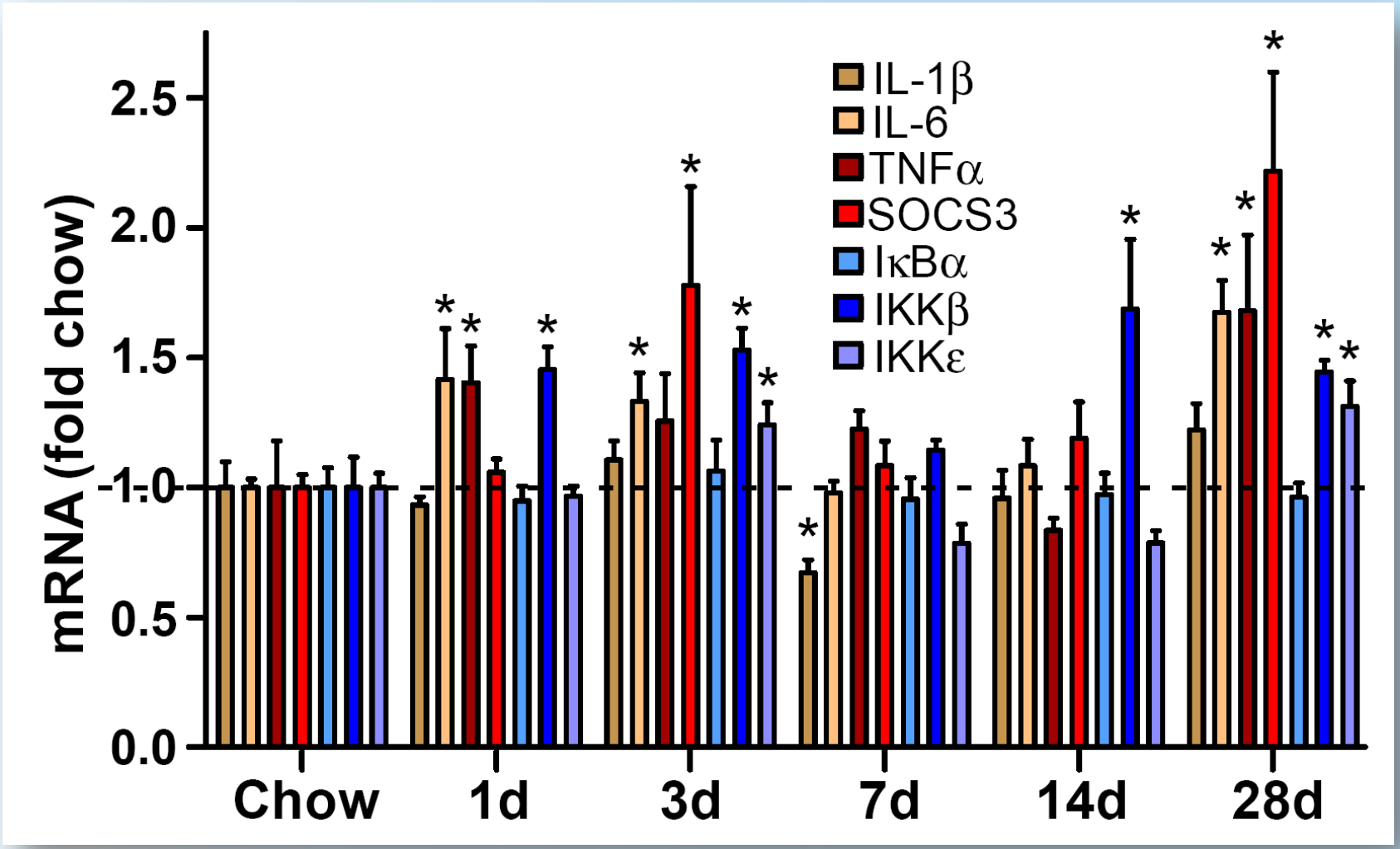
High-Fat Diets Induce Hypothalamic Inflammation





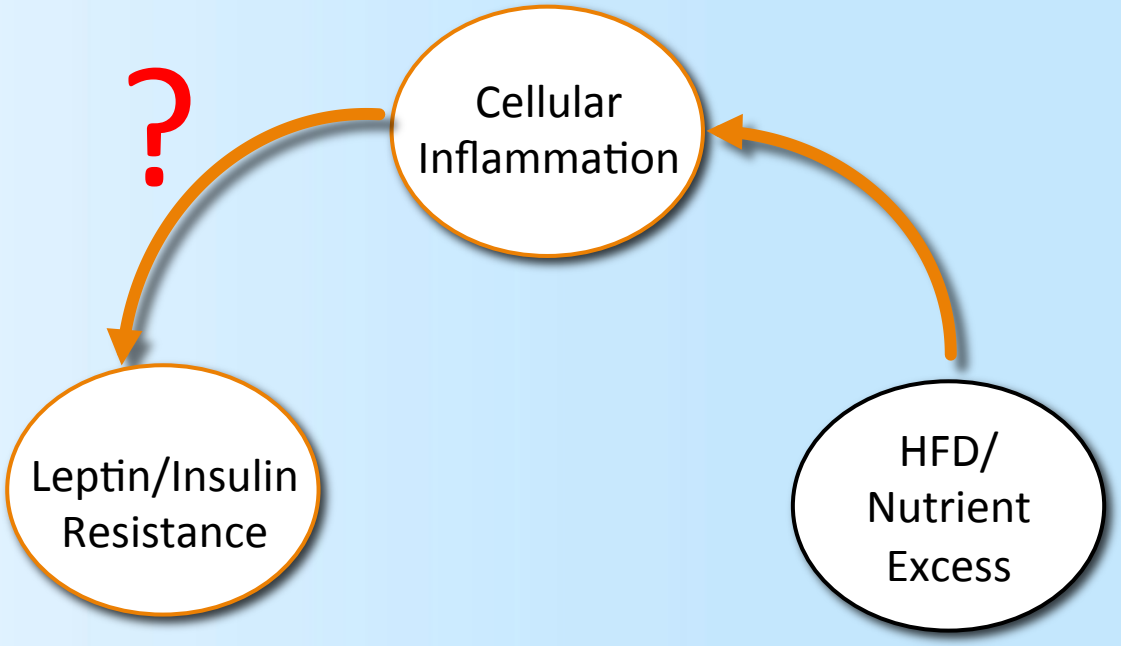
DeSouza et al. Endocrinology. 2005;146:4192-99. Posey et al. AJP Endo & Metab .2009;296:1003-12.

Hypothalamic Inflammation Begins Within First 3 days of HFD



Thaler et al. JCI 2012;122:153-62.

HYPOTHALAMUS



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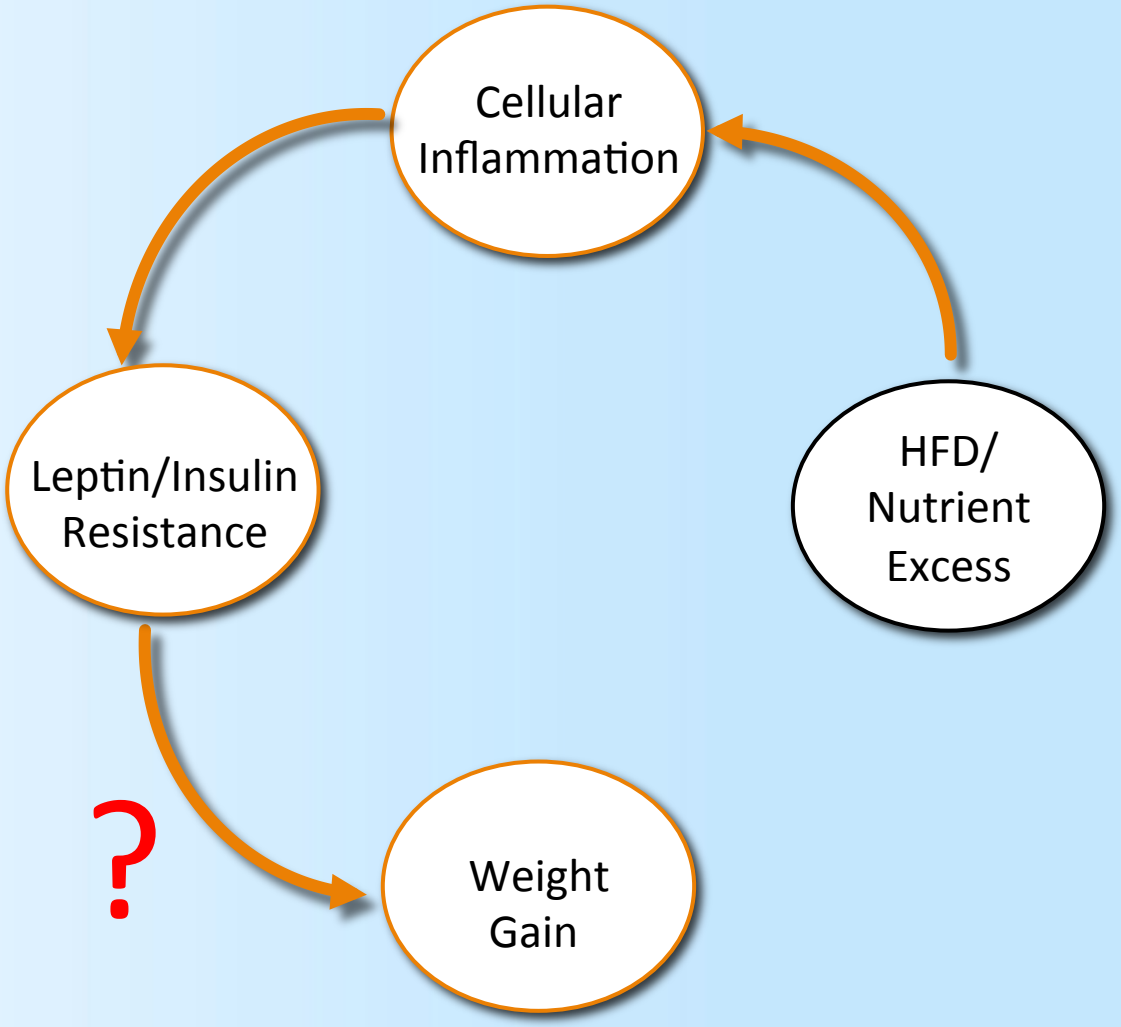
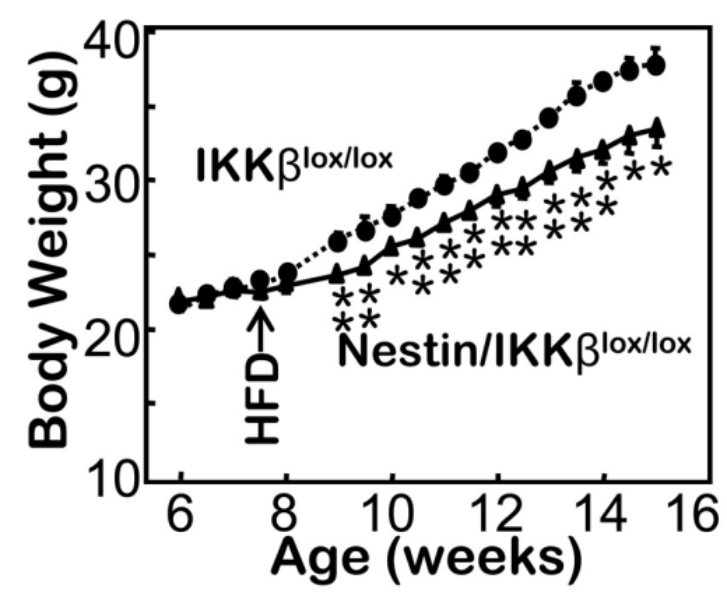
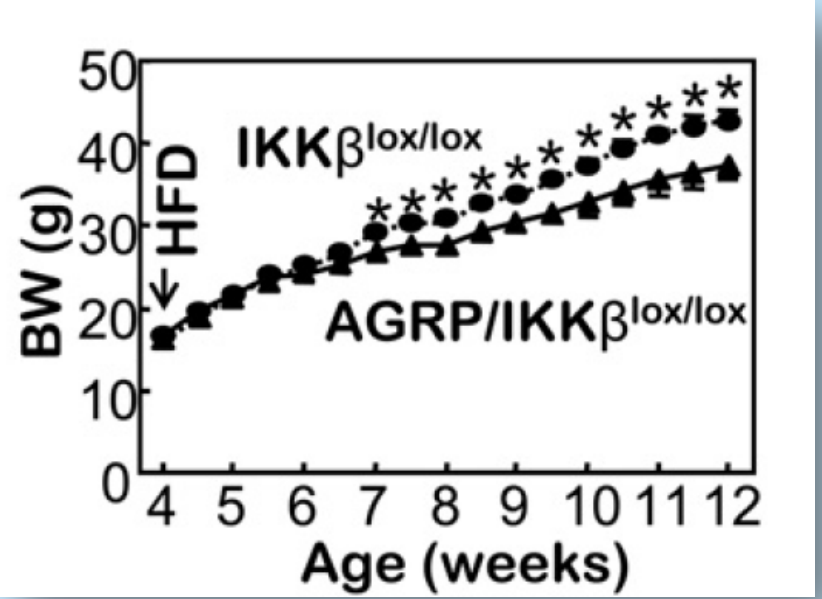


Hypothalamic inflammation is necessary for diet-induced obesity

NF-κB pathway

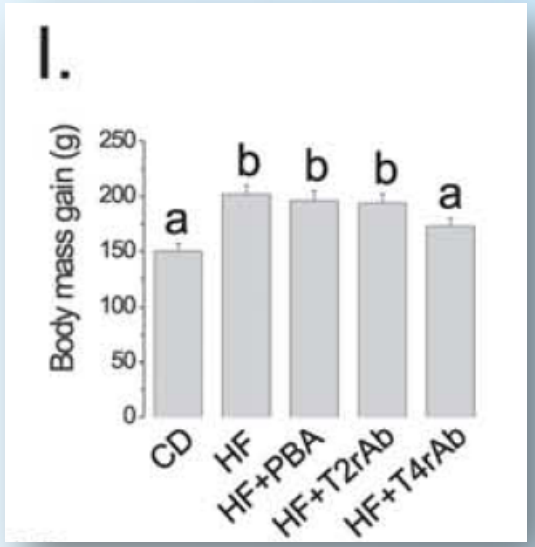


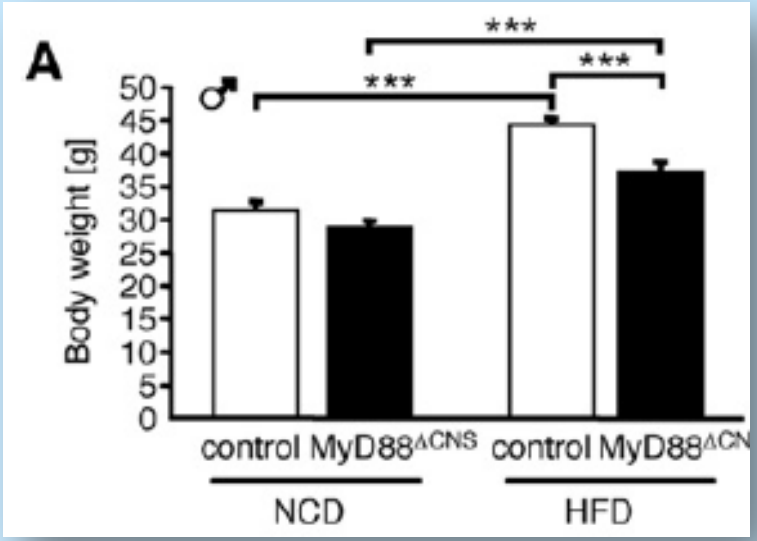


Zhang X et al. Cell 2008; 135:61-73.

Hypothalamic Inflammation is Necessary for Diet-Induced Obesity

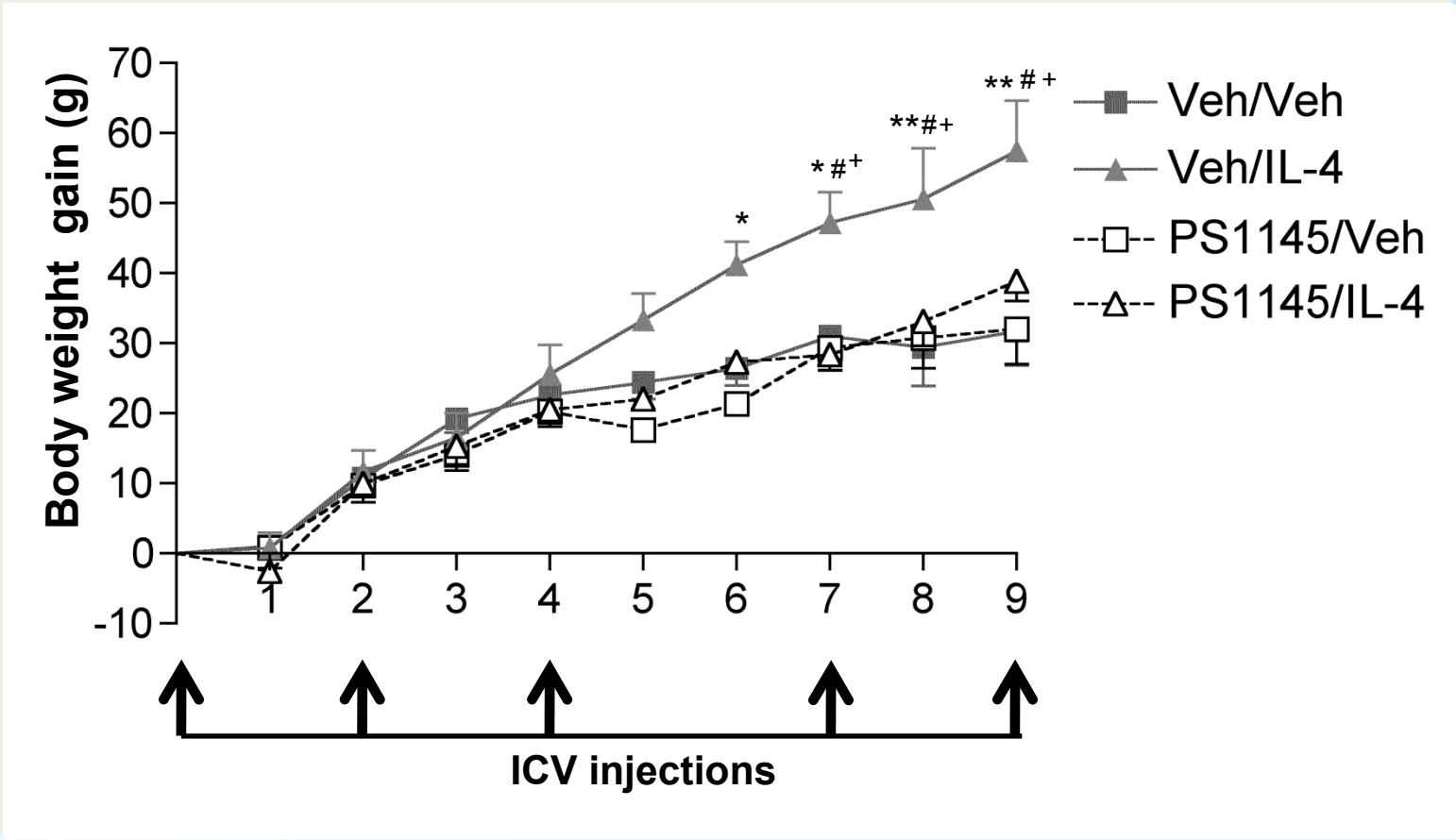
TLR4-MyD88 pathway





Milanski et al. J Neurosci 2009;29:359-70. Kleinridders et al. Cell Metabolism 2009;10:249-59.

Hypothalamic inflammation is sufficient for diet-induced obesity



Oh et al. AJP Endo & Metab 2010; 299:47-53.

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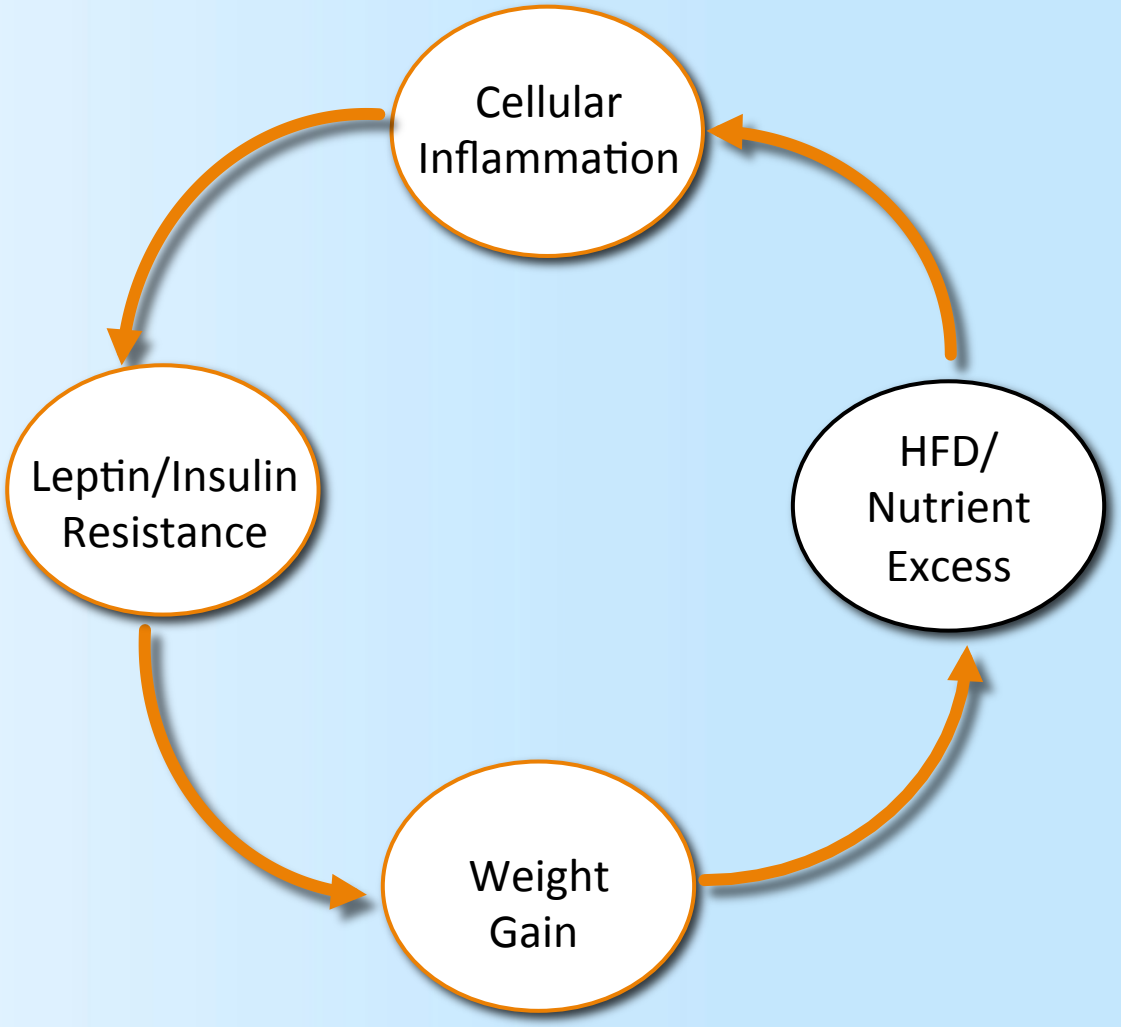

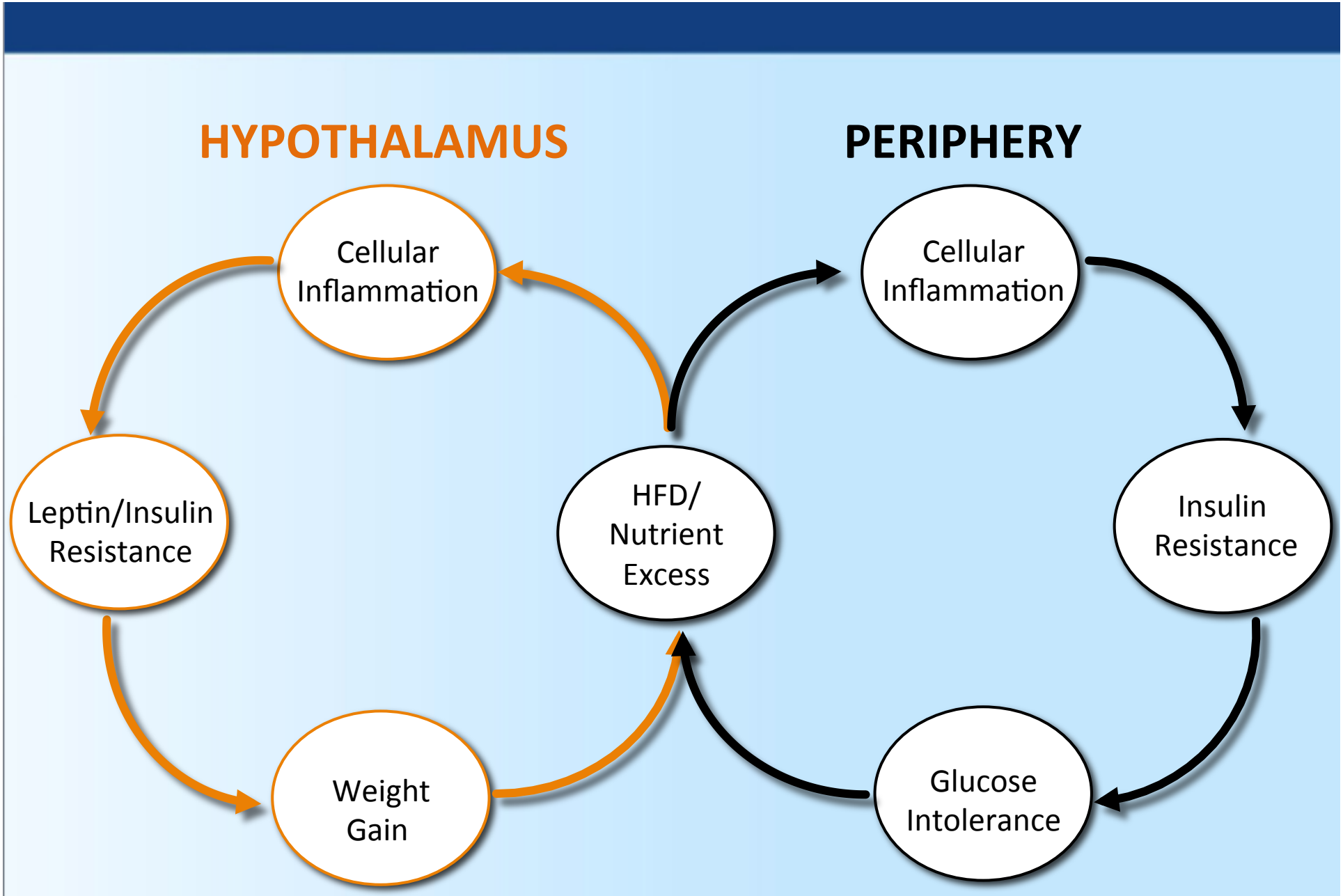

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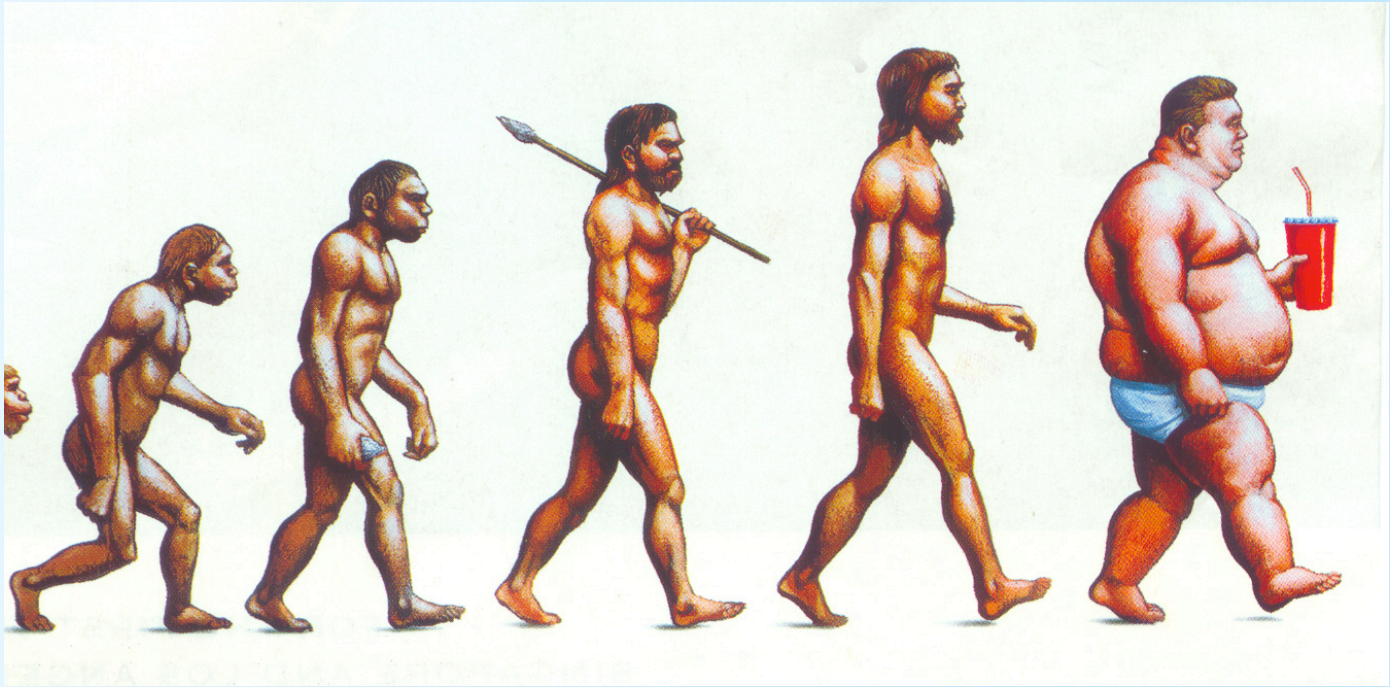

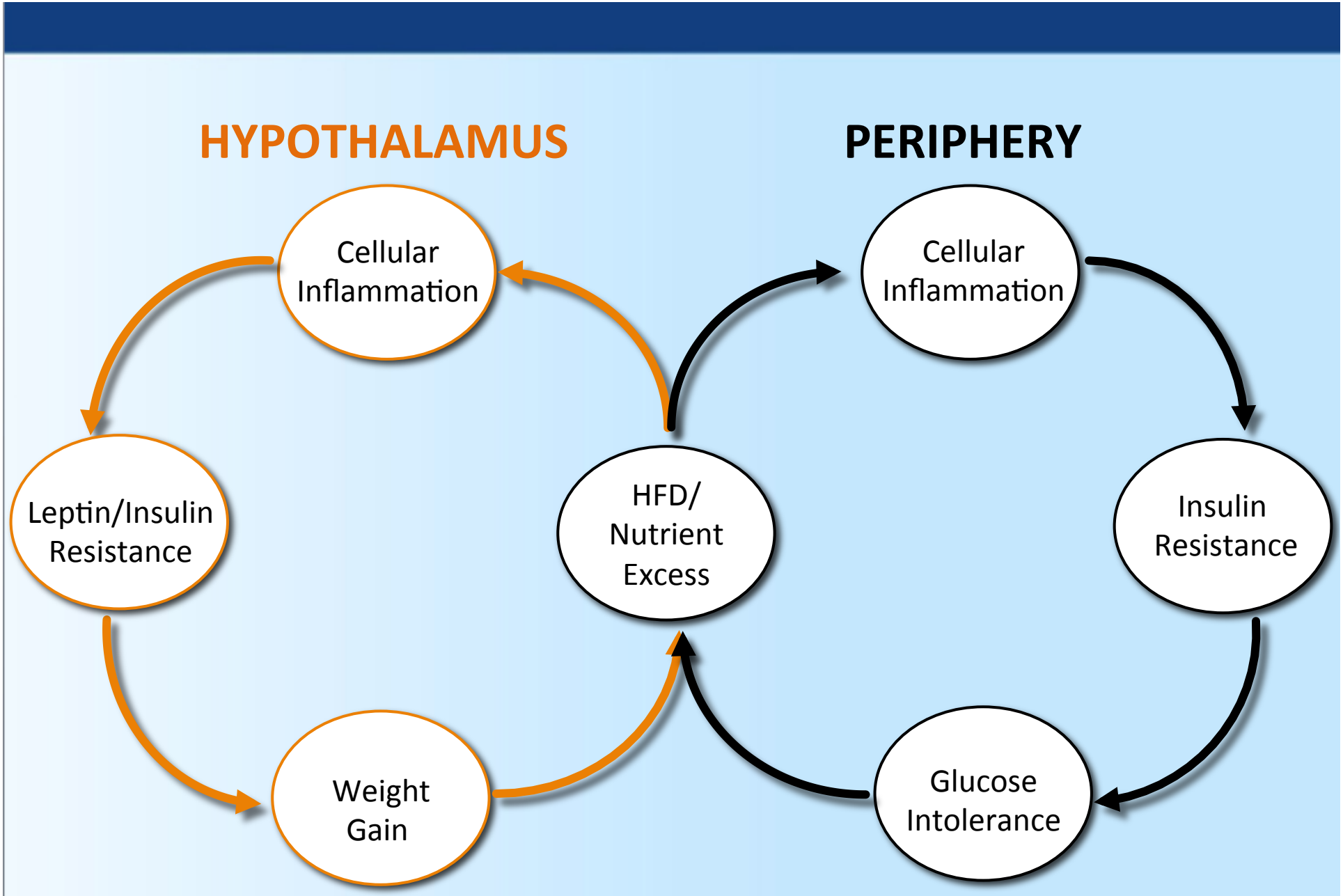

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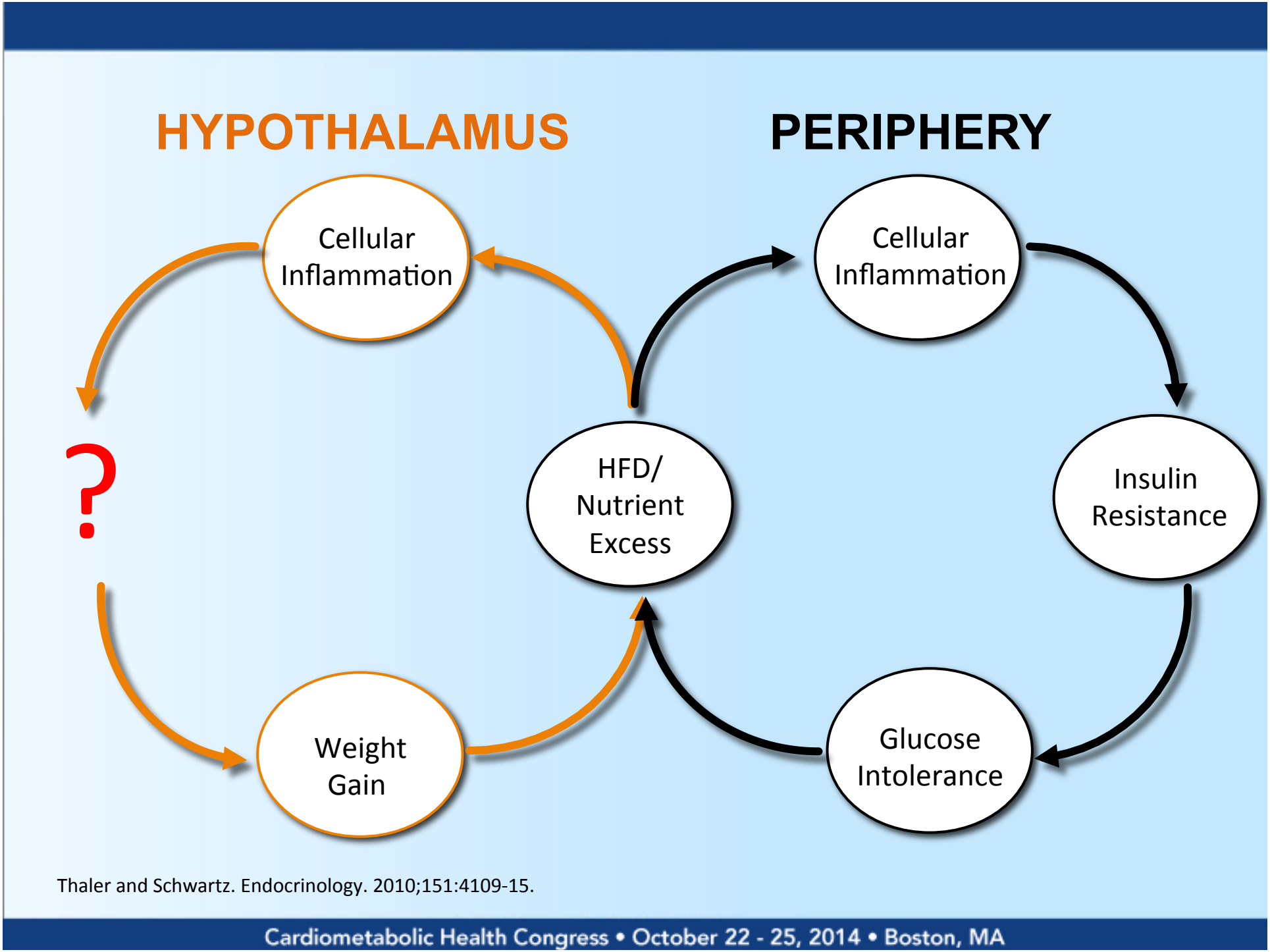

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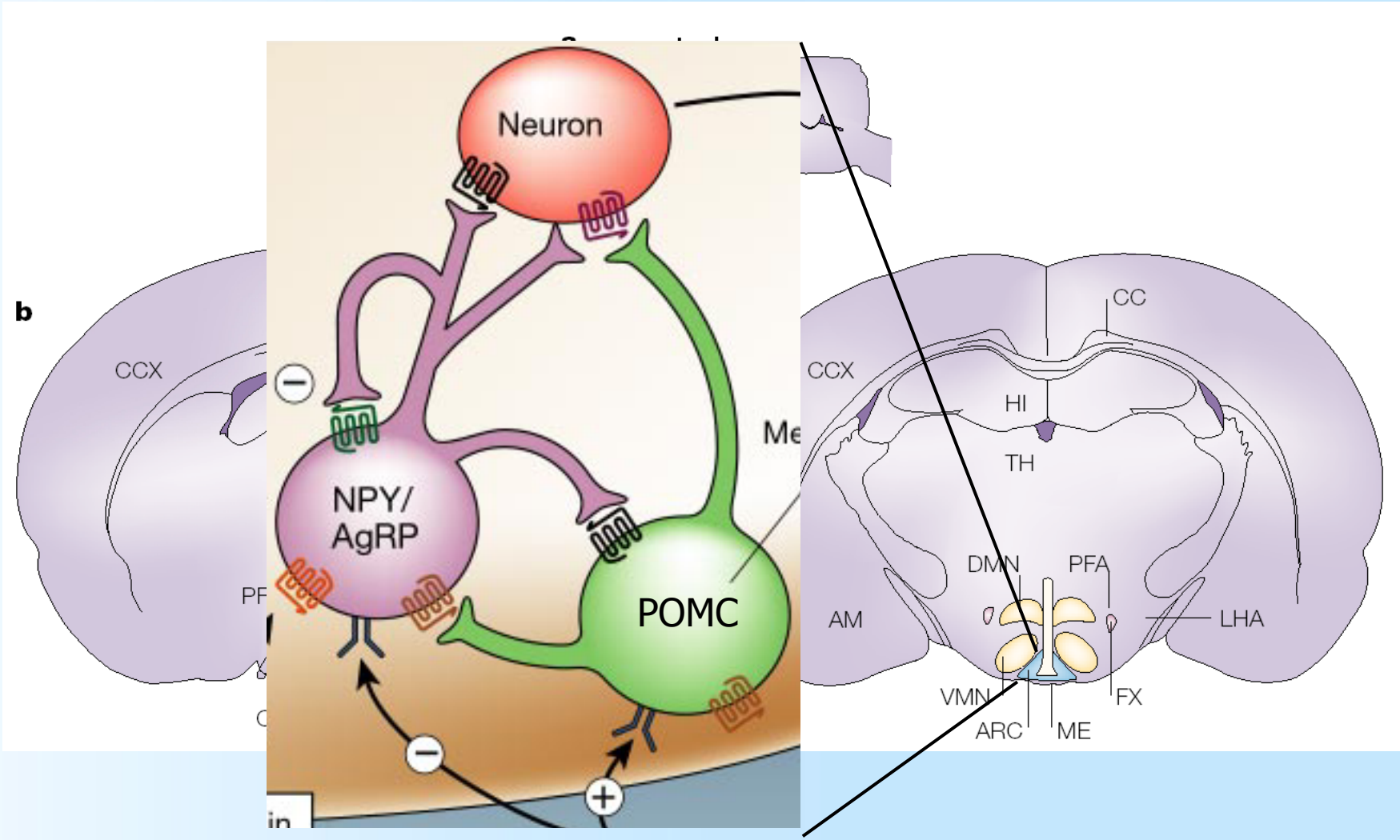
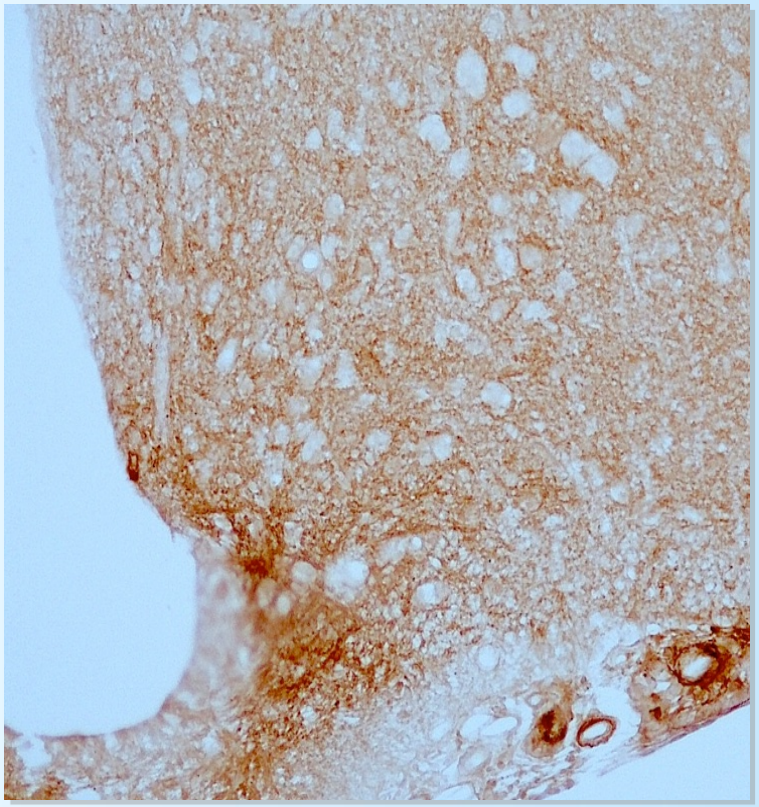
Brain Regions Involved in Energy Balance



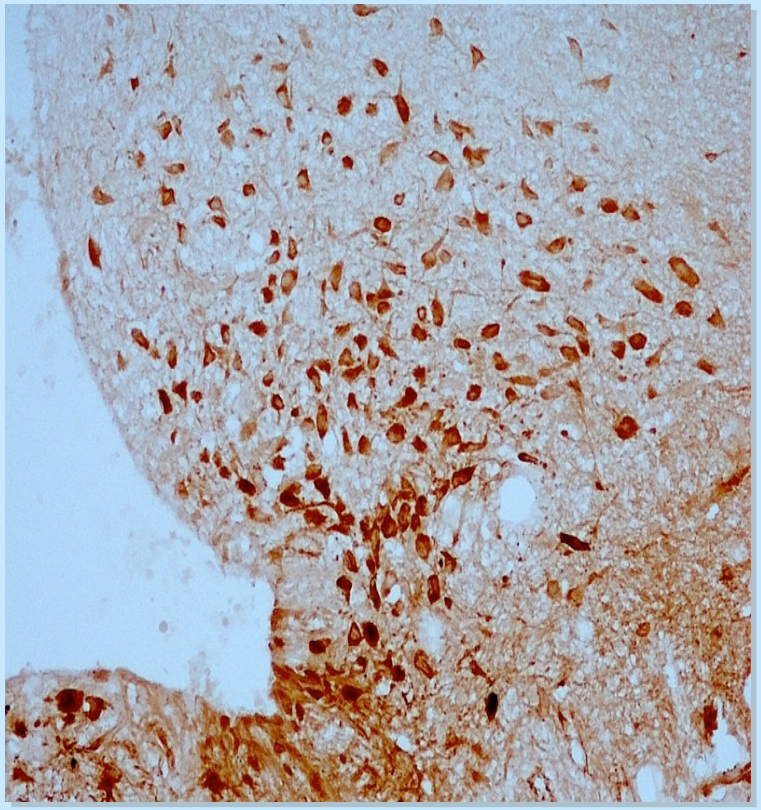
Adapted from Schwartz et al. Natur.e 2000;404:661-71.

Evidence for Neuronal Stress

Hsp72



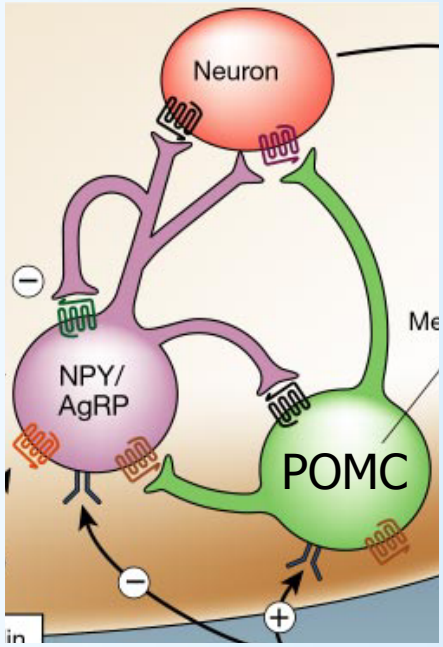
Chow

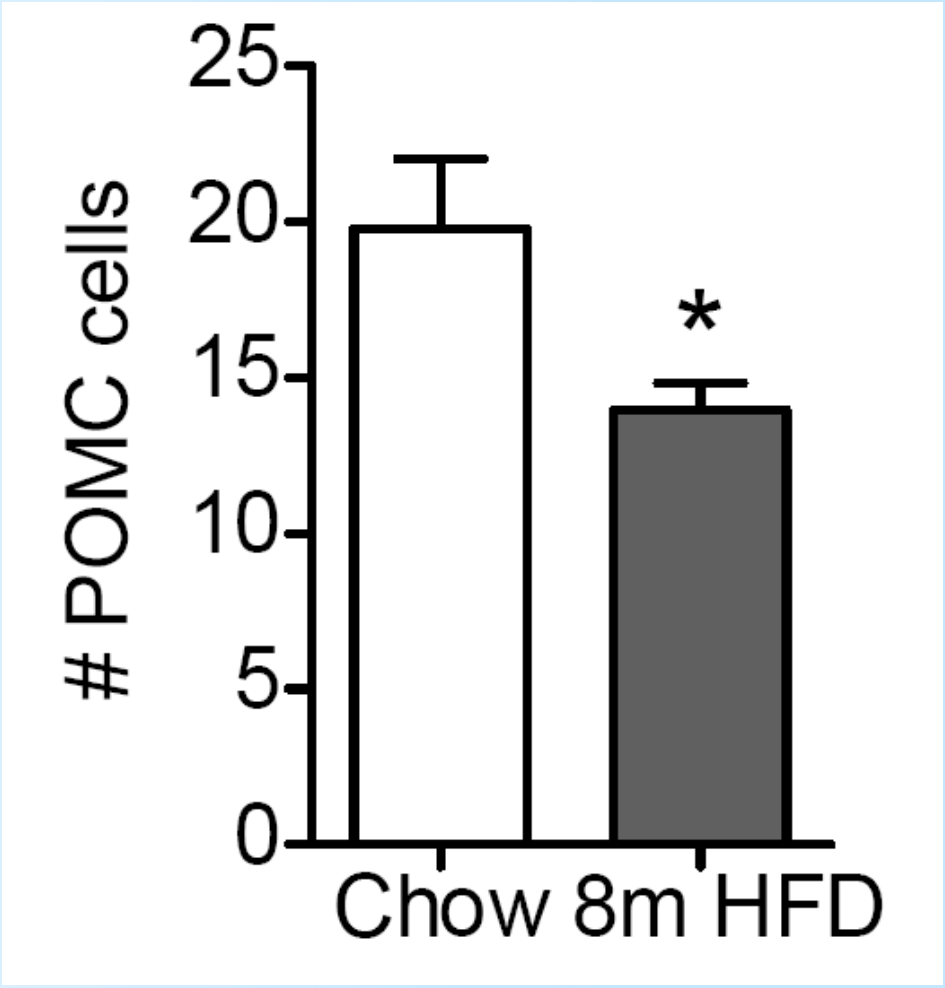


7d HFD

Thaler et al. JCI 2012;122:153-62.

POMC Cell Loss in High-Fat Diet

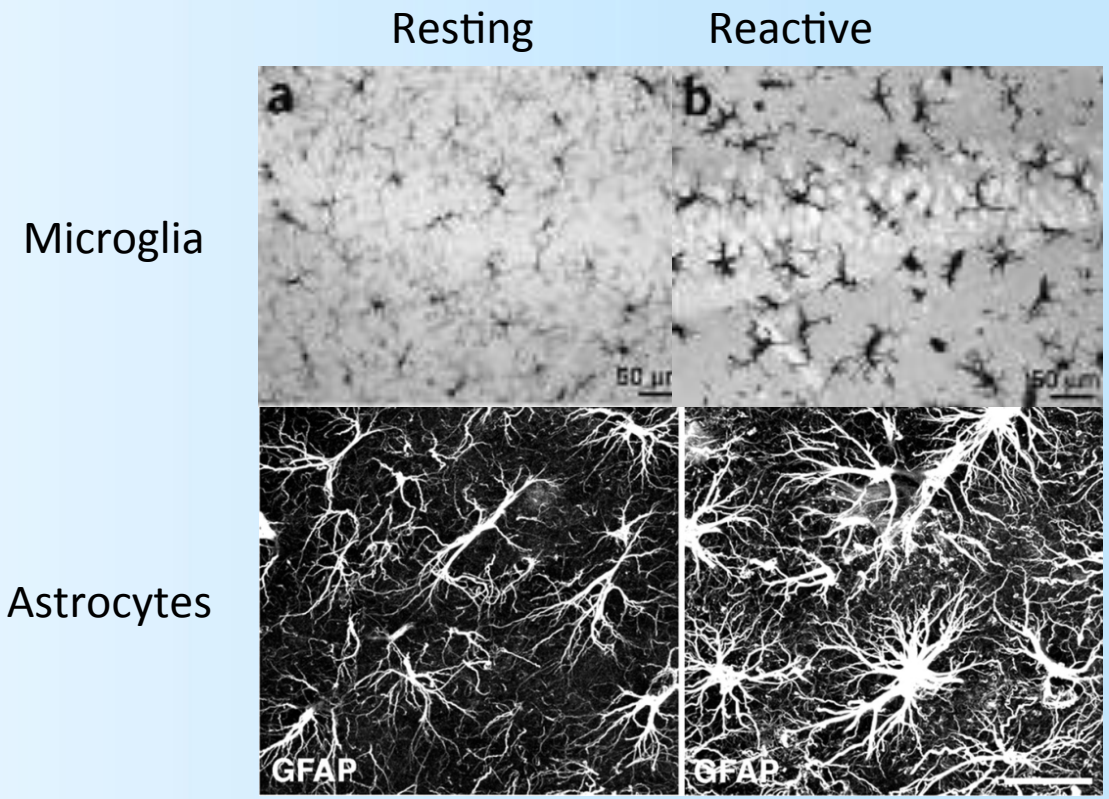




Thaler et al. JCI 2012;122:153-62.

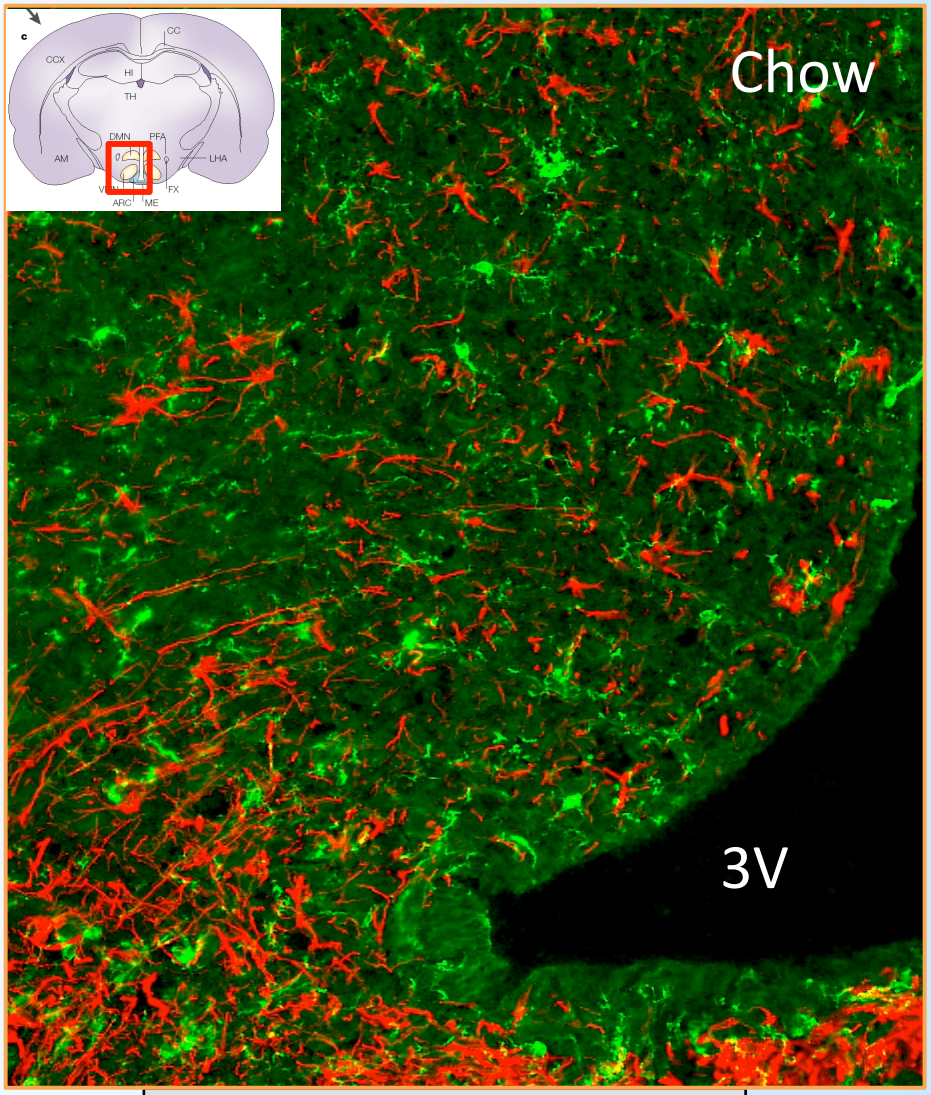
Gliosis

Glial response to CNS injury



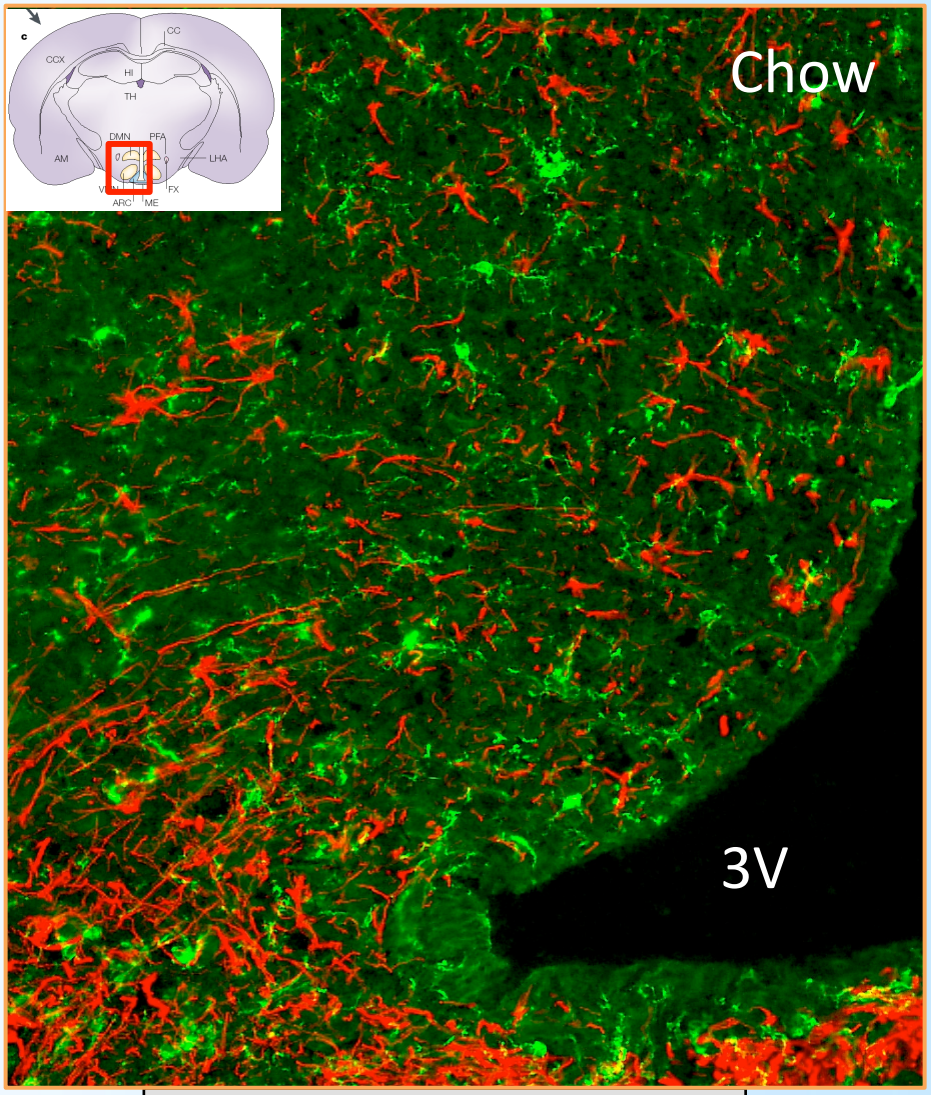
Wilhelmsson et al. PNAS. 2006;103:17513-8.

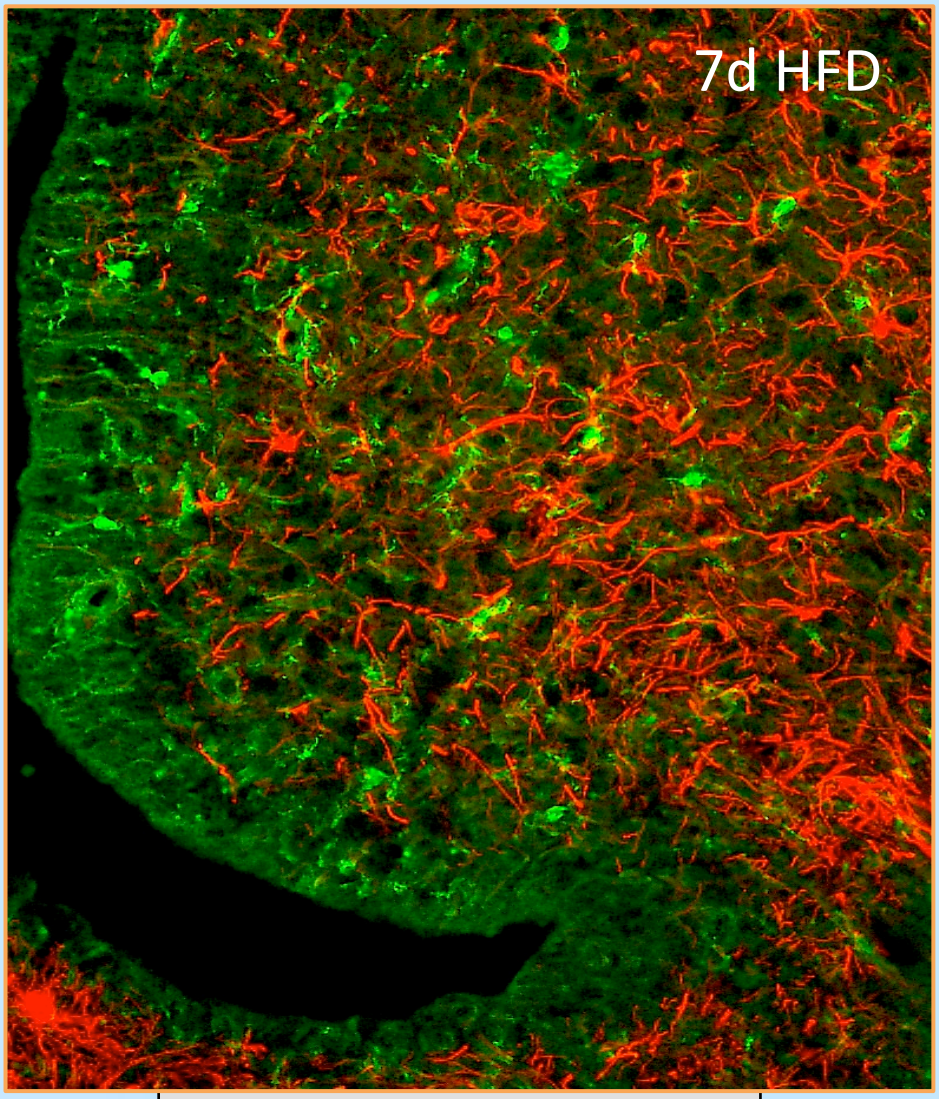
Gliosis During HFD Consumption



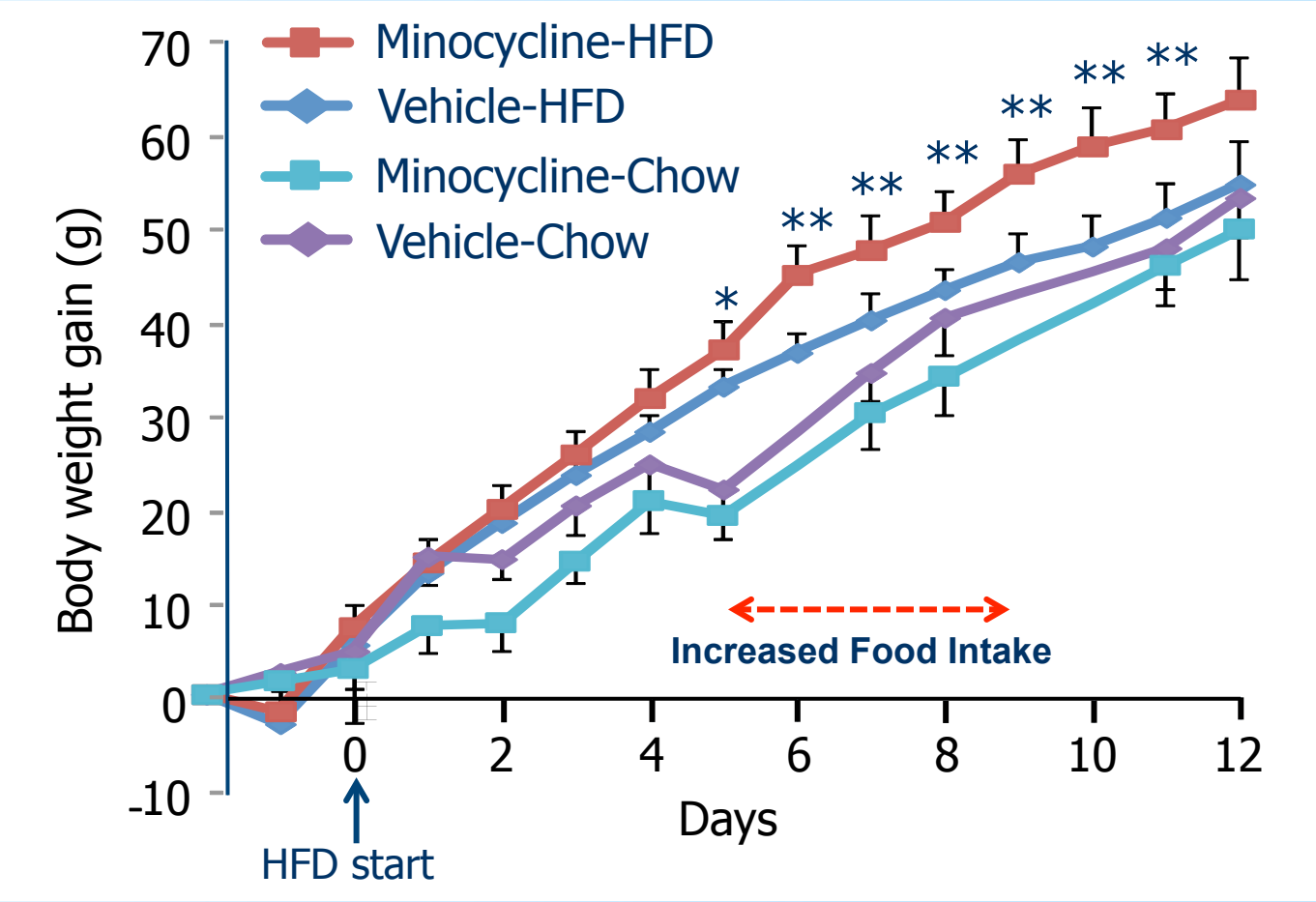
Iba1/GFAP

Gliosis During HFD Consumption



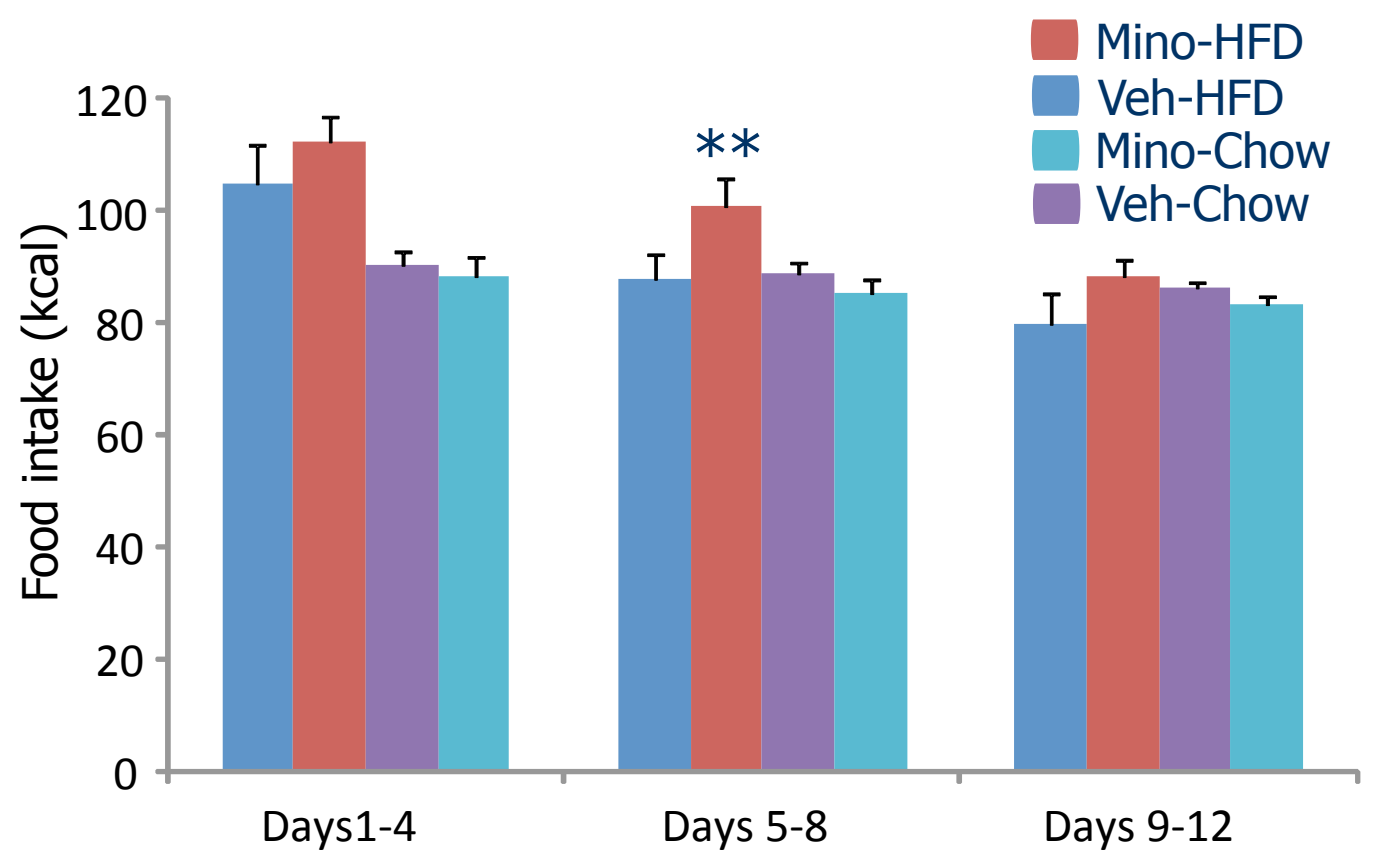


Microglial Inactivation Accelerates HFD-Induced Weight Gain



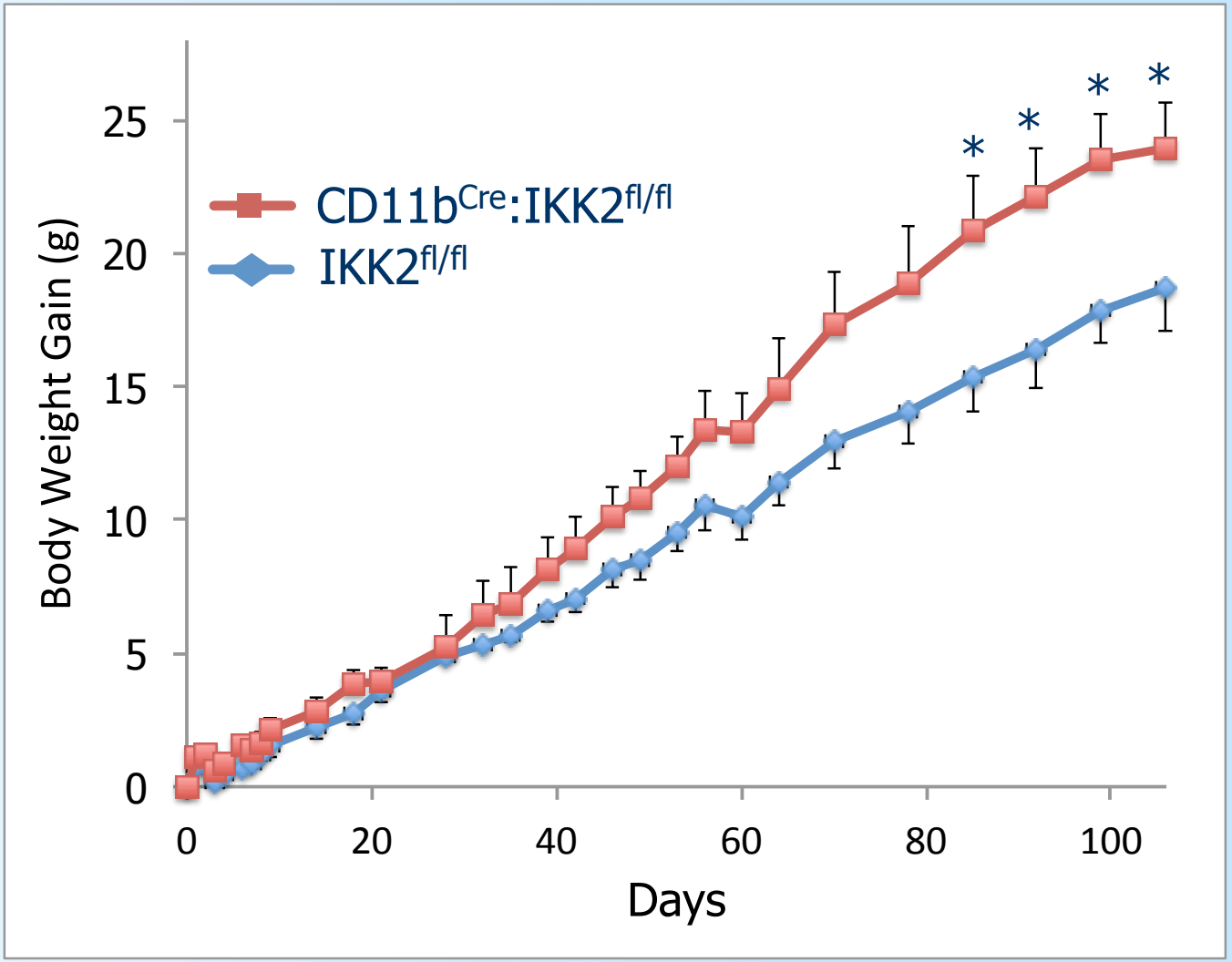
Thaler et al, unpublished data.

Microglial Inactivation Increases HFD-Induced Food Intake

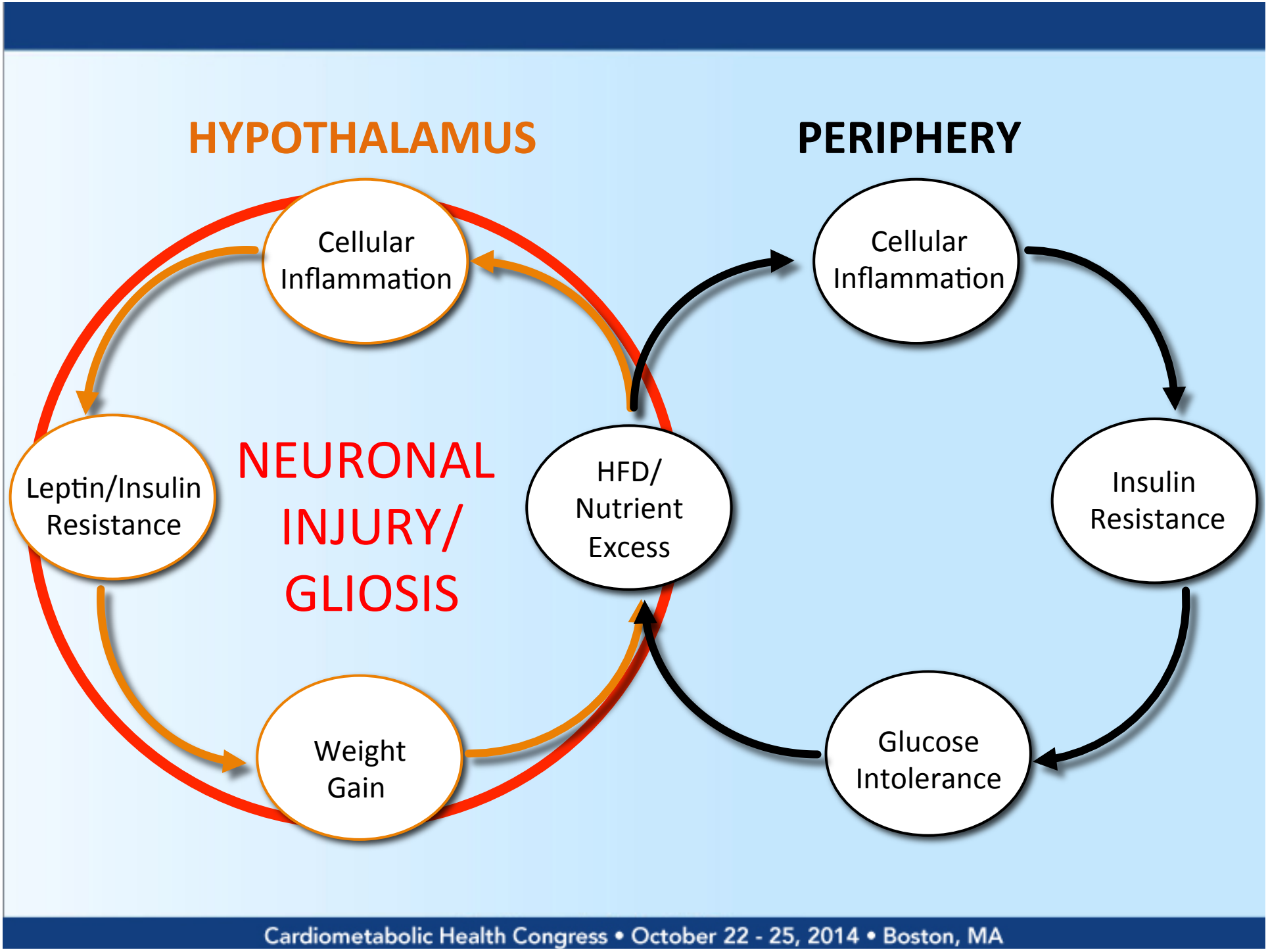


Thaler et al, unpublished data.

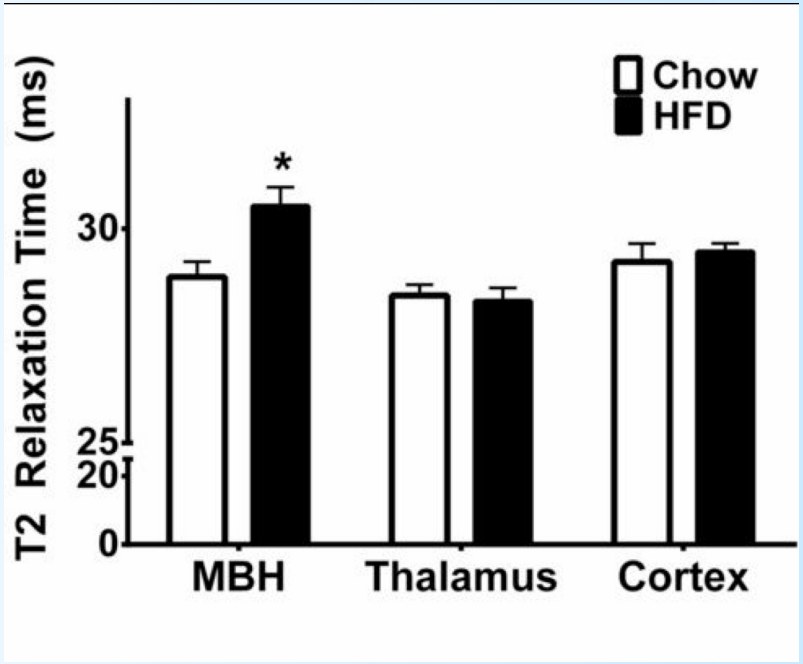
Microglial Inflammatory Signaling Offsets Diet-Induced Obesity

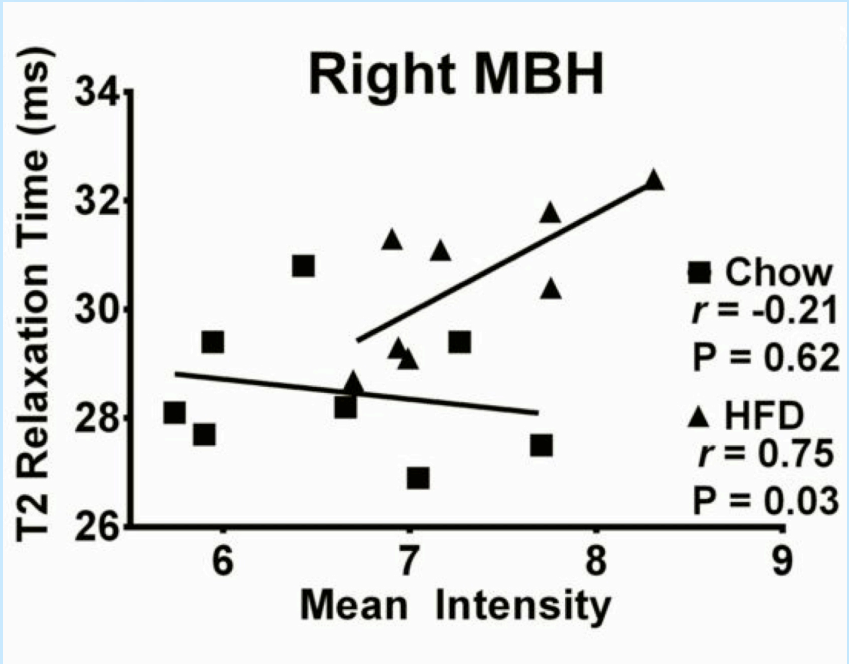


Thaler et al, unpublished data.


HYPOTHALAMUS
PERIPHERY
Cellular Inflammation
Leptin/Insulin Resistance
NEURONAL INJURY/ GLIOSIS
HFD/ Nutrient Excess
Weight Gain
Cellular Inflammation
Insulin Resistance
Glucose Intolerance

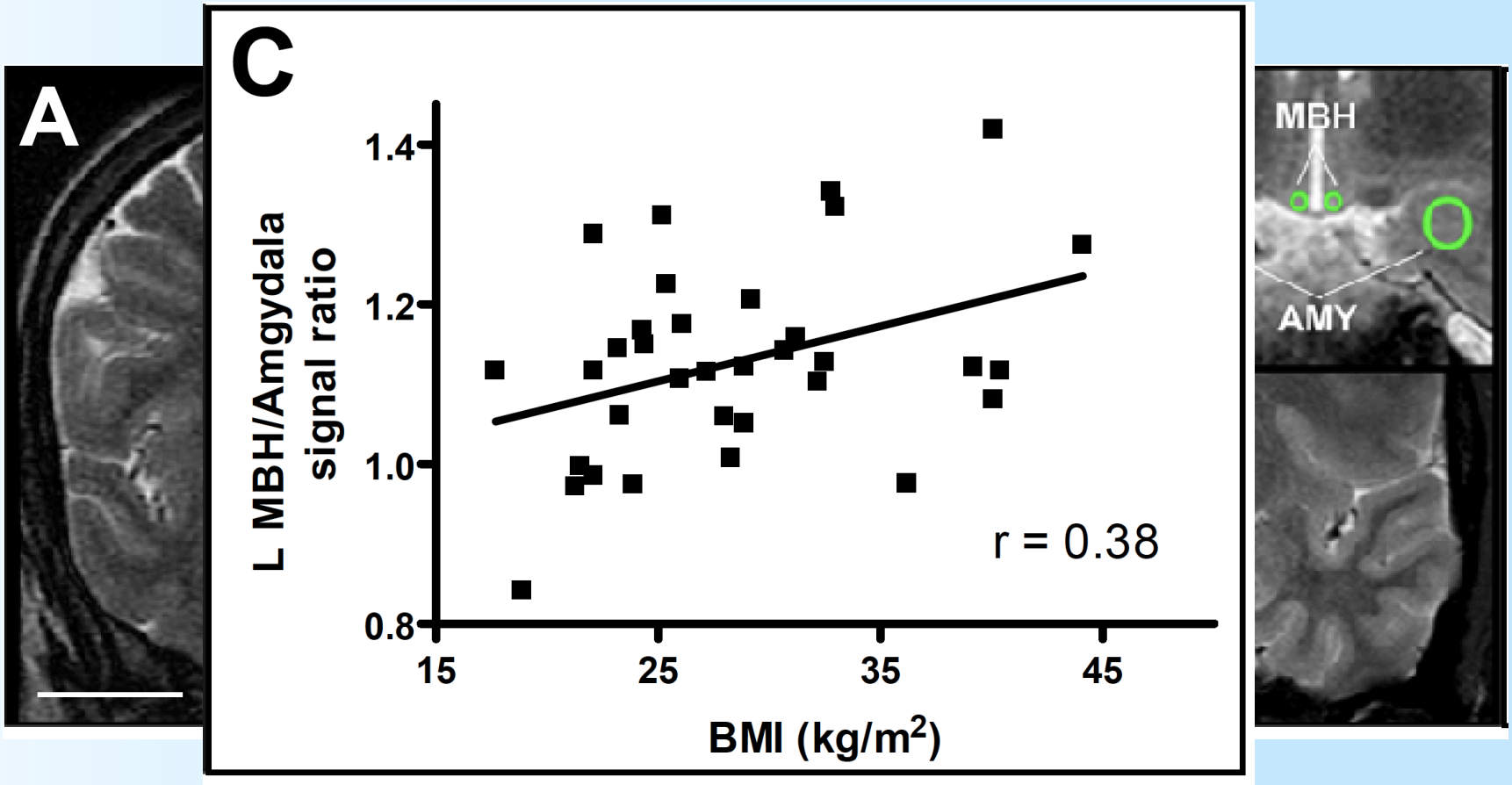
Monitoring Gliosis by MRI





Lee et al. AJP Endo & Metab. 2013;304:1245-50.

Gliosis in Human Obesity



Thaler et al. JCI 2012;122:153-62.

Summary

- High-fat diet consumption is associated with rapid onset of hypothalamic inflammation and leptin resistance.
- Signs of neuronal stress and reactive gliosis occur early with high-fat feeding.
- Prolonged high-fat feeding causes structural changes to the hypothalamus that may affect energy homeostasis.
- Microglia and astrocytes may be important contributors to body weight regulation.
- Cell-centric vs gene-centric obesity therapeutics?

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Advances in Therapeutic Interventions for Achieving and Maintaining Weight Loss

Louis J. Aronne, MD, FACP
Sanford I. Weill Professor of Metabolic Research
Weill Medical College of Cornell University
Medical Director, Center for Weight Management and Metabolic Clinical Research
New York Presbyterian Hospital
New York, New York

Presentation Highlights

- Rationale for use of medical therapies to treat obesity
- Overview of efficacy and safety data on current weight-loss therapies as well as those in late-stage development

Anti-obesity Medications

Rationale and Criteria

- Non-drug interventions should be attempted for at least 6 months before considering pharmacotherapy[1]
- For patients with BMI $\geq$ 30
- For patients with BMI $\geq$ 27 or above with concomitant risk factors or diseases (hypertension, dyslipidemia, CHD, type 2 diabetes, sleep apnea)[1]

1. NIH Clinical Guidelines Evidence Report, Sept 1998.

Hypertension Treatment

Let's think about for a minute:

>120 drugs in 10 categories

Up to triple drug combinations available

- Diuretics
- Beta-blockers
- ACE inhibitors
- Angiotensin II receptor blockers
- Calcium channel blockers
- Alpha blockers
- Alpha-2 receptor agonists
- Combined alpha and beta-blockers
- Central agonists
- Peripheral adrenergic inhibitors

Source: L. Aronne

Rationale for Next-Generation Drugs:

Reduce Comorbidities Associated with Obesity

FDA approval criteria of anti-obesity drugs:

- 35% of treated persons must lose at least 5% of their body weight
- That group should include at least twice as many individuals as the number of patients who achieve a similar weight loss on placebo
- Alternatively, the therapy must result in at least 5% placebo-corrected weight loss
- On a population level, such figures will contribute to a lower incidence of comorbidities

Use medication to treat the obesity instead of using medication to treat each of the complications of obesity

Why do we need medication?

Why don't people just lose weight?

Related Commentary, page 22 Research article

Obesity is associated with hypothalamic injury in rodents and humans

Joshua P. Thaler,[1,2] Chun-Xia Yi,[3] Ellen A. Schur,[2] Stephan J. Guyenet,[1,2] Bang H. Hwang,[1,2,4] Marcelo O. Dietrich,[5] Xiaolin Zhao,[1,2,6] David A. Sarruf,[1,2] Vitaly Izgur,[7] Kenneth R. Maravilla,[7] Hong T. Nguyen,[1,2] Jonathan D. Fischer,[1,2] Miles E. Matsen,[1,2] Brent E. Wisse,[1,2] Gregory J. Morton,[1,2] Tamas L. Horvath,[5,8] Denis G. Baskin,[1,2,4] Matthias H. Tschöp,[3] and Michael W. Schwartz[1,2]

[1]Division of Metabolism, Endocrinology and Nutrition, Diabetes and Obesity Center of Excellence, and [2]Department of Medicine, University of Washington, Seattle, Washington, USA. [3]Metabolic Diseases Institute, Division of Endocrinology, Department of Medicine, University of Cincinnati, Cincinnati, Ohio, USA. [4]Research and Development Service, Department of Veterans Affairs Puget Sound Health Care System, Seattle, Washington, USA. [5]Program in Integrative Cell Signaling and Neurobiology of Metabolism, Section of Comparative Medicine, Yale University School of Medicine, New Haven, Connecticut, USA. [6]Department of Physiology and Pathophysiology, School of Medicine at Xi'an Jiaotong University, Xi'an, China. [7]Department of Radiology, University of Washington, Seattle, Washington, USA. [8]Department of Obstetrics/Gynecology and Reproductive Sciences, Yale University School of Medicine, New Haven, Connecticut, USA.

Rodent models of obesity induced by consuming high-fat diet (HFD) are characterized by inflammation both in peripheral tissues and in hypothalamic areas critical for energy homeostasis. Here we report that unlike inflammation in peripheral tissues, which develops as a consequence of obesity, hypothalamic inflammatory signaling was evident in both rats and mice within 1 to 3 days of HFD onset, prior to substantial weight gain. Furthermore, both reactive gliosis and markers suggestive of neuron injury were evident in the hypothalamic arcuate nucleus of rats and mice within the first week of HFD feeding. Although these responses temporarily subsided, suggesting that neuroprotective mechanisms may initially limit the damage, with continued HFD feeding, inflammation and gliosis returned permanently to the mediobasal hypothalamus. Consistent with these data in rodents, we found evidence of increased gliosis in the mediobasal hypothalamus of obese humans, as assessed by MRI. These findings collectively suggest that, in both humans and rodent models, obesity is associated with neuronal injury in a brain area crucial for body weight control.

Thaler et al. J Clin Invest. 2012;122:153-62.

Rationale for Next-Generation Drugs:

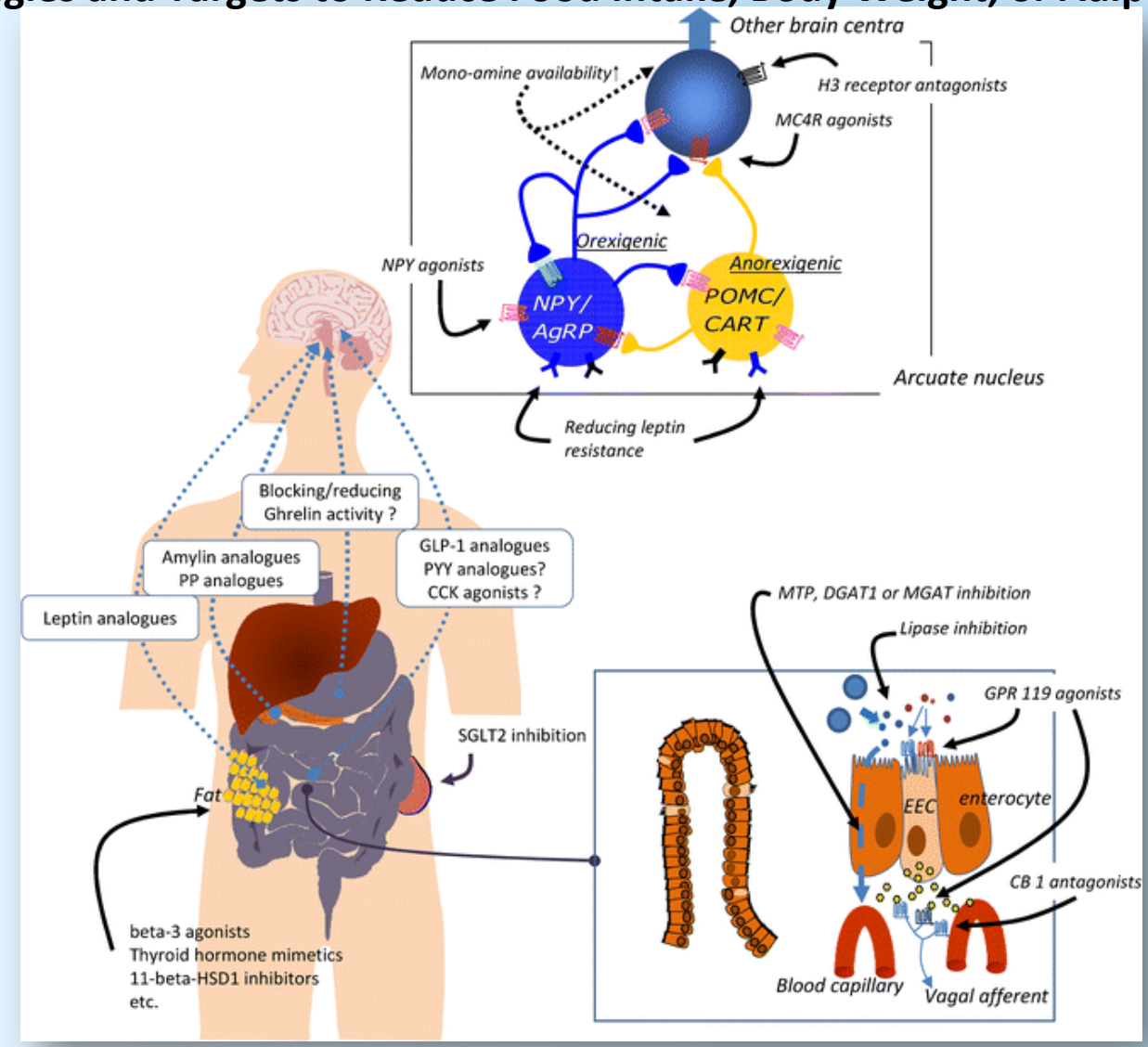
Injury to Weight-Regulating Neurons Makes Weight Gain Hard to Reverse

- Fattening food leads to early demise of POMC neurons
- There are fewer hypothalamic POMC neurons because of premature death and inability of stem cell mechanism to keep up
- There is inflammation in the hypothalamus that may be related to leptin resistance – stem cell mechanism is leptin dependent
- The signals from periphery to CNS may be dampened because of degradation in signaling
- Fat mass increases and fullness is diminished
- Giving leptin – doesn't work
- Mimicking the effect of leptin and other inputs by stimulating or blocking hypothalamic pathways should help reduce weight

POMC=proopiomelanocortin

Next-Generation Weight Loss Medications:

Potential Strategies and Targets to Reduce Food Intake, Body Weight, or Adipose Tissue Mass



Witkamp. Pharm Res. 2011 Aug;28:1792-818.

New Compounds and Combination Interventions

Naltrexone

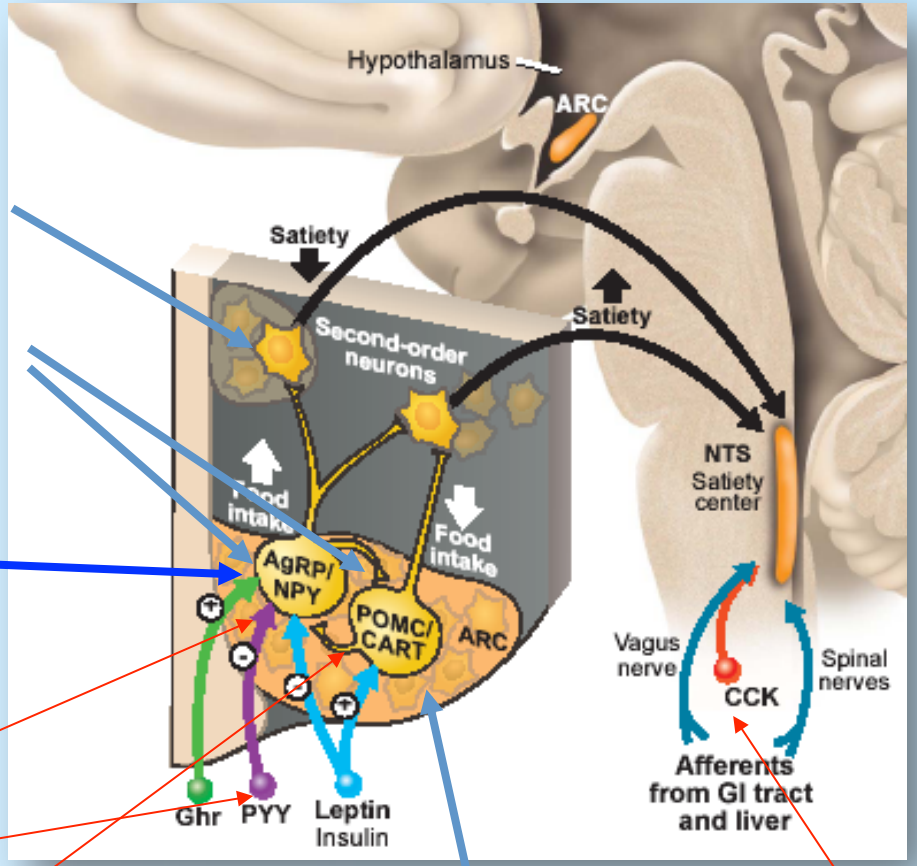
Bupropion
Phentermine
GLP=1

↑ Food intake
- energy expenditure

Topiramate

Lorcaserin

Leptin



- Food intake
-energy expenditure

Pramlintide
GLP-1

Marx. *Science*. 2003;299:846-9. Illustrations by Katharine Sutliff/ISSN 0036-8075 (print), 1095-9203 (online).

Leptin Appears to Act via GABA

Neuron. 2011 Jul 14;71(1):142-54. doi: 10.1016/j.neuron.2011.05.028.

Leptin action on GABAergic neurons prevents obesity and reduces inhibitory tone to POMC neurons.

Vong L, Ye C, Yang Z, Choi B, Chua S Jr, Lowell BB.

Division of Endocrinology, Department of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, 330 Brookline Avenue, EC/CLS717, Boston, MA 02215, USA.

Abstract

……. Remarkably, the vast majority of leptin's antiobesity effects are mediated by GABAergic neurons; glutamatergic neurons play only a minor role. Leptin, working directly on presynaptic GABAergic neurons, many of which appear not to express AgRP, reduces inhibitory tone to postsynaptic POMC neurons. As POMC neurons prevent obesity, their disinhibition by leptin action on presynaptic GABAergic neurons probably mediates, at least in part, leptin's antiobesity effects.

Serotonin Stimulation Acts via the Melanocortin Pathways

Ann N Y Acad Sci. 2003 Jun;994:169-74.

Central serotonin and melanocortin pathways regulating energy homeostasis.

Heisler LK, Cowley MA, Kishi T, Tecott LH, Fan W, Low MJ, Smart JL, Rubinstein M, Tatro J, Zigman JM, Cone RD, Elmquist JK.

Dept of Medicine and Neurology, Beth Israel Deaconess Medical Center and Program in Neuroscience, Harvard Medical School, Boston, MA 02215, USA.

Abstract

…….5-HT drugs require functional melanocortin pathways to exert their effects on food intake. Specifically, we observed that anorectic 5-HT drugs activate pro-opiomelanocortin (POMC) neurons in the arcuate nucleus of the hypothalamus (Arc). We provide evidence that the serotonin 2C receptor (5-HT(2C)R) is expressed on POMC neurons and contributes to this effect. Finally, we found that 5-HT drug-induced hypophagia is attenuated by pharmacological or genetic blockade of downstream melanocortin 3 and 4 receptors. We review candidate brain regions expressing melanocortin 3 and 4 receptors that play a role in energy balance. A model is presented in which activation of the melanocortin system is downstream of 5-HT and is necessary to produce the complete anorectic effect of 5-HT drugs. The data reviewed in this paper incorporate the central 5-HT system to the growing list of metabolic signals that converge on melanocortin neurons in the hypothalamus.

GLP-1 Works in Both Hindbrain and Hypothalamus to Reduce Food Intake

Endocrinology. 2014 Aug 13:en20141248. [Epub ahead of print]

GLP-1 receptor stimulation of the lateral parabrachial nucleus(PBN) reduces food intake: neuroanatomical, electrophysiological and behavioral evidence.

Richard JE, Farkas I, Anesten F, Anderberg RH, Dickson SL, Gribble FM, Reimann F, Jansson JO, Liposits Z, Skibicka KP.

Department of Physiology, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at the University of Gothenburg, Sweden.

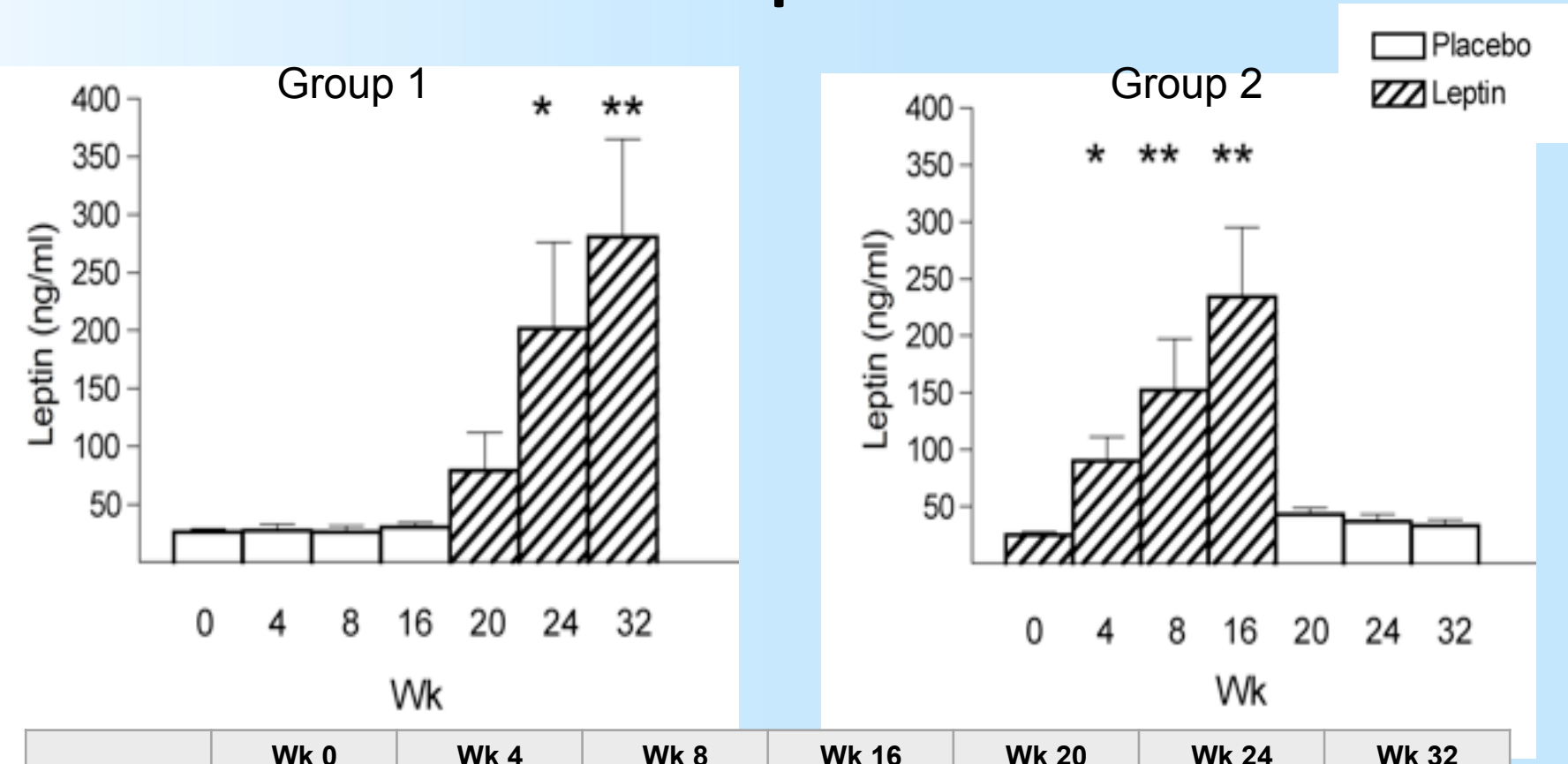
Abstract

…. Stimulation of lPBN GLP-1 receptors (GLP-1R) reduced the intake of chow and palatable food and decreased body weight in rats. …

We show that within the PBN, GLP-1R activation increased gene expression of two energy balance regulating peptides, calcitonin gene related peptide (CGRP) and interleukin-6. Moreover, nearly seventy percent of the lPBN GLP-1 fibers innervated lPBN CGRP neurons. Direct intra-lPBN CGRP application resulted in anorexia.

Collectively, our molecular, anatomical, electrophysiological, pharmacological and behavioral data provide evidence for a functional role of the GLP-1R for feeding control in the PBN.

RNYGB Improves Insulin Sensitivity. What Happens When You Give Leptin Post RNYGB?



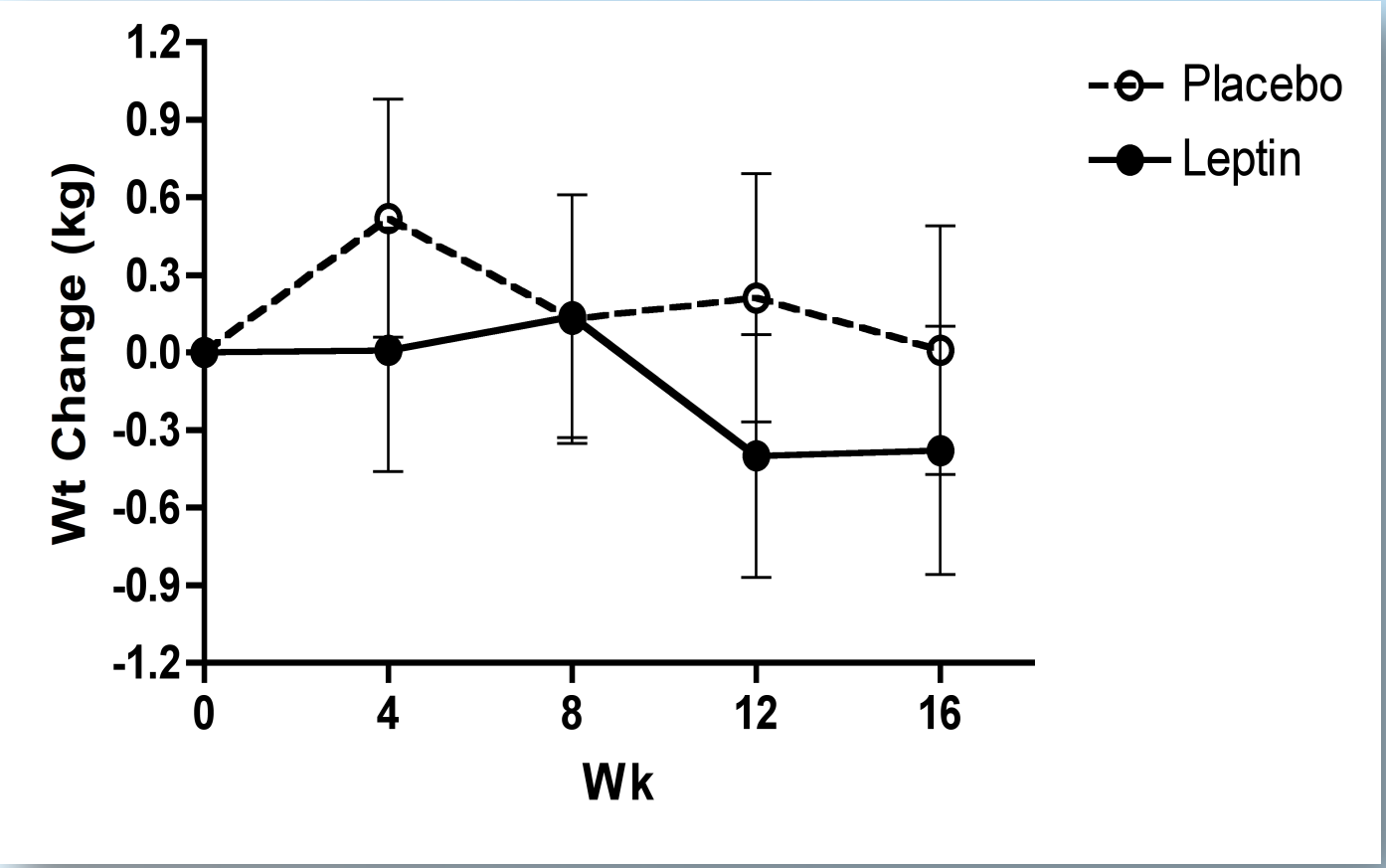
	Wk 0	Wk 4	Wk 8	Wk 16	Wk 20	Wk 24	Wk 32
Placebo-Leptin	26 ± 2.8	27 ± 5.7	26 ± 5.1	30 ± 4.5	79 ± 3.3	202 ± 74*	281 ± 84**
Leptin-Placebo	25 ± 2.5	90 ± 21*	152 ± 45**	234 ± 61**	43 ± 5.6	37 ± 6.1	33 ± 5.5

RNYBG=Roux-n-Y

Korner et al. *Obesity*. 2013;21:951-6.

Leptin in Patients Post RNYGB Weight Change Not Different During Leptin and Placebo Period

No difference was noted when adjusted for baseline leptin, % wt loss after surgery, or duration of post-op period



Korner et al. Obesity. 2013;21:951-6.

Medications We Use to Achieve Weight Loss or Prevent Weight Regain

Medications Approved for Weight Loss	Medications for Type 2 Diabetes that Promote Weight Loss or are Weight Neutral	Medications for Other Illnesses that Cause Weight Loss
• **Phentermine** (short term) • **Phentermine + topiramate** • **Lorcaserin** • **Orlistat**	• **Metformin** • **GLP-1s: Liraglutide, exenatide** • **SGLT-2 inhibitors: Canagliflozin, dapagliflozin, empagliflozin** • **DPP-4 inhibitors: Sitagliptin, saxagliptin, linagliptin** • **Pramlintide--if patient requires insulin** • **Alpha-glucosidase inhibitors: acarbose**	• **Bupropion** • **Topiramate, zonisamide**

Obesity Treatments Recently Approved and in Late Development

Agents	Action
Phentermine/ Topiramate	• Sympathomimetic • Anticonvulsant (GABA receptor modulation/glutamate antagonism, carbonic anhydrase inhibition)
Lorcaserin	• 5-HT_{2C} serotonin agonist: potent and selective • Little affinity for other serotonergic receptors
Bupropion/ Naltrexone	• Dopamine/noradrenaline reuptake inhibitor • Opioid receptor antagonist
Liraglutide*	• GLP-1 agonist

- Not FDA Approved For Weight loss. Recommended for FDA Approval September 2014.
- Kushner. Expert Opin Pharmacother. 2008;9:1339-50.

2012

Lorcaserin

Lorcaserin

- Approved in 2012 (10 mg twice daily) for long-term weight management
- Selective 5-HT2C receptor agonist—increases satiety
- Most common AEs: headache, nausea, dizziness, fatigue, dry mouth, constipation
- No increase in rate of valvulopathy in pivotal trials

Bays. Expert Rev Cardiovasc Ther. 2009;7:1429-45.
Belviq [prescribing information]. Woodcliff Lake, NJ: Eisai, Inc.; 2012.

Lorcaserin: Notes

- Start with 10 mg before dinner
- Discontinue if 5% weight loss is not achieved by week 12
- Extreme care when using with drugs that affect the serotonin system
- DEA Schedule IV
- Pregnancy category X

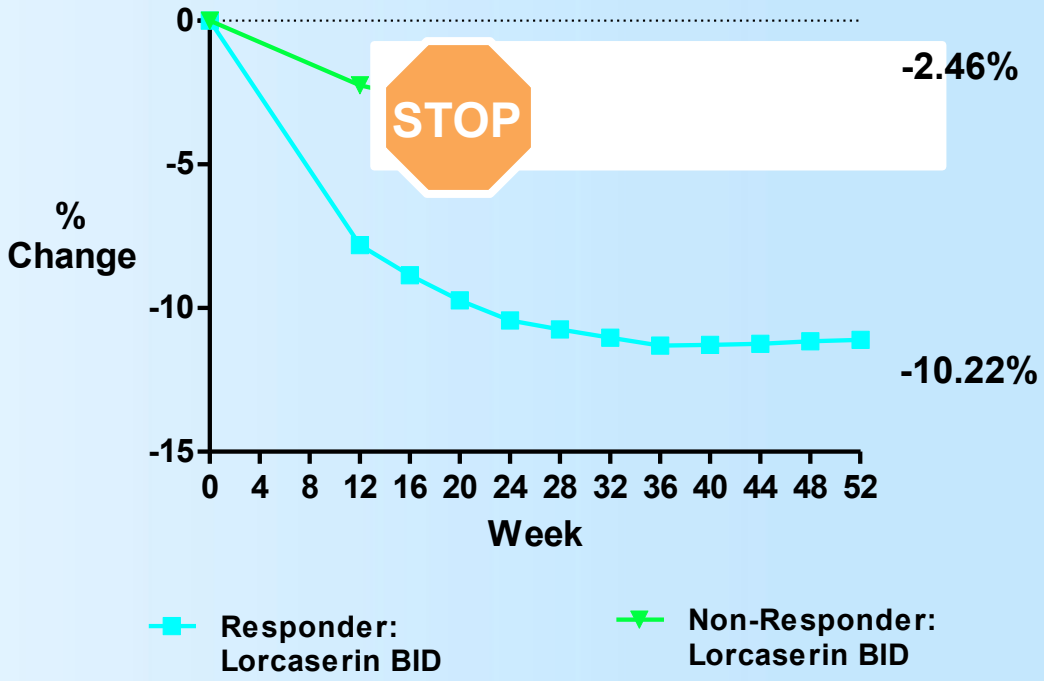
DEA = Drug Enforcement Administration.

Bays. Expert Rev Cardiovasc Ther. 2009;7:1429-45.
Belviq [prescribing information]. Woodcliff Lake, NJ: Eisai, Inc.; 2012.

Lorcaserin: Weight Loss

Those who lost ≥ 4.5% total body weight by week 12 went on to lose 10%

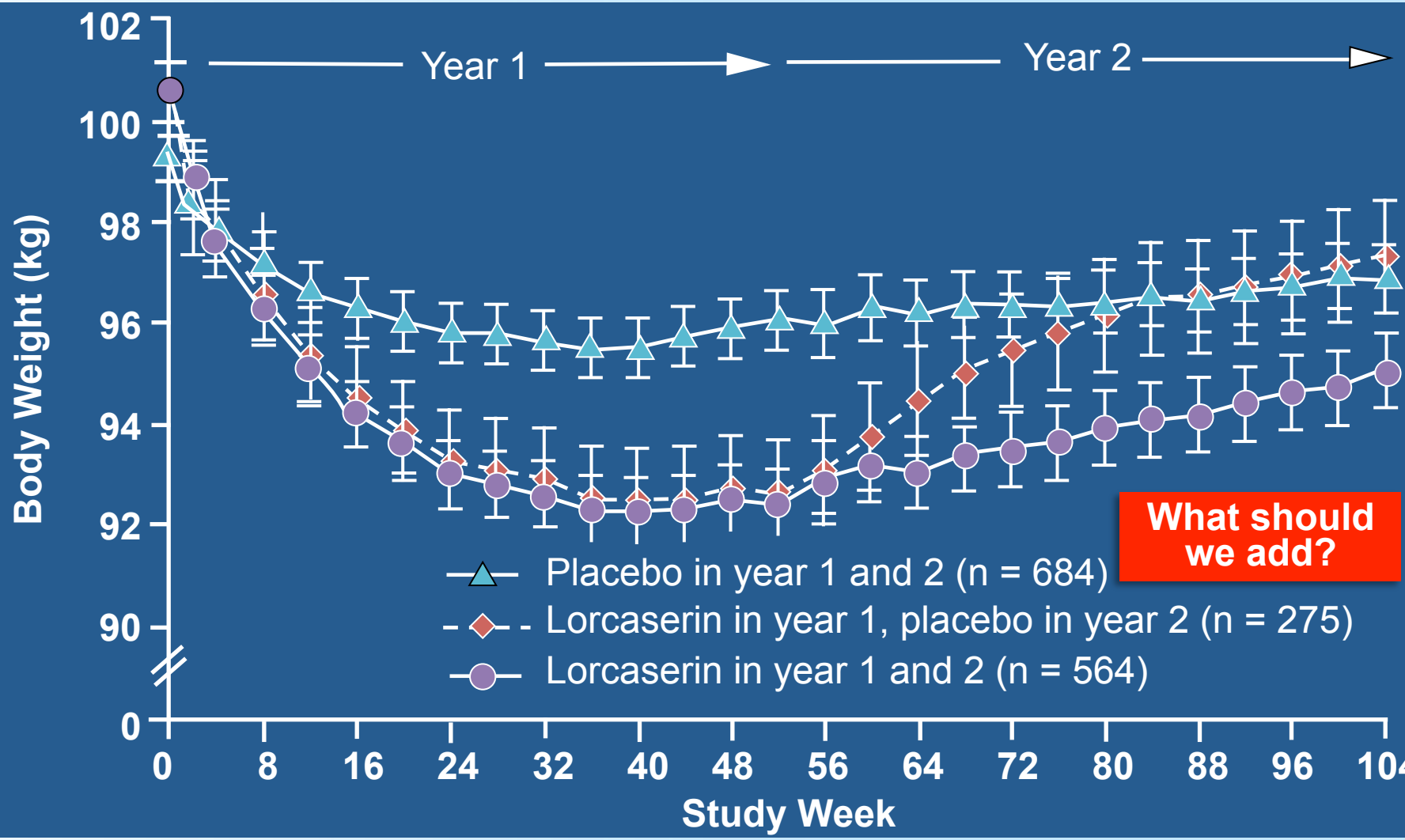
Studies 009 and 011, MITT



MITT Lorcaserin BID	Week 12	Completed Week 12	Completed Week 52
N = 3097	≥4.5% wt loss	1369/3097 (44.2%)	1083/1369 (79.1%)
	<4.5% wt loss	1168/3097 (37.7%)	680/1168 (58.2%)

Slide courtesy Dr. Steve Smith

Lorcaserin: BLOOM Study
Body Weight Over Years and 2



Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM) trial: 2-year, randomized, placebo-controlled, double-blind clinical trial
Smith et al. N Engl J Med 2010; 363:245-56.

Lorcaserin – BLOOM Study: Key Secondary Endpoints

Endpoint		Lorcaserin	Placebo	*P* value
Waist circumference (cm)	↓	−6.8	−3.9	<0.001
SBP/DBP (mm Hg)	↓	−1.4 / −1.1	−0.8 / −0.6	0.04/0.01
Cholesterol (% Δ)				
Total	↓	−0.90	0.57	0.001
LDL	↓	2.87	4.03	0.049
HDL		0.05	−0.21	0.72
Triglycerides (%)	↓	−6.15	−0.14	<0.001
Safety				
HR (beats/min)	↓	−2.0	−1.6	0.049
Beck depression II		−1.1	−0.9	0.26

Intention-to-Treat Analysis with LOCF Imputation

Smith et al. N Engl J Med 2010; 363:245-56.

2012

Phentermine/Topiramate

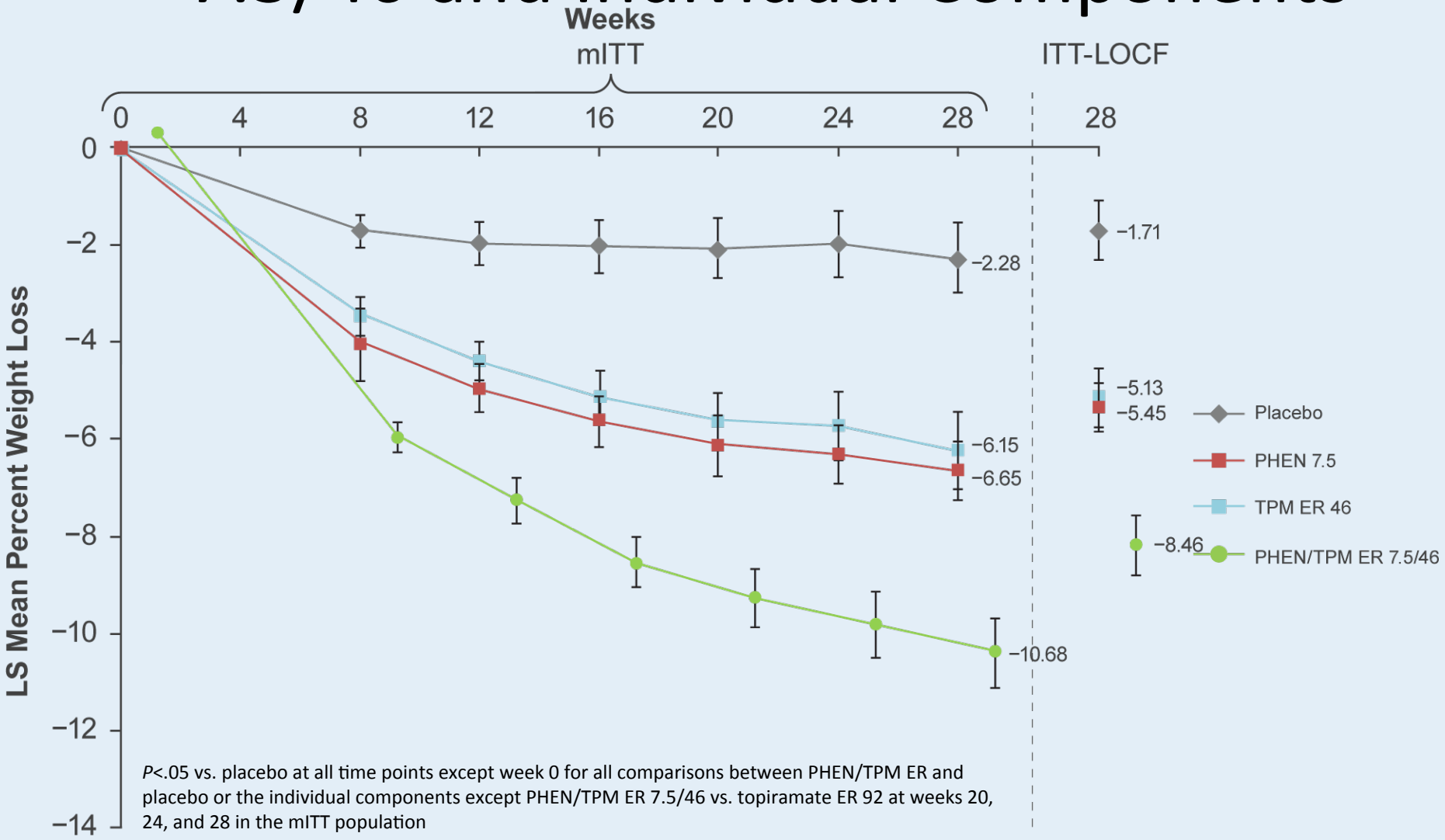
Phentermine/Topiramate

- Phentermine HCl/topiramate ER approved for weight management in 2012
  - Titrated in am from 3.75/23 up to 7.5/46 mg/d; max 15/92 mg/d
- Phentermine: decreases short-term appetite
- Topiramate: decreases longer-term appetite, and may have glycemic effects
- Most common AEs: paresthesia, dizziness, cognitive dysfunction, dysgeusia (change in taste), insomnia, constipation, dry mouth, metabolic acidosis, elevated creatinine
- Significant improvements in multiple CV and DM risk factors

IR = immediate release

Bays, Gadde. *Drugs Today.* 2011;47:903-14; Bays. *Expert Rev Cardiovasc Ther*. 2010;8:1777-1801. Qsymia [prescribing Information]. Mountain View, CA: Vivus, Inc.; 2012; Qsymia. http://www.qsymiarems.com. Accessed October 29, 2013.

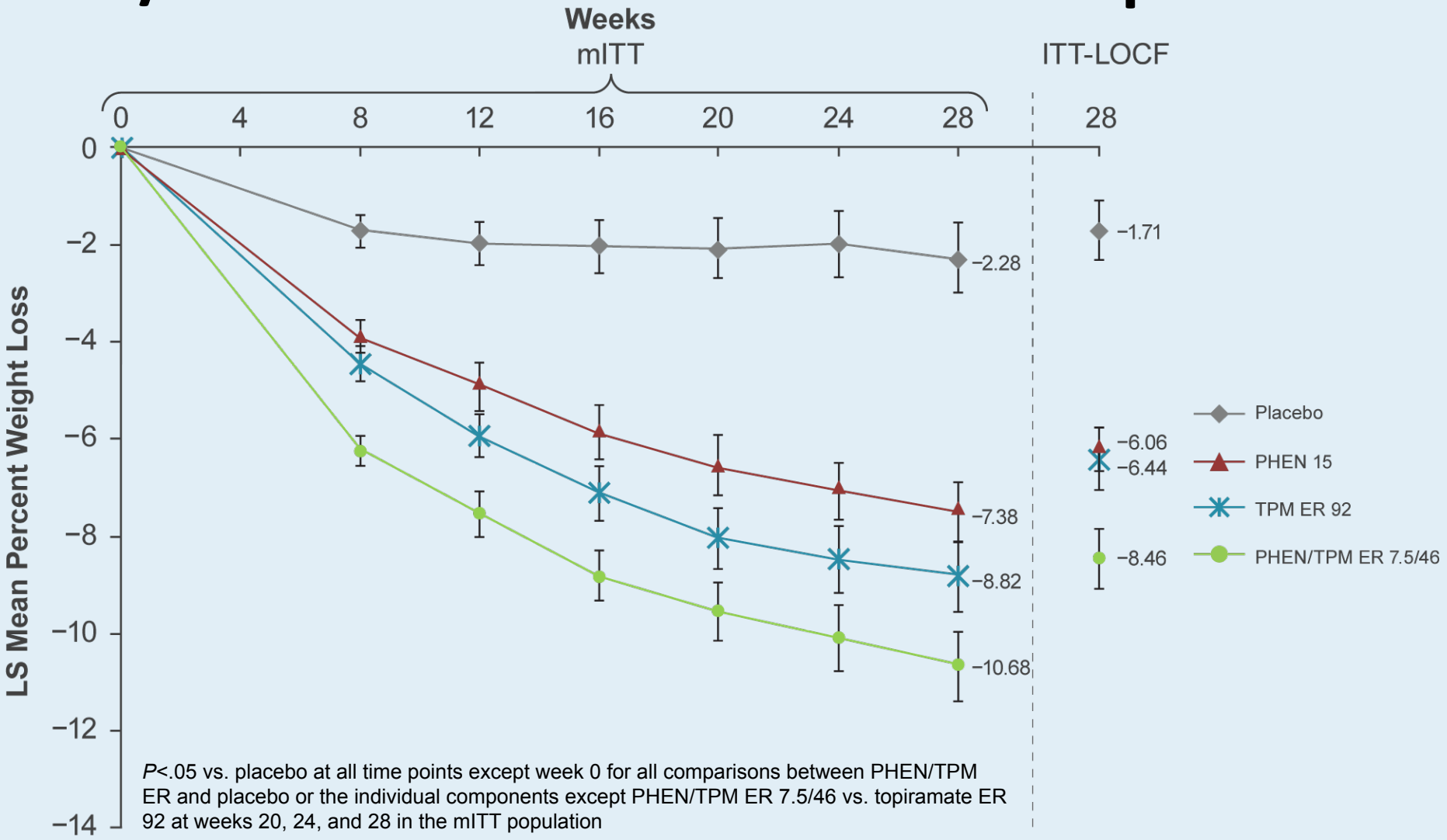
Percent Weight Loss with PHEN/TPM ER 7.5/46 and Individual Components



P<.05 vs. placebo at all time points except week 0 for all comparisons between PHEN/TPM ER and placebo or the individual components except PHEN/TPM ER 7.5/46 vs. topiramate ER 92 at weeks 20, 24, and 28 in the mITT population

Aronne et al. Obesity. 2013;21:2163-71.

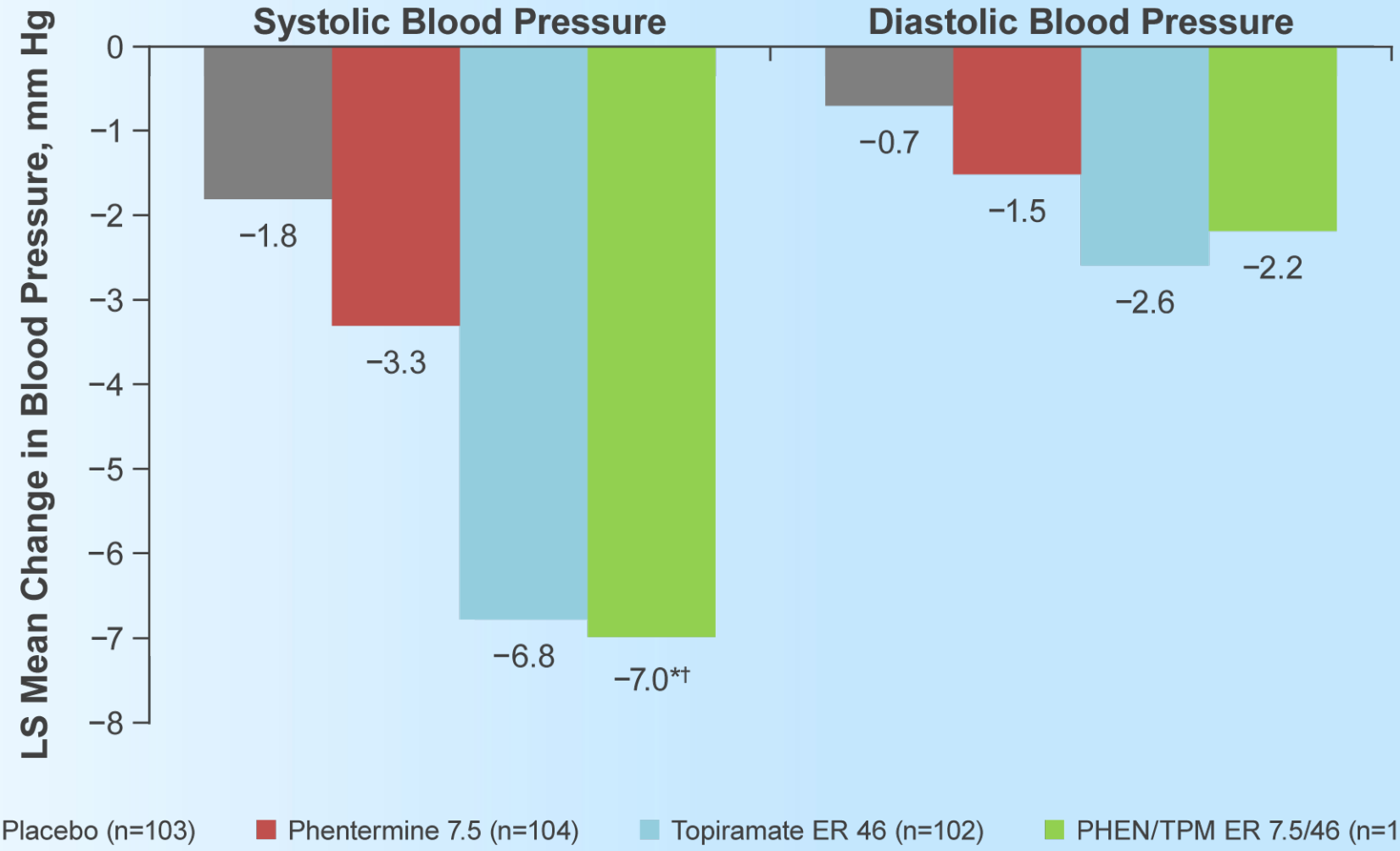
Percent Weight Loss with PHEN/TPM ER 7.5/46 and Phentermine 15 and Topiramate



P<.05 vs. placebo at all time points except week 0 for all comparisons between PHEN/TPM ER and placebo or the individual components except PHEN/TPM ER 7.5/46 vs. topiramate ER 92 at weeks 20, 24, and 28 in the mITT population

Aronne et al. Obesity. 2013;21:2163-71.

Change in Blood Pressure with PHEN/TPM ER 7.5/46 and Individual Components (ITT-LOCF)

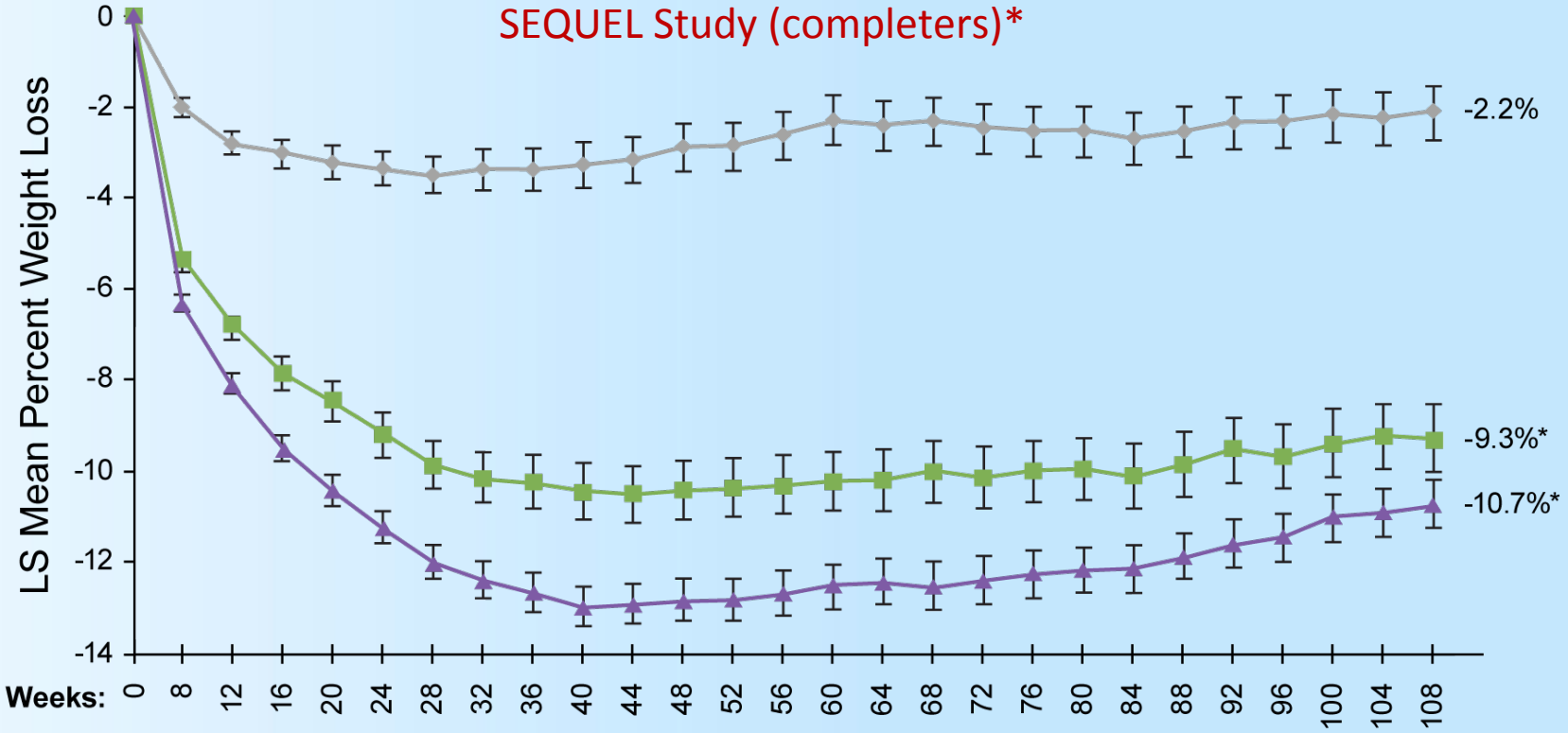


*P = 0.0004 vs. placebo; †P = 0.0108 vs. phentermine 7.5

Aronne et al. Obesity. 2013;21:2163-71.

Effect of Phentermine/Topiramate ER on Weight Loss in Obese Adults Over 2 Years

SEQUEL Study (completers)*



*Data from patients who completed 56 weeks on treatment (observed data, no imputation); †P<.0001 vs placebo

Garvey et al. Am J Clin Nutr. 2012;95:297-308.

Emerging Pharmacotherapies

Agents	Action	Approval/Phase
Liraglutide*	• GLP-1 receptor agonist	• Pending; recommended for approval • (3.0 mg dose for obesity)
Bupropion/ Naltrexone	• Dopamine/noradrenaline reuptake inhibitor • Opioid receptor antagonist	• FDA approved, September 2014

*Not FDA Approved for Weight loss. Recommended for Approval September 2014.

Clinicaltrials.gov. Cardiovascular Outcomes Study of Naltrexone SR/Bupropion SR in Overweight and Obese Subjects With Cardiovascular Risk Factors (The Light Study). 2012.; Clinicaltrials.gov.

Effect of Liraglutide on Body Weight in Non-diabetic Obese Subjects or Overweight Subjects With Co-morbidities: SCALE - Obesity and Pre-diabetes. 2011.

September 2014

Naltrexone SR/Bupropion

Naltrexone/Bupropion

- Mechanism of Action
  - Naltrexone – Opioid receptor antagonist
  - Bupropion – Dopamine/noradrenaline reuptake inhibitor

- Approved by FDA committee but FDA did not approve until a CVD outcome study was performed due to concerns about blood pressure and pulse in some patients

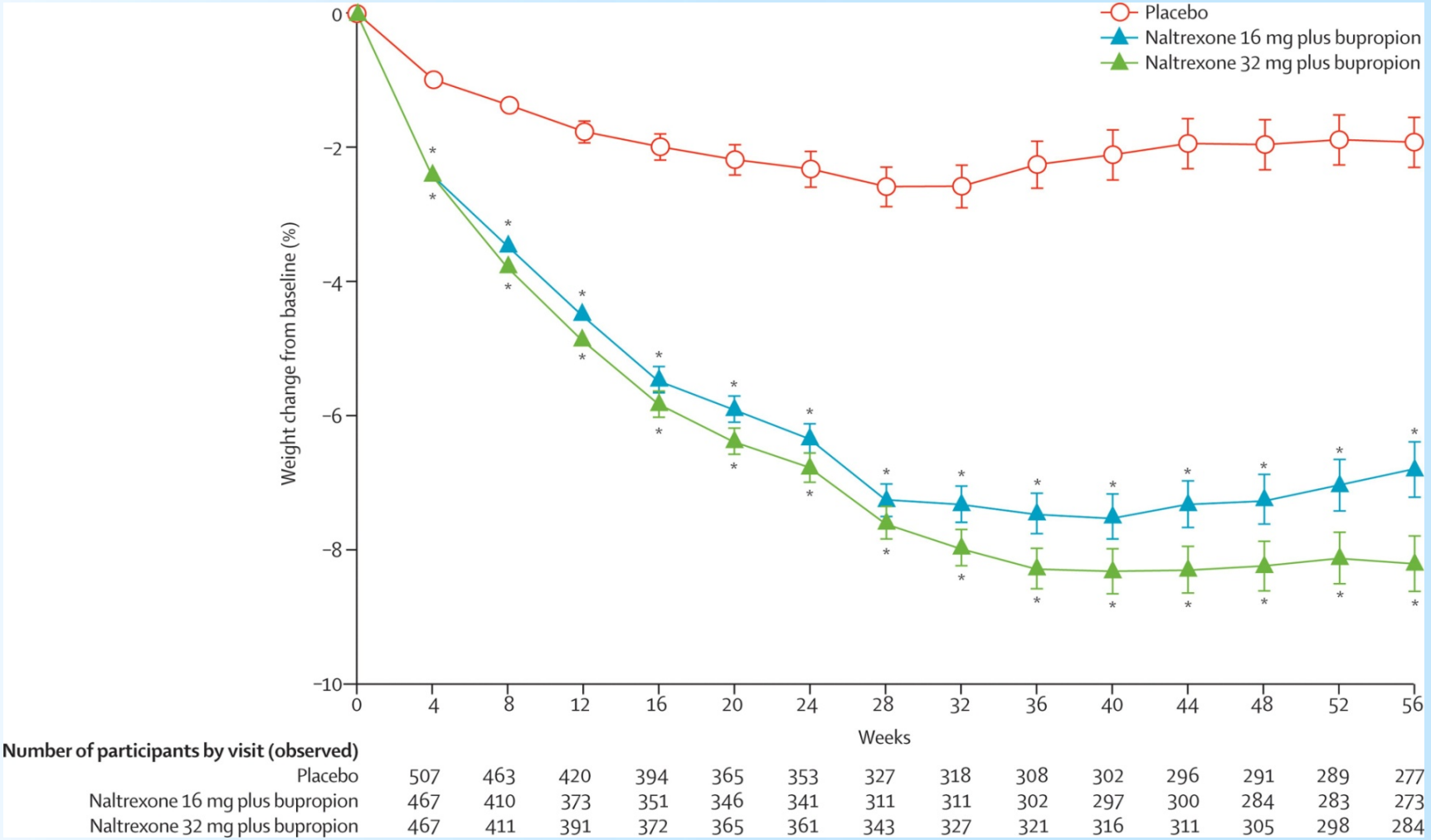
- The Light Study (CVD outcomes) is under way; estimated completion: July 2017

Clinicaltrials.gov. Cardiovascular Outcomes Study of Naltrexone SR/Bupropion SR in Overweight and Obese Subjects With Cardiovascular Risk Factors (The Light Study). 2012. http://clinicaltrials.gov/show/NCT01601704
Apovian et al. Obesity. 2013;21:935-43.

Naltrexone/Bupropion: Mean Weight Loss

COR-I Phase 3

56 Weeks – Completer Population

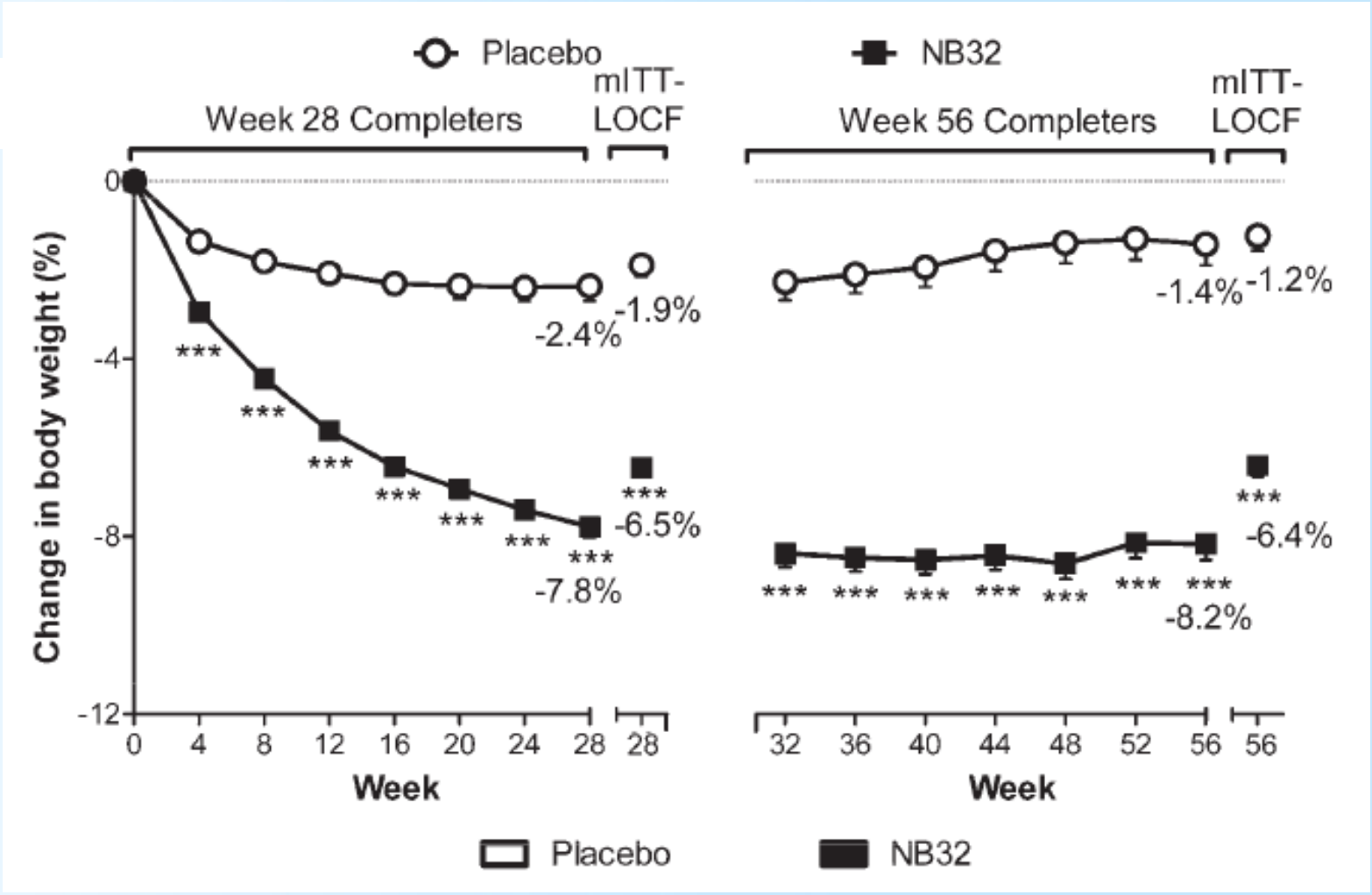


Number of participants by visit (observed)														
Placebo	507	463	420	394	365	353	327	318	308	302	296	291	289	277
Naltrexone 16 mg plus bupropion	467	410	373	351	346	341	311	311	302	297	300	284	283	273
Naltrexone 32 mg plus bupropion	467	411	391	372	365	361	343	327	321	316	311	305	298	284

Greenway et al. Lancet. 2010;376:595-605.

Naltrexone SR / Bupropion SR

Phase 3 Trial (COR-II)



A randomized, phase 3 trial of naltrexone SR/bupropion SR on weight and obesity-related risk factors (COR-II)

Apovian et al. Obesity. 2013;21:935-43.

Naltrexone SR / Bupropion SR

Improvement in Risk Factors

Measure	Week 56		
	Placebo *N* = 456	NB32 *N* = 702	*P*-value
Waist circumference, cm			
Baseline	108.6 ± 11.8	109.0 ± 11.8	
Change	−2.1 ± 0.5	−6.7 ± 0.3	<0.001
Triglycerides, mg/dL			
Baseline	112.8 ± 1.6	118.9 ± 1.6	
Percent change (95% CI)	−0.5% (−4.5%, +3.7%)	−9.8% (−12.4%, −7.1%)	<0.001
HDL-cholesterol, mg/dL			
Baseline	51.6 ± 12.9	51.8 ± 13.6	
Change	−0.9 ± 0.5	+3.6 ± 0.4	<0.001
LDL-cholesterol, mg/dL			
Baseline	116.8 ± 32.9	120.5 ± 30.2	
Change	−2.1 ± 1.3	−6.2 ± 0.9	0.008
Fasting blood glucose, mg/dL			
Baseline	94.2 ± 10.4	95.0 ± 11.3	
Change	−1.3 ± 0.6	−2.8 ± 0.5	0.051
Fasting insulin, µIU/mL			
Baseline	10.7 ± 1.9	11.4 ± 1.9	
Percent change (95% CI)	+3.5% (−3.8%, +11.2%)	−11.4% (−15.9%, −6.6%)	<0.001
Systolic blood pressure, mm Hg			
Baseline	118.2 ± 10.5	117.9 ± 10.0	
Change	−0.5 ± 0.4	+0.6 ± 0.3	0.039
Diastolic blood pressure, mm Hg			
Baseline	76.8 ± 7.0	76.7 ± 7.0	
Change	+0.3 ± 0.3	+0.4 ± 0.2	0.847

Apovian et al. Obesity. 2013;21:935-43.

Naltrexone/Bupropion: Side Effects

Most frequent events:

- Nausea
  - N=171 (29.8%) naltrexone 32 mg plus bupropion
  - N=155 (27.2%) naltrexone 16 mg plus bupropion
  - N=30 (5.3%) placebo
- Headache, constipation, dizziness, vomiting, and dry mouth were also more frequent in the naltrexone plus bupropion groups vs. placebo
- Transient increase of ~1·5 mm Hg in mean systolic and diastolic blood pressure was followed by a reduction of around 1 mm Hg below baseline in the naltrexone plus bupropion groups
- Combination treatment was not associated with increased depression or suicides vs. placebo

Greenway et al. Lancet. 2010;376:595-605.

2010

FDA Advisory Panel recommended for approval for weight management September 2014.

Liraglutide

- Not FDA Approved for weight loss. Recommended for FDA Approval September 2014.

Liraglutide*

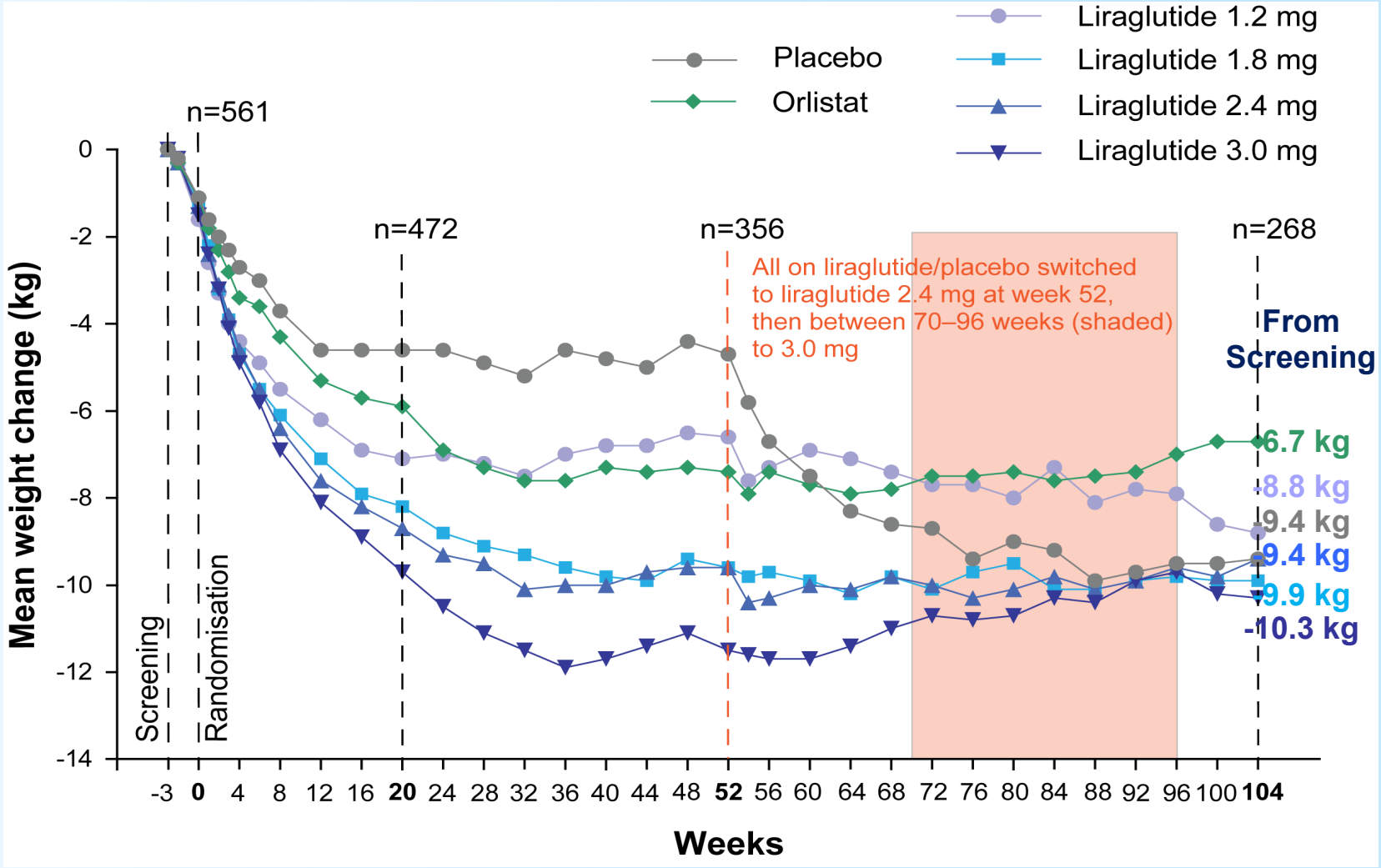
- Glucagon-Like Peptide 1 (GLP-1) receptor agonist approved in 2010 for treatment of type 2 diabetes (1.8 mg/day)
- Phase III trials assessing effects of high dose (3.0 mg/day) to promote weight loss
- Anorectic effect mediated both by the activation of GLP-1 receptor expressed on vagal afferents and by the GLP-1R activation in hypothalamus, Direct central action on arcuate nucleus and NYS, suppresses appetite. Delays gastric emptying
- Affects visceral fat adiposity, appetite, food preference, and cardiovascular biomarkers in patients with type 2 diabetes

*Not FDA Approved for weight loss. Recommended for Approval September 2014.

Clinicaltrials.gov. Effect of Liraglutide on Body Weight in Non-diabetic Obese Subjects or Overweight Subjects With Co-morbidities: SCALE - Obesity and Pre-diabetes. 2011. Effect of Liraglutide on Body Weight in Overweight or Obese Subjects With Type 2 Diabetes: SCALE - Diabetes. 2011.

Inoue et al. Cardiovasc Diabetol. 2011;10:109.

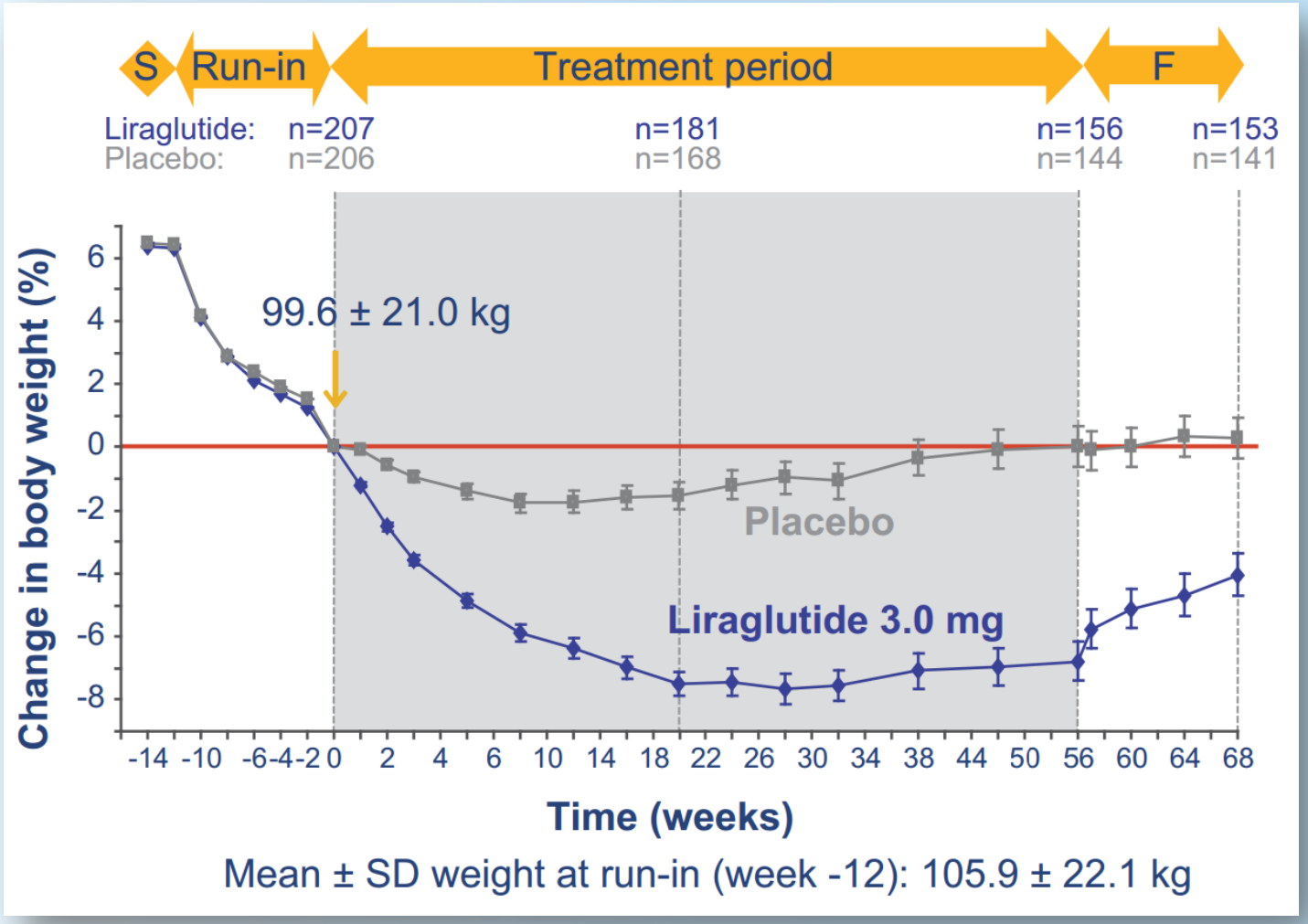
Liraglutide* Weight Loss: Two Years



*Not FDA Approved for weight loss. Recommended for Approval September 2014.

Astrup et al. Int J Obes. Jun 2012;36: 843-54.

Liraglutide* 3 mg – Induced Weight Loss Following Hypocaloric Diet Run-In



*Not FDA Approved for weightloss. Recommended for Approval September 2014.

Wadden et al. Int J Obes. 2013;37:1514.

Obesity Drugs in the Pipeline
Beloranib

Belorani*: Phase 1 Trial Results: 4 Weeks

Fumagillin-class methionine aminopetidase-2 (MetAP2) inhibitor

Dosage	Weight Loss (kg)
Placebo	**-0.6 kg** (-4.5, -0.1)
0.1 mg/m^2 (n=7)	**-0.6 kg** (-4.5, -0.1)
0.3 mg/m^2 (n=6)	**-0.6 kg** (-4.5, -0.1)
0.9 mg/m^2 (n=8)	**-3.8 kg** (95% CI -5.1, -0.9)

No evidence of major tolerability or safety issues (Phase 1 trials)

- N=19 obese women
- Mean BMI 38 kg/m^2
- Dosage at 0.9 mg/m^2 associated with a 42% reduction in triglycerides 18% reduction in LDL-cholesterol
  - Improvement in C-reactive protein and reduced sense of hunger
- Most frequent AEs: headache, infusion site injury, nausea, and diarrhea
- Nausea and infusion site injury occurred more with beloranib vs placebo
- Loss of venous access most common reason for discontinuation

*Not FDA Approved.

Hughes et al. Obesity. 2013;21:1782-8.

Belorani*: Phase 1 Trial Results: 12 Weeks

Fumagillin-class methionine aminopetidase-2 (MetAP2) inhibitor
Randomized, double-blind, placebo-controlled trial

Dosage	12 Week Weight Loss Results (kg) p<0.0001
Placebo (n=38)	-0.4 kg (+/- 0.4 kg)
0.6 mg (n=37)	-5.5 kg (+/- 0.5 kg)
1.2 mg (n=37)	-0.69 kg (+/- 0.6 kg)
2.4 mg (n=35)	10.9 (+/- 1.1 kg)

- N=122 completers
- Mean age 48.4 years
- Mean BMI 37.6 kg/m^2
- Mean body weight 100.9 lbs

Systolic blood pressure reductions:
1.2 mg = 7.6 mmHg 2.4
mg = 12.0 mmHg

Improvements in LDL, HDL, and triglycerides

Most frequent AE's: nausea, diarrhea, headache, injection site bruising, and insomnia

*Not FDA Approved.
http://zafgen.com/docs/default-source/press-releases/zafgen-ada-release-6-17-13-for-website.pdf?sfvrsn=0

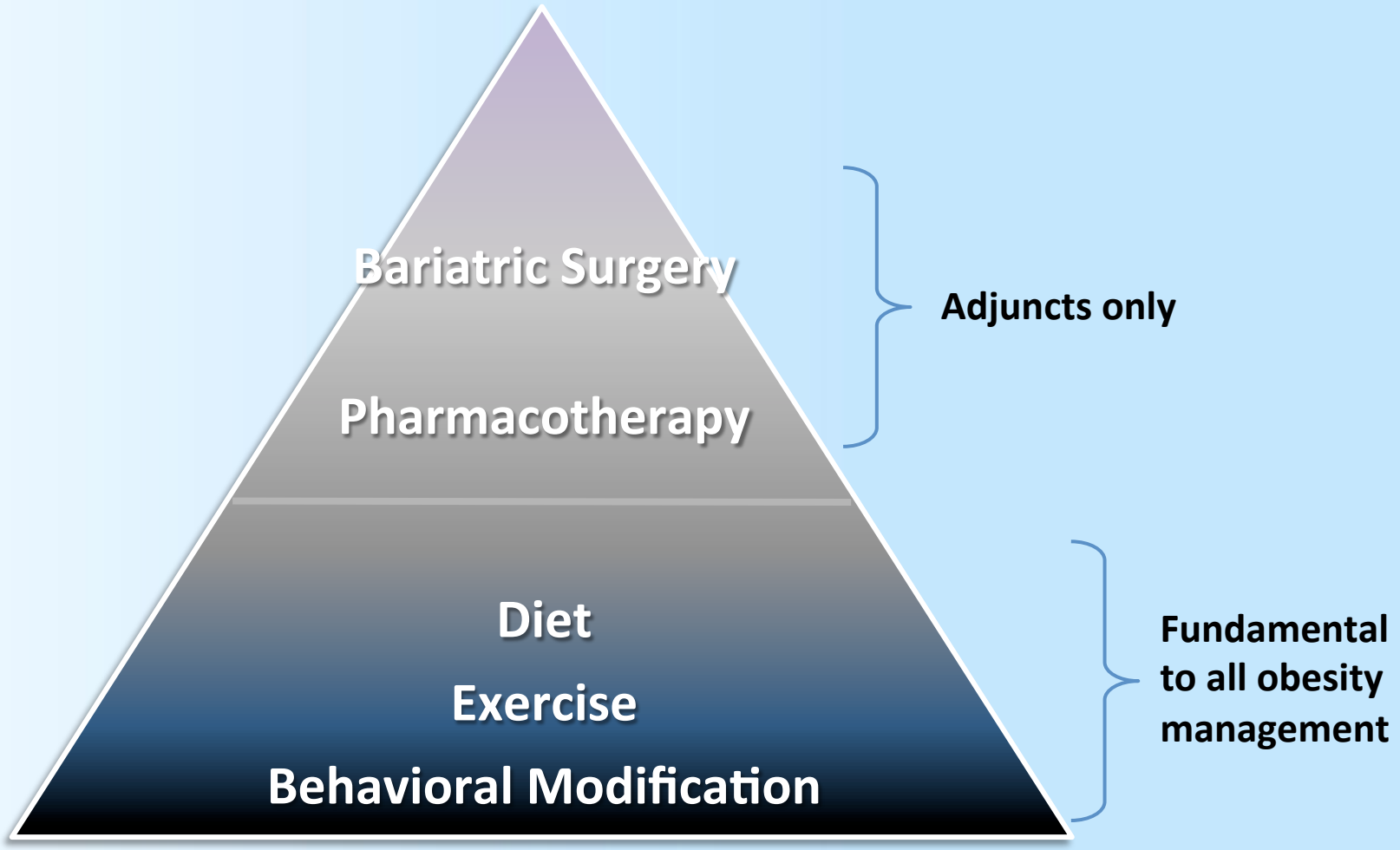
Summary

- Few choices of anti-obesity medications
- Two new medications approved in 2012
- Two more approved in Sept/Oct 2014
- Medications can enhance weight loss for select candidates and improve cardiometabolic outcomes
- Medications are always only adjunct to diet and exercise
- When we have more medications, we will treat obesity more frequently

Complex Cases in Obesity: The Expert Faculty Panel "Weigh In" on Effective Weight Loss Strategies to Reduce Cardiometabolic Risk

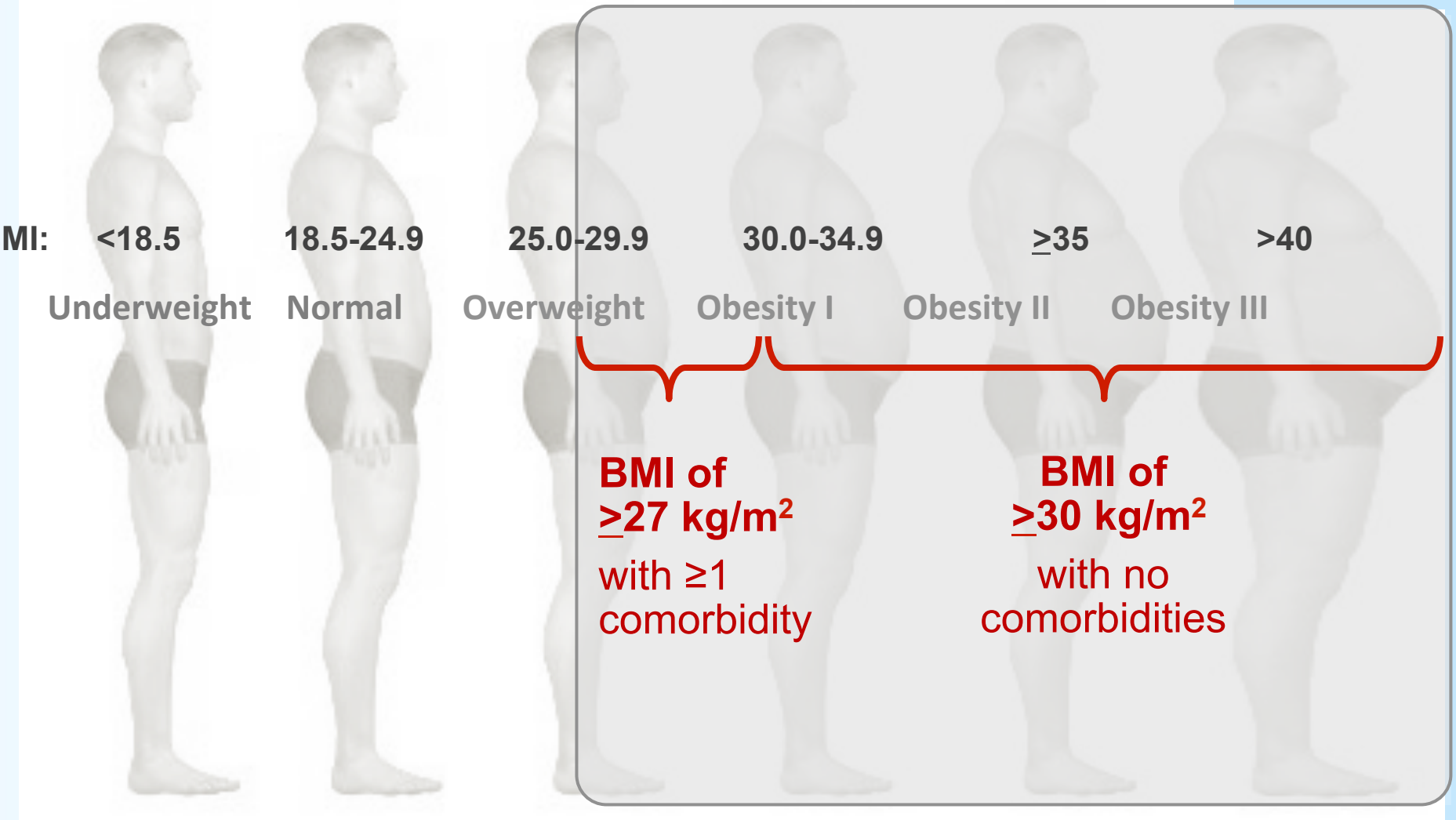
Caroline M. Apovian, MD
Louis J. Aronne, MD
Lee M. Kaplan, MD, PhD
Joshua Thaler, MD, PhD

Fundamentals of Care



Criteria for Using Approved Medications

Adjunct to an energy deficient diet, increased physical activity and behavior modification



www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/

Weight Loss Drugs: Dosage and Duration

Long-term Obesity Treatment:
Start with lowest dose

- Phentermine/topiramate 7.5 mg/46 mg
- Lorcaserin 10 mg bid
- Naltrexone and bupropion 8 mg/90 mg tablets
- Orlistat 120 mg tid
- Orlistat OTC 60 mg tid

Intermittent Use

- For situations or times of year where lifestyle factors promote weight regain
- Several months on, one month off

Waiting for Approval

- Liraglutide (for obesity)

Matching Medication to Patient

When NOT TO USE:

Lorcaserin

- Patient on a lot of SSRI and/or SNRI

Orlistat

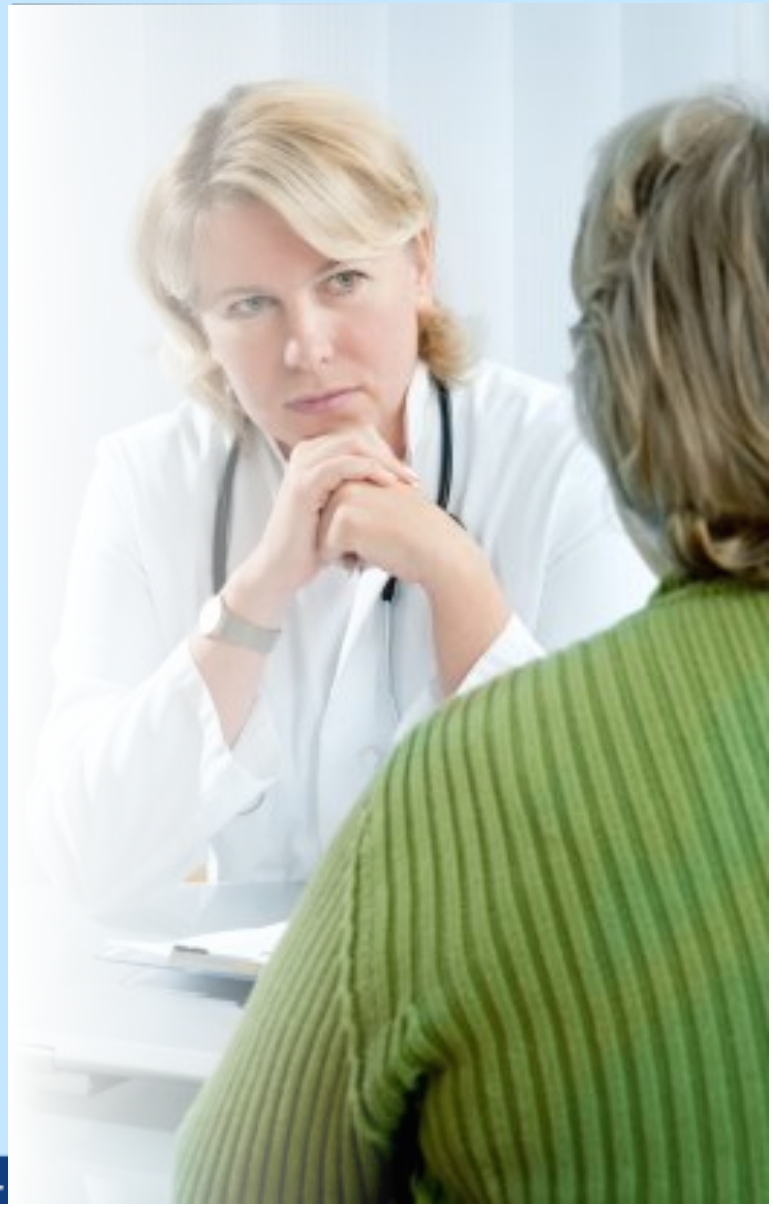
- GI disorders

Phen/top

- Pregnant-age women not on birth control
- Uncontrolled HTN
- Uncontrolled or active CVD

Naltrexone/Bupropion

- Patient on opiates
- Patient with seizure disorder history
- Uncontrolled HTN



Case #1

55-yr-old male with metabolic syndrome

CC:
Cannot lose weight despite personal training 3x/week

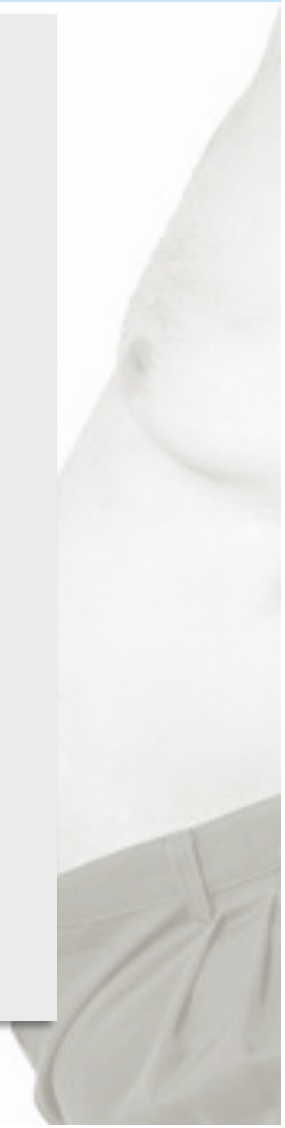
FH: DM and CAD

Medications

- Atenolol 50 mg QD
- Valsartan 80mg QD
- Glipizide 5 BID
- Pioglitazone 30mg QD
- Metformin 500 BID
- Atorvastatin 40mg QD
- Insulin - glargine 20 units/ night

Lab Data

- Weight 264 lbs
- Height 5' 10"
- BMI 38 kg/m^2
- WC 45 in
- BP 150/95
- HbA1c 7.2%
- FBG 150-175 mg/dL
- TC 220 mg/dL
- TG 300 mg/dL
- LDL-C 130 mg/dL
- HDL-C 40 mg/dL



Case #1-Question 1

55-yr-old male with metabolic syndrome

Before starting a low-calorie diet, which of the following medication(s) would you stop:

1. Insulin
2. Glipizide
3. Pioglitazone
4. Insulin and Glipizide

Case #1-Question 2

55-yr-old male with metabolic syndrome

Which of his medications does *NOT* cause weight gain?

1. Atenolol
2. Glipizide
3. Pioglitazone
4. Valsartan

Discussion: Case #1

55 yr old male with metabolic syndrome

- An obese, 55-year-old man with metabolic syndrome due to hypertension, diabetes, and elevated lipids is having trouble losing weight on his own through lifestyle interventions. He has hired a personal trainer, working out three times a week, to no avail. He takes seven medications to control his comorbidities.

- Path number one for the provider would be to evaluate his medications to see if there are any that exacerbate weight gain, and to consider alternatives.

- He is a candidate for bariatric surgery because of his Type 2 DM and BMI between 35 and 40. Adding obesity pharmacology to his exercise routine with a low-calorie, high-protein diet would be an important first step.

- The medications to stop and/or reduce while undergoing weight loss with a high-protein/ low-carbohydrate diet, would be the anti-hyperglycemic agents: insulin, glipizide, and pioglitazone. Slowly reduce these medications based on blood glucose, one at a time, by one-half dose at a time.

Discussion: Case #1 con't

55 yr old male with metabolic syndrome

- During down titration, metformin can be maximized to 1000 mg a day, and a GLP-1 agonist such as liraglutide or exenatide could be added.
- Continue to downtitrate antihyperglycemic medications that cause weight gain until most or all have been stopped.
- He should also be weaned off atenolol if possible, replacing with another agent such as a thiazide diuretic.
- Should weight loss plateau after these changes, obesity pharmacology can be added such as lorcaserin, phentermine/topiramate or naltrexone/bupropion.

Case #2

61-yr-old female with postmenopausal weight gain

- Severe obesity, referred for surgery
- Asthma, arthritis, fibromyalgia
- Undiagnosed high blood pressure

FH Obesity

Medications

- Zafirlukast
- Albuterol inhaler
- Metoprolol
- Loratadine
- Etodolac
- Nortriptyline
- Paroxetine
- Vitamin B, MVI, Calcium

Lab Data

Weight	200 lbs
Height	5’ 5”
BMI	33 kg/m^2
WC	34 in
BP	160/95
HbA1c	5.9%
FBG	105 mg/dL
TC	250 mg/dL
TG	260 mg/dL
LDL-C	150 mg/dL
HDL-C	50 mg/dL

Case #2- Question 1

1
2

61-yr-old female with postmenopausal weight gain

Which of the following comorbidities should improve with weight loss?

1. Asthma
2. Arthritis
3. Fibromyalgia
4. Asthma and Arthritis
5. Asthma, Arthritis and Fibromyalgia

Case #2-Question 2

61-yr-old female with postmenopausal weight gain

Which of her medications can cause weight gain?

1. Zafirlukast
2. Loratadine
3. Etodolac
4. Paroxetine

Discussion: Case #2

61-yr-old female with postmenopausal weight gain

- Weighing 200 pounds on a 5' 5" frame, this 61-year-old woman is severely obese and has been referred for bariatric surgery. She has gained weight steadily since the onset of menopause and is on an array of medications to control her comorbidities (zafirlukast, albuterol inhaler, loratadine, etodolac, nortriptyline, metoprolol, and paroxetine).

- With a BMI of 33 she does not meet the surgical criteria (BMI >40, or 35 with comorbidities) therefore, she is a candidate for diet, exercise, and behavior therapy with or without a pharmacological option. She is also on an antidepressant (paroxetine), which can cause weight gain. Replace paroxetine with citalopram or escitalopram.

- Her asthma and arthritis will improve with weight loss, as will her high blood pressure and metoprolol can be weaned off as she loses weight. Elevated lipids will also improve.

Discussion: Case #2 Con't

61-yr-old female with postmenopausal weight gain

- If she is on phentermine/topiramate combination, blood pressure must be monitored carefully as it is already elevated.

- If lorcaserin is considered, use with extreme caution due to the risk of serotonin syndrome because she is on a SSRI. Also pertinent for serotonin-norepinephrine reuptake inhibitors (SNRIs) are monoamine oxidase inhibitors (MAOIs), triptans, bupropion, dextromethorphan, and St. John's wort. Phentermine/topiramate or naltrexone/bupropion is a better choice.

- Her lipids and asthma suggests she is in a chronic state of inflammation which may also improve with weight loss.

Case #3

27-yr-old female post-breastfeeding weight gain

Medications

- Prenatal vitamins

Lab Data: Baseline

- Weight was 150 lbs
- Weight now 185 lbs
- Height 5’ 5”
- BMI was 25 kg/m^2
- BMI now 31 kg/m^2
- All other parameters normal

35 lb weight gain

from **Overweight** to **Obese**

Case #3-Question 1

27-yr-old female post-breastfeeding weight gain

If this patient reaches her pre-pregnancy weight of 150 pounds, what will be her % *excess* weight loss?

1. 19%
2. 100%
3. 40%
4. 50%

Case #3-Question 2

27-yr-old female post-breastfeeding weight gain

If this patient reaches her pre-pregnancy weight of 150 lbs, what will be her % *total* weight loss? (35 divided by 185 = 19%)

1. 19%
2. 100%
3. 40%
4. 50%

Discussion: Case #3

27-yr-old female post-breastfeeding weight gain

- A 27-year-old woman has gained 35 pounds since stopping breastfeeding several months ago. Her pre-pregnancy weight was 150 at a BMI of 25. She now weighs 185 with a BMI of 31 and she is looking to her get back to her pre-pregnancy weight. All of her other parameters are normal.

- With a BMI of 31 she is a candidate for diet, exercise, and behavioral therapy - with or without an obesity medication.

- She is a candidate for either phentermine/topiramate, lorcaserin, or naltrexone/ bupropion.

- A weight loss of 10% is what would be considered successful (~ 20 lbs). It is conceivable that she could achieve pre-pregnancy weight loss. At that point a decision would have to be made with patient and the provider as to if and when to stop the obesity medication, and monitor for weight regain.

Case #4

50-yr-old female post gastric-bypass weight gain

CC:

- Lost 100 pounds with surgery
- 2 years post surgery 40 lb gain
- Blood glucose creeping up
- Pouch dilatation

Pre-op Medications

- Metformin
- Glipizide

Hx: Diabetes, for 3 years pre-surgery

Height 5'4"	Pre-surgery	1 Year Post Surgery	2 Years Post Surgery
BMI	41 kg/m^2	24 kg/m^2	31 kg/m^2
Weight	240 lbs	140 lbs	180 lbs
FBG	135 mg/dL	94 mg/dL	120 mg/dL
HbA1c	10%	5%	6.5%

Case #4-Question 1

50-yr-old female post gastric-bypass weight gain

This patient should be placed back on:

1. Metformin
2. Glipizide
3. Both of the above
4. None of the above

Case #4-Question 2

50-yr-old female post gastric-bypass weight gain

What other information is needed to work up this case?

1. More diet history
2. Upper GI series
3. CT scan of abdomen
4. MRI of abdomen

Discussion: Case #4

50-yr-old female post gastric-bypass weight gain

- A 50-year-old woman underwent a successful gastric bypass 2 years earlier. She has gained 35 pounds since her surgery. Her diabetes, which resolved after surgery, is back to a pre-diabetes level.
- She should be monitored on a high-protein, low-carbohydrate diet,* and given an exercise regimen.
- Consider re-starting metformin and perhaps adding a GLP-1 agonist as well.
- Follow up on her metformin and GLP-1. She should be losing 1-2 pounds of weight per week. After 3 months, she should have lost 12-20 pounds; if she has not: consider phentermine/topiramate, lorcaserin, or naltrexone/bupropion.

*Shai et al. N Engl J Med. 2008;359:229-41.

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Panel Discussion

Questions and Answers