Obesity Management 2014: New Perspectives and Therapeutic Options for a Growing Problem

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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.

Spaced Education Activity

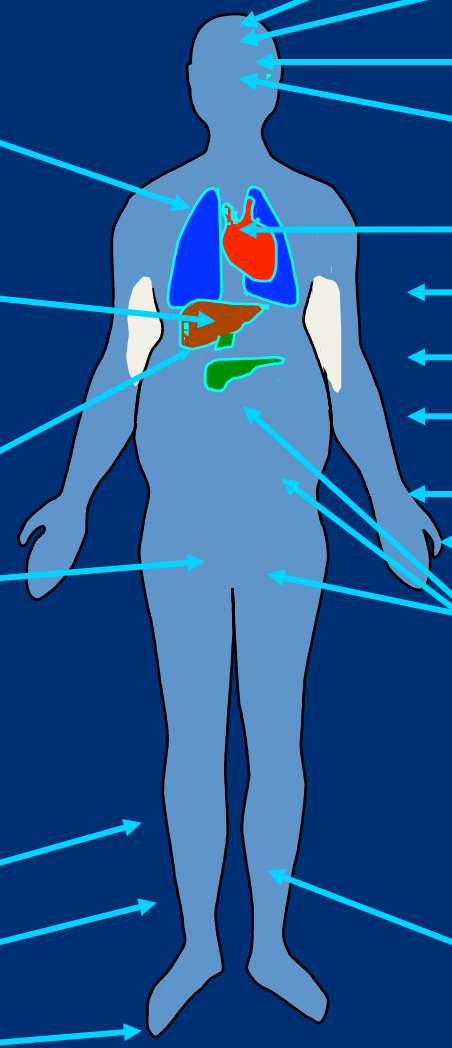
- A CME-certified **"Spaced Education"** activity will be developed and distributed to the attendees via email after the live symposium.
- This innovative learning methodology will deliver 1-2 regularly scheduled multiple choice questions over a 40-day period.
- Please look for these emails and participate in the activity to supplement and reinforce the learning objectives and key messages that are presented today.

Managing Obesity and Comorbid Conditions:

Welcome, Introductions, Opening Remarks

Robert H. Eckel, M.D.
Professor of Medicine
Professor of Physiology and Biophysics
Charles A. Boettcher II Chair in Atherosclerosis
University of Colorado Anschutz Medical Campus

Medical and CVD Comorbidities of Obesity



Pulmonary disease
abnormal function
obstructive sleep apnea
hypoventilation syndrome
pulmonary embolism
pulmonary hypertension

Nonalcoholic fatty liver disease
steatosis
steatohepatitis
cirrhosis

Gall bladder disease

Gonadal abnormalities
abnormal menses
infertility
polycystic ovarian syndrome
erectile dysfunction

Osteoarthritis

Skin

Gout

Idiopathic intracranial hypertension

Stroke

Cognitive impairment

Cataracts

Coronary heart disease

CHF, arrhythmias

Diabetes

Hypertension

Dyslipidemia

Inflammation

Cancer
breast, uterus, cervix
colon, esophagus, pancreas
kidney, prostate, thyroid

Phlebitis
venous stasis

Anti-Obesity Drugs Currently Approved and Pending Approval

FDA-Approved Drug	Company	Mechanism of Action	Comments
Benzphetamine (Didrex)	Pharmacia	Norepinephrine/dopamine releasing stimulator	Schedule III drug, approved 1960 for short-term use
Phendimetrazine (Bontril)	Valeant	Norepinephrine/dopamine releasing stimulator	Schedule III drug, approved 1961 for short-term use
Phentermine (Adipex, Suprenza)	Gates, Alpex	Noradrenaline/dopamine releasing stimulator	Schedule IV drug, approved 1973 for short-term use
Diethylpropion (Tenuate)	Watson Labs/ Corepharma	Norepinephrine/dopamine releasing stimulator	Schedule IV drug, approved 1973 for short-term use
Orlistat (Xenical) (Alli –OTC)	Roche, GSK	Pancreatic lipase inhibitor	Approved for long-term use in 1999
Lorcaserin (Belviq)*	Arena Pharma	Selective 5-HT_{2C}receptor agonist	Approved June 2012
Phentermine/Topiramate (Qysmia)* *(formerly Qnexa)*	Vivus	Noradrenaline releasing + modulator of ɣ aminobutyric acid (GABA)/ carbonic anhydrase inhibition	Approved July 2012
Bupropion/Naltrexone (Contrave)	Orexigen	Inhibitor of dopamine and noradrenaline reuptake + μ opiate antagonist	Approved September 2014
Anti-obesity Drug Pending Final Approval			
Liraglutide	Novo Nordisk	GLP-1 agonist	Approved January 2010 for treatment of Type 2 DM; phase III for anti-obesity at higher doses **Recommended for FDA Approval September 2014. Final decision is expected by Oct. 20.**

Modified from Zhi-yun et al. Acta Pharmacologica Sinica. 2012;33:145–47.

*Schedule IV drug

ARS Case Study:

44-year-old man – depression, allergies, seizure disorder, and regular marijuana user.

Which compound would not affect his appetite?

1. Bupropion
2. Cannabis
3. Montelukast
4. Diphenhydramine
5. Topiramate

ARS

All of the following gut hormones decrease food intake, except:

1. Cholecystokinin
2. Glucagon-like peptide-1
3. Oxyntomodulin
4. Ghrelin

The *MOST* important consideration in developing a treatment strategy for a patient with obesity is:

1. Current weight and age
2. Body mass index and associated risk factors
3. Obesity stage (overweight, stage I, II, or III)
4. Dietary preferences and ability to exercise

Individualizing Treatment Strategies: Stratifying Cardiometabolic Risk in Obese Patients

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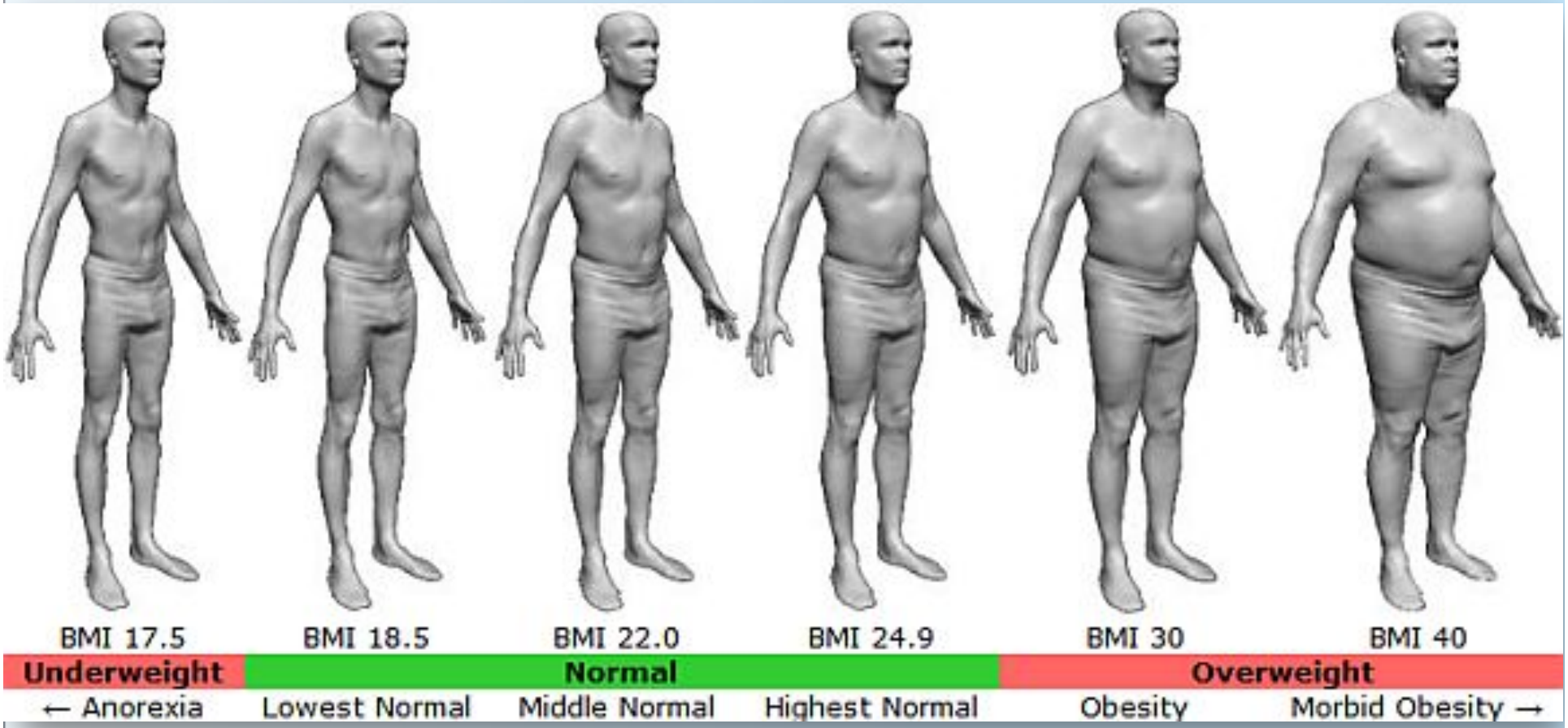
Assoc. Professor, Division of Public Health Sciences
Wake Forest School of Medicine
Winston-Salem, NC

Our Objectives

- Clinical guidelines for obesity treatment- how to use them
- Diagnostic strategies and communicating risks associated with obesity
- Matching treatment with risk
- Escalating treatment

Obesity Guidelines

Going Beyond Simple BMI

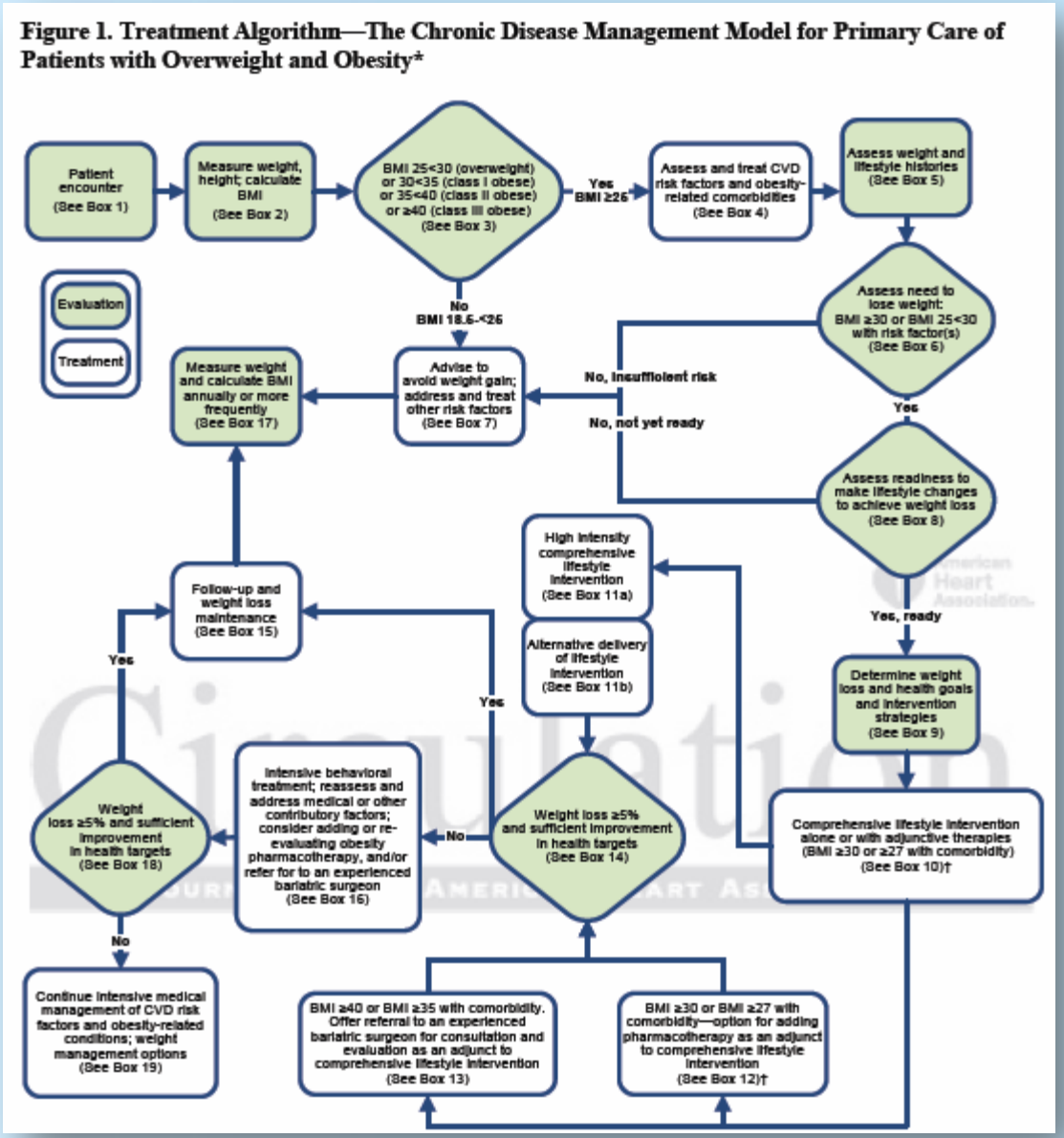


Moving to Complication Focus

- Weight loss not just for the sake of weight loss
- AHA/ACC/TOS guidelines- identify risks associated with weight status
- AACE guidelines link risk status with weight status to create complication-specific staging

Algorithms

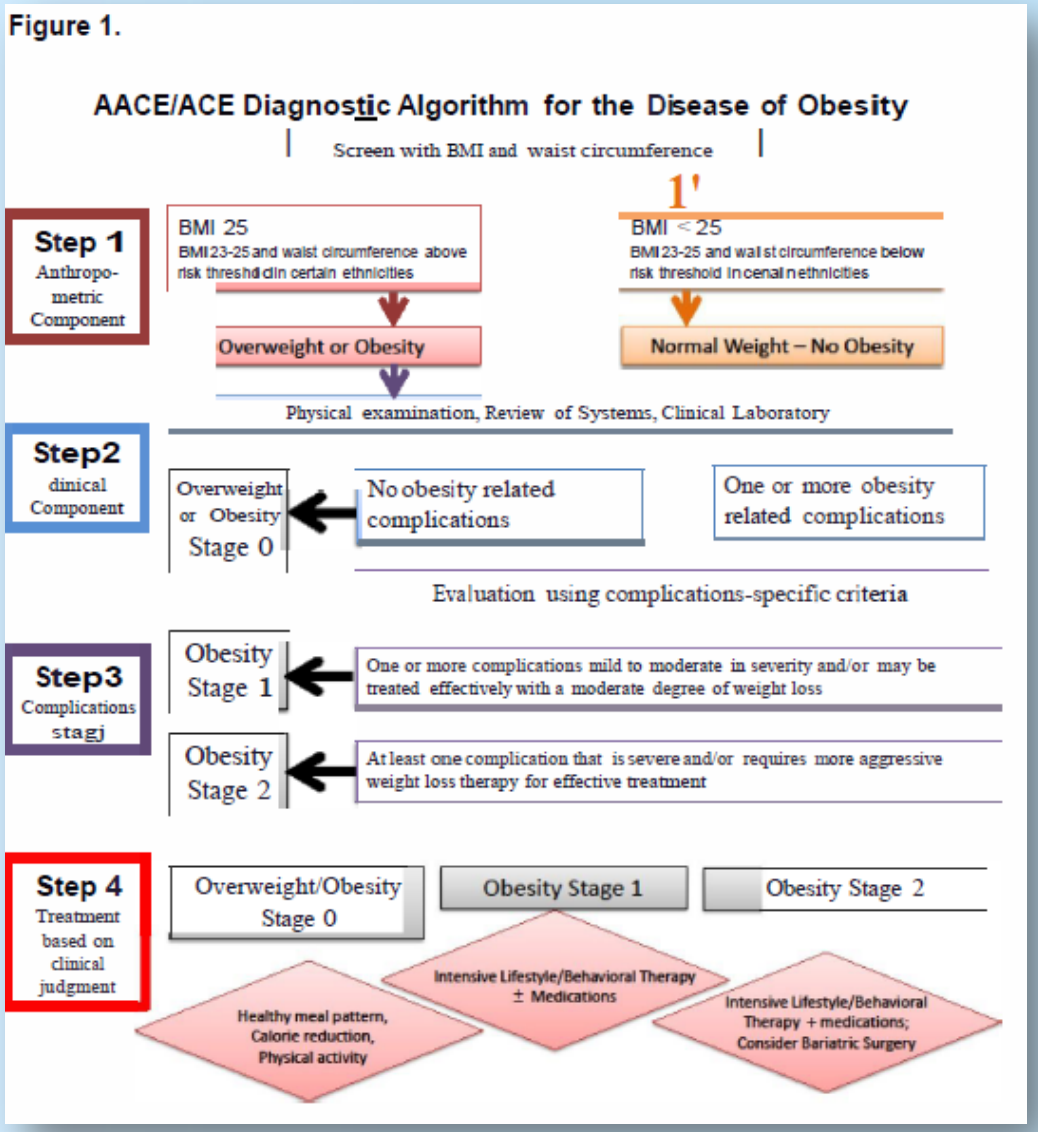
AHA/ACC/TOS



Jensen et al. Circulation 2014; 129: S102-38.

Algorithms

AACE/ACE



Garvey et al. https://www.aace.com/files/2014-advanced-framework-for-a-new-diagnosis-of-obesity-as-a-chronic-disease.pdf.

Assess, Communicate, Treat

Don't have paralysis from analysis

Assess the risk
- Anthros, History/Exam, Labs

Communicate the risk
- Ready, Willing, Able?

Treat the risk
- Appropriate and targeted treatment

Assess the Risk

CLASSIFICATION OF OVERWEIGHT AND OBESITY
BY BMI, WAIST CIRCUMFERENCE AND ASSOCIATED DISEASE RISK*

	BMI (KG/M²)	OBESITY CLASS	DISEASE RISK* RELATIVE TO NORMAL WEIGHT AND WAIST CIRCUMFERENCE	
			MEN ≤102cm (≤40in)	MEN ≥102cm (≤40in)
			WOMEN ≤88cm (≤35in)	WOMEN ≥88cm (≤35in)
UNDERWEIGHT	<18.5			
NORMAL†	18.5 - 24.9			
OVERWEIGHT	25.0 - 29.9		INCREASED	HIGH
OBESITY	30.0 - 34.9	I	HIGH	VERY HIGH
	35.0 - 39.9	II	VERY HIGH	VERY HIGH
EXTREME OBESITY	≥40	III	EXTREMELY HIGH	EXTREMELY HIGH

* Disease risk for Type 2 diabetes, hypertension, and CVD

† Increased waist circumference can also be a marker for increased risk even in persons of normal weight

NIH Expert Panel Report. Am J Clin Nutr. 1998;68:899-917.

Assess the Risk

Cardiometabolic	Biomechanical	Other
• Type 2 DM • Hypertension • NAFLD • Hyperlipidemia	• Osteoarthritis • Obstructive Sleep Apnea • GERD	• Certain cancers • Gallstones • Infertility

Communicate the Risk

Most patients understand they are too heavy

They may not understand

- the ***degree*** of excess weight
- the ***relationship*** between their weight and health problems
- that ***you can help*** them lose weight and improve their health

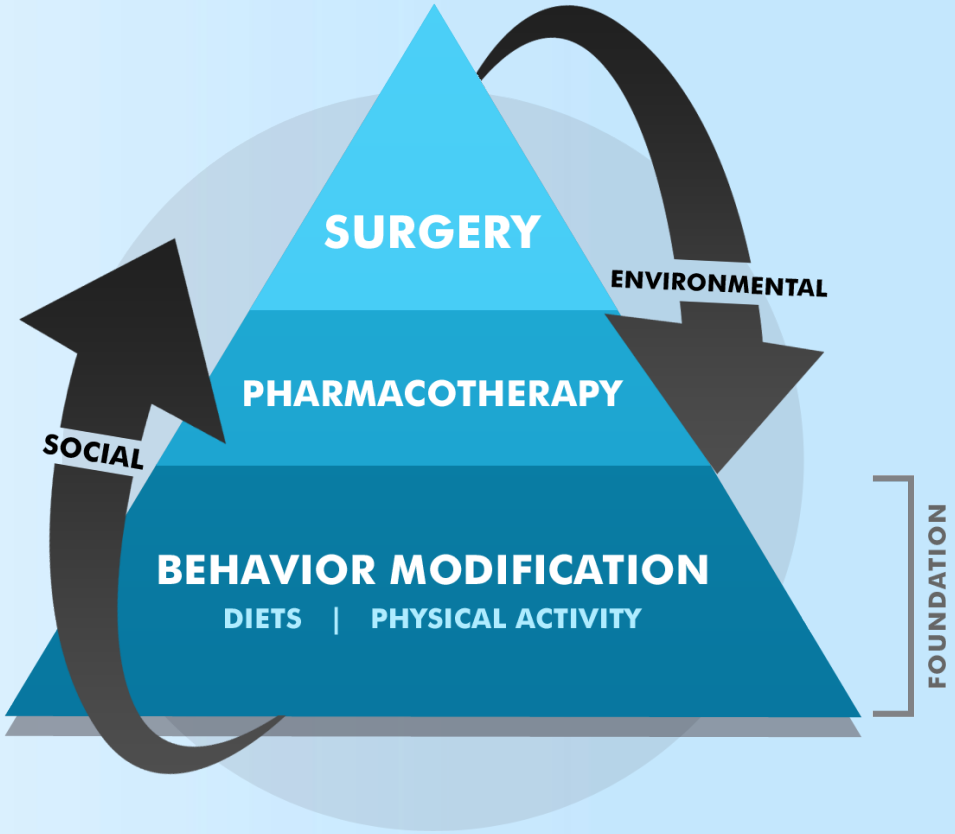
Communicate the Risk

- Is the patient ***ready*** to lose weight?
- Is the patient ***willing*** to do what is necessary to lose weight?
- Are they ***able*** to lose weight at this time?

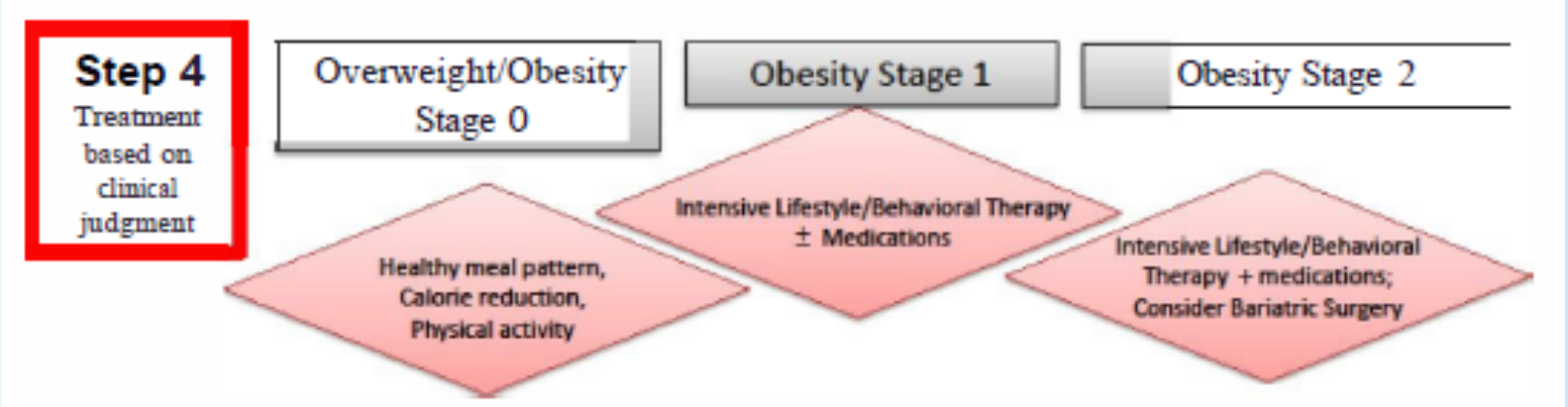
Treat the Risk

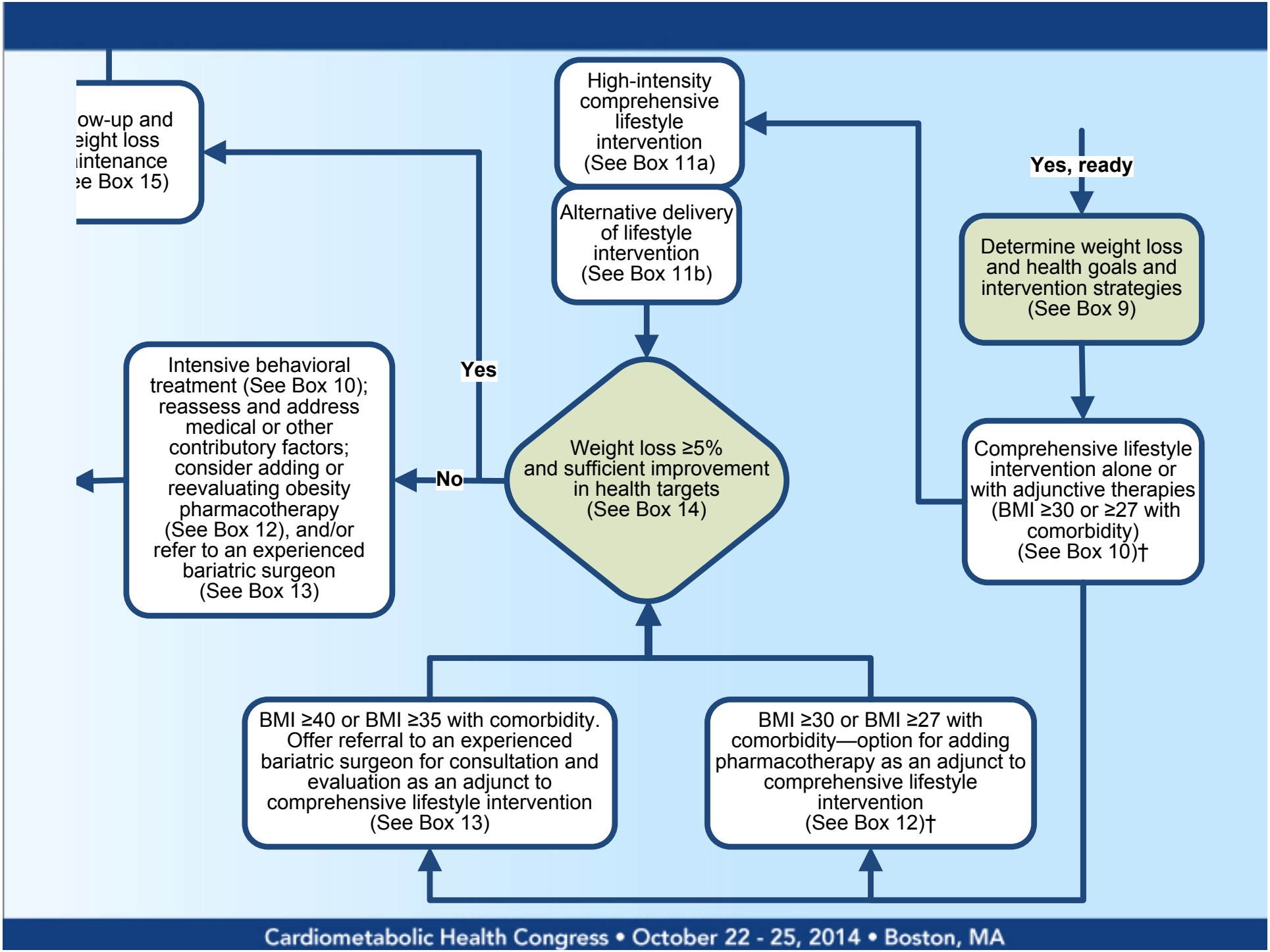
Goal: Produce a ***behavior change*** that leads to lower caloric intake and greater energy expenditure

Treat the Risk



Treatment Based on Clinical Judgment




ow-up and
eight loss
intenance
ee Box 15)
High-intensity comprehensive lifestyle intervention (See Box 11a)
Alternative delivery of lifestyle intervention (See Box 11b)
Yes, ready
Determine weight loss and health goals and intervention strategies (See Box 9)
Intensive behavioral treatment (See Box 10); reassess and address medical or other contributory factors; consider adding or reevaluating obesity pharmacotherapy (See Box 12), and/or refer to an experienced bariatric surgeon (See Box 13)
Yes
No
Weight loss ≥5% and sufficient improvement in health targets (See Box 14)
Comprehensive lifestyle intervention alone or with adjunctive therapies (BMI ≥30 or ≥27 with comorbidity) (See Box 10)†
BMI ≥40 or BMI ≥35 with comorbidity. Offer referral to an experienced bariatric surgeon for consultation and evaluation as an adjunct to comprehensive lifestyle intervention (See Box 13)
BMI ≥30 or BMI ≥27 with comorbidity—option for adding pharmacotherapy as an adjunct to comprehensive lifestyle intervention (See Box 12)†

Summary

- Obesity is a ***complicated*** disease
- Guidelines are more and more focused on ***risk reduction***
- **ACT!**-Assess, Communicate, Treat
- Comprehensive lifestyle interventions promote ***behavior change***
- Pharmacotherapy and surgery are ***targeted*** tools that support the behavior process

How the Gut Talks to the Brain: Clinical Implications for Weight Loss

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Chair, Department of Clinical Obesity and Metabolism
Pennington Biomedical Research Center
Baton Rouge, LA

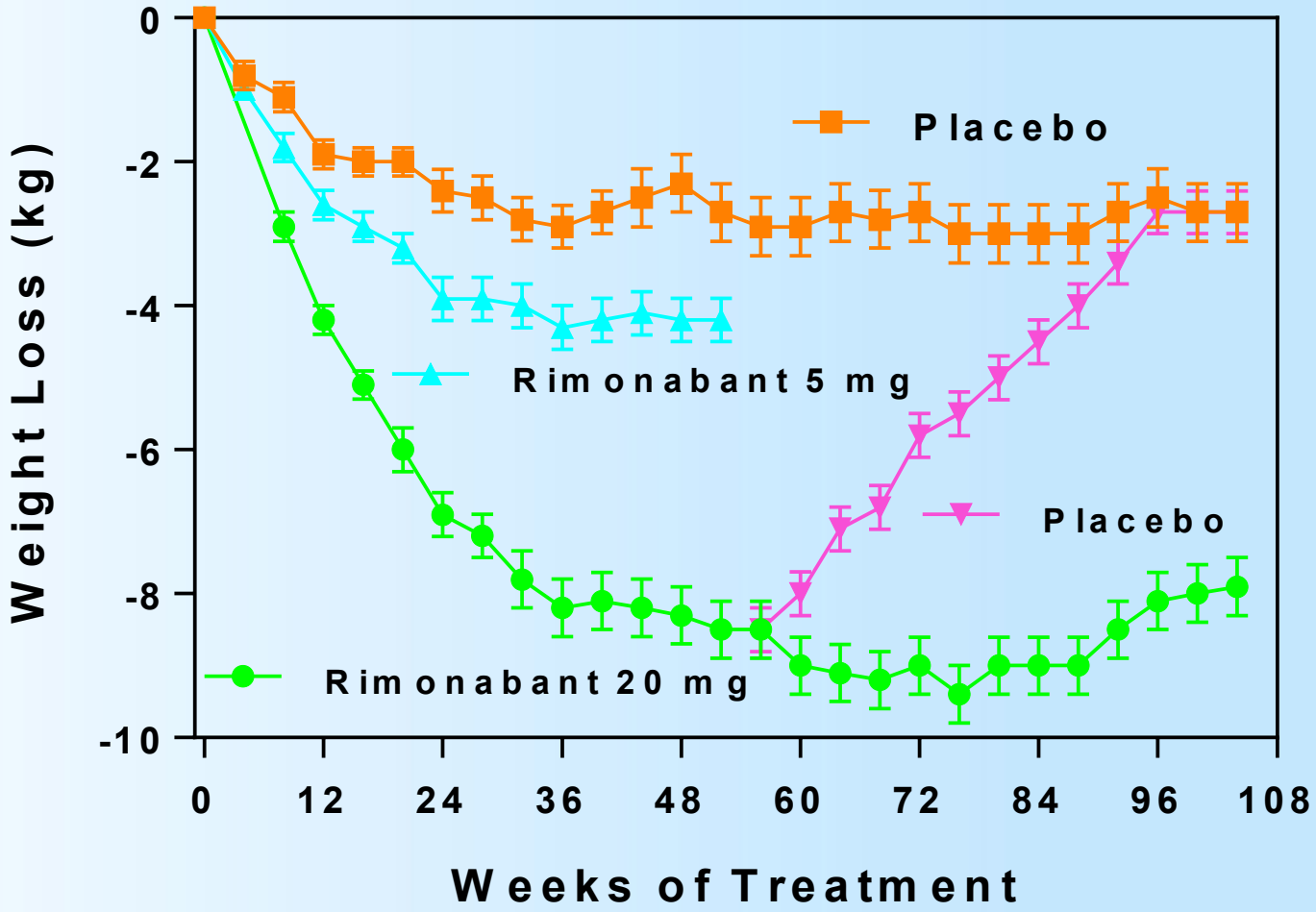
Objectives

- To show that body weight is physiologically regulated
- That disturbance in this system can produce obesity
- That it is modulated by adiposity and satiety signals
- Weight loss induces metabolic changes that favor weight regain

Body Weight Is a Regulated System

- The body weight HOMEOSTATICALLY regulates to limit weight loss (or gain) and restores baseline weight following caloric restriction and/or exercise. This works better in the long than the short term.

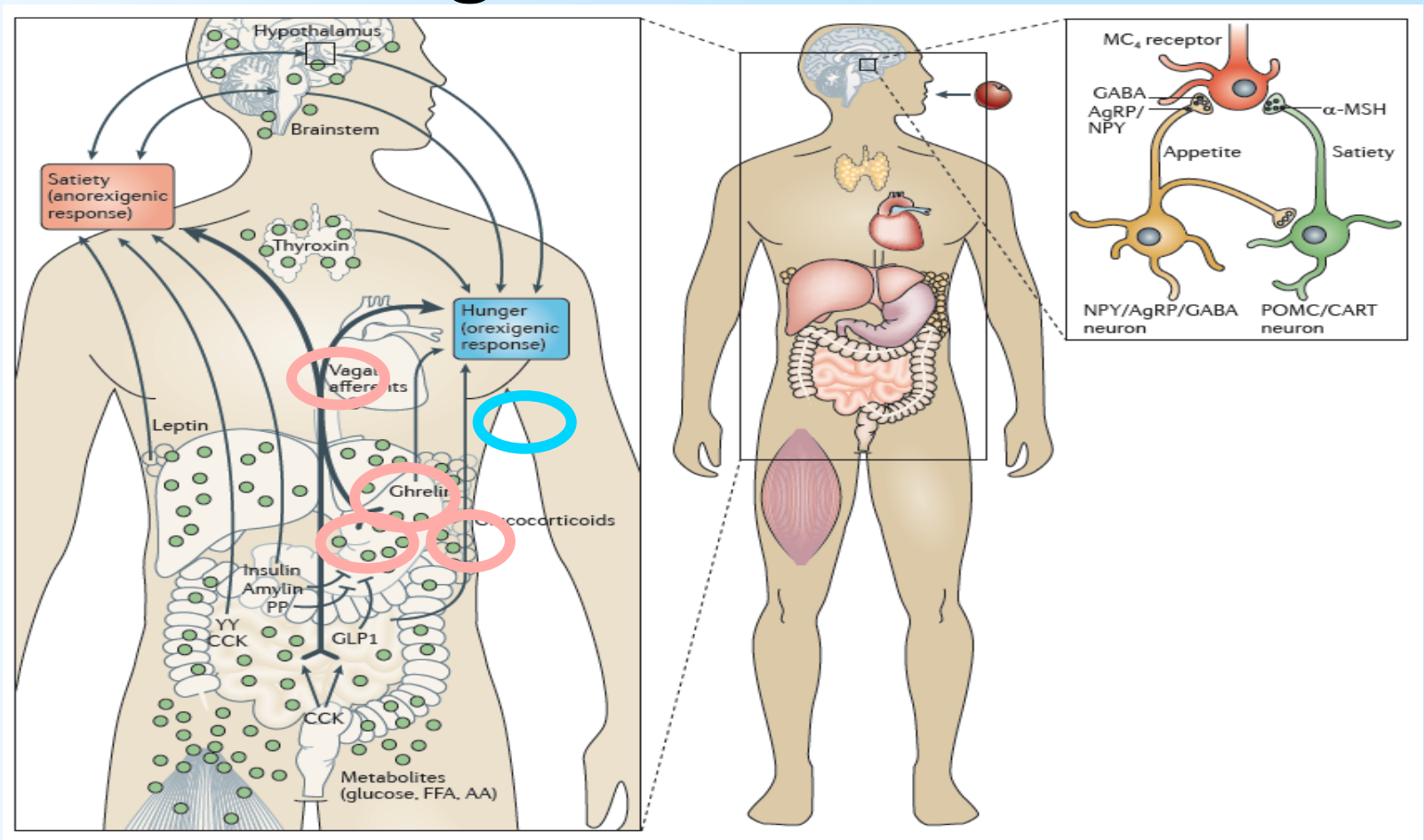
Body Weight Is a Homeostatically Regulated System in Humans



Pi-Sunyer et al JAMA 2006;761-75.

Rimonabant withdrawn from European market in 2009; not approved in US

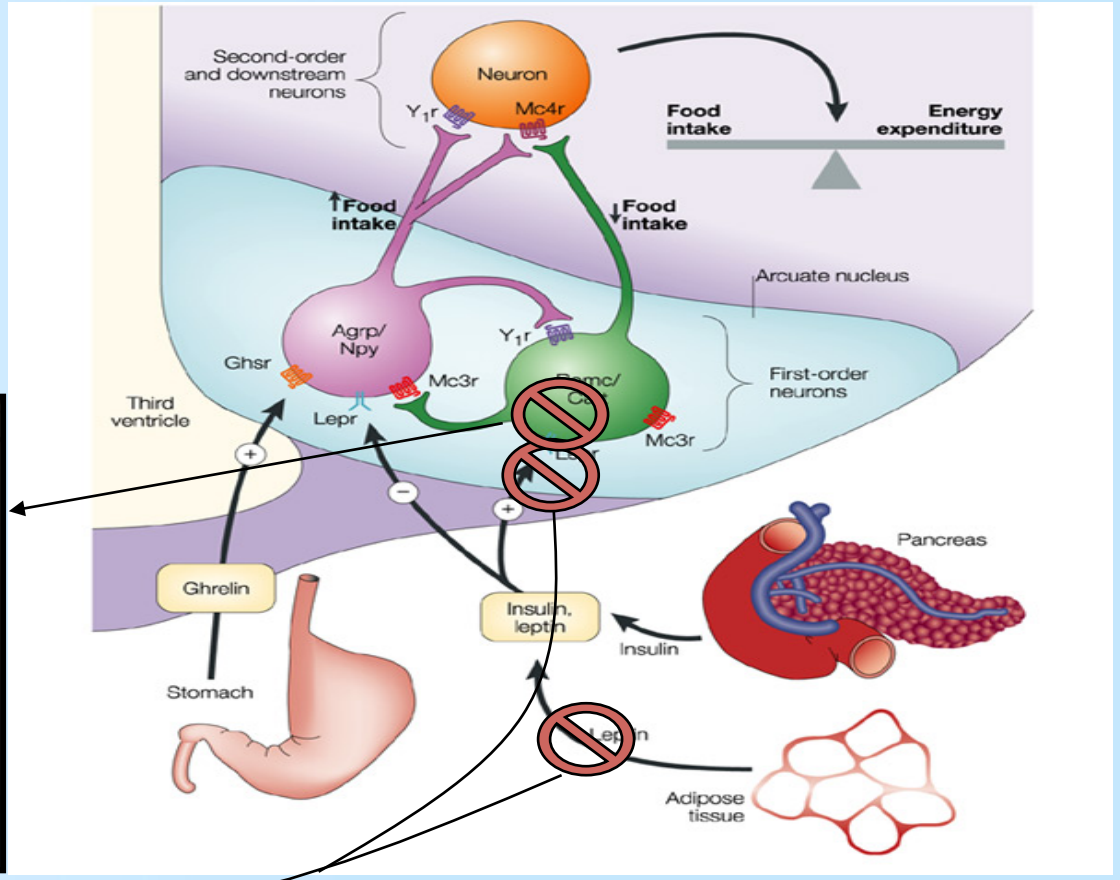
Homeostasis Is Maintained Through Feedback Signals from Fat and the Gut



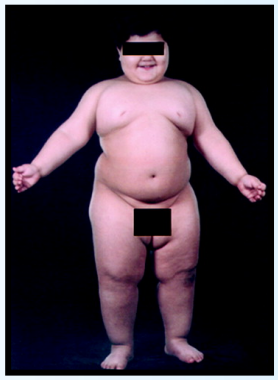
PP=pancreatic polypeptide; FFA=free fatty acids; AA=amino acids; MC_4=melanocortin 4;α-MSH=alpha-melanocyte-stimulating hormone; NPY= neuropeptide Y; GABA=γ-aminobutyric acid; AgRP=agouti-related peptide; POMC/CART= proopiomelanocortin/cocaine-and-amphetamine-regulated transcript

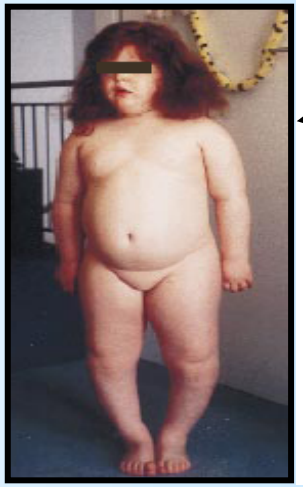
Dietrich and Horvath. Nat Rev Drug Disc. 2012;11:675-91,

Hypothalamic Systems Control Body Weight in Humans



JCI 2002

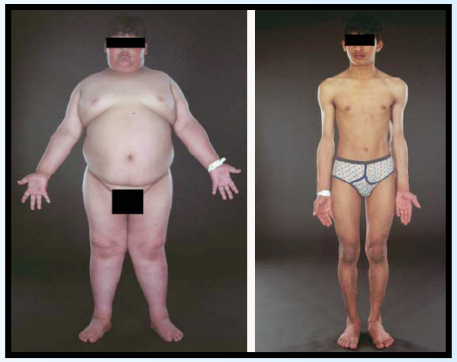




Nature 1998

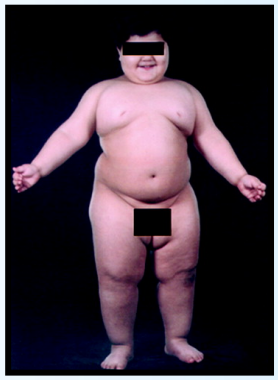
Barsh and Schwartz. Nat Rev Gen. 2002;3:589-600.

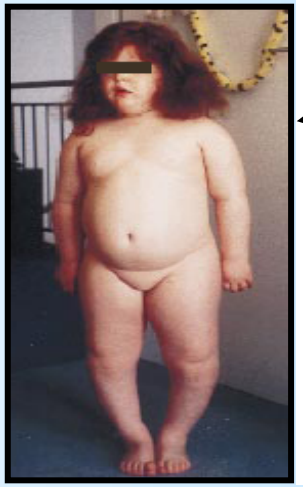
Hypothalamic Systems Control Body Weight in Humans



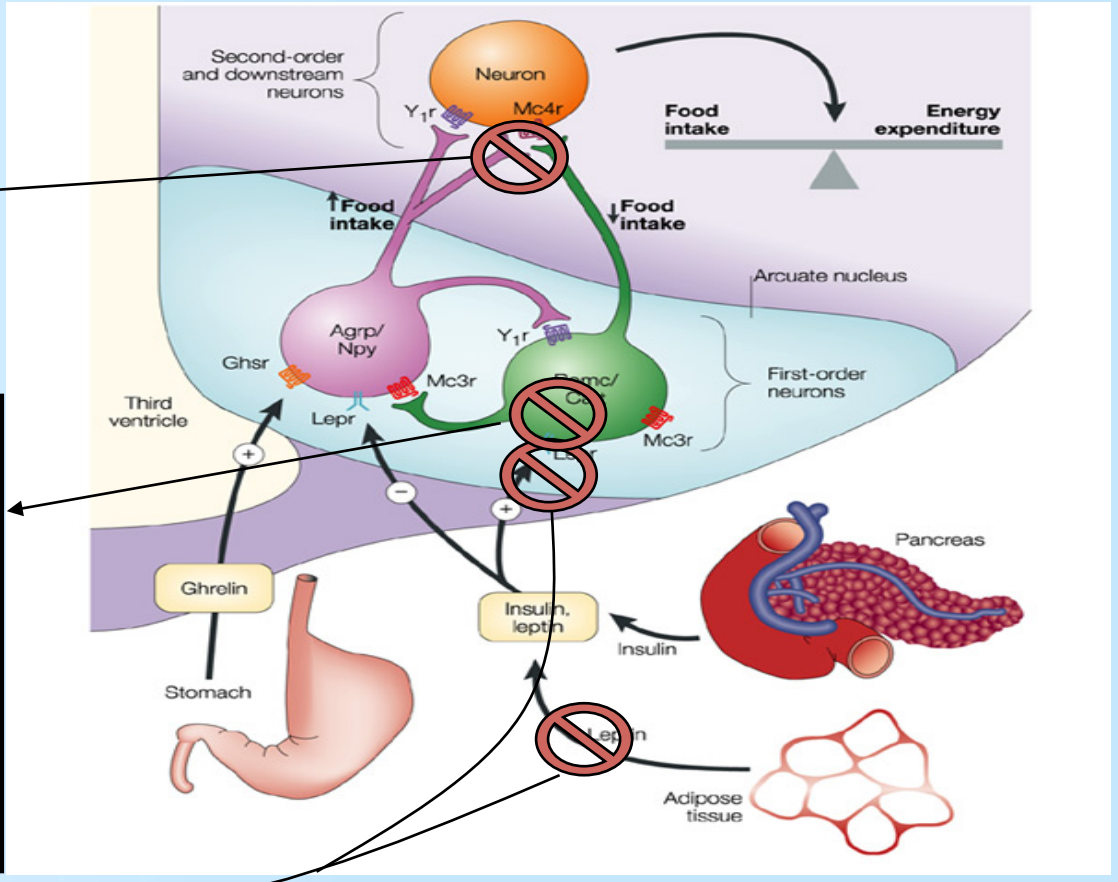
NEJM 2003

JCI 2002





Nature 1998



Barsh and Schwartz.2002; Nat Rev Gen. 3:589-600.

Obesity Results from Defects in Melanocortin-2 Receptor Accessory Protein-2

- Melanocortin-4 receptor is a central control point for food intake – activation inhibits food intake.
- Melanocortin receptor accessory proteins modulate melanocortin activity.
- Melanocortin-2 receptor accessory protein -2 interacts with MCR-4 to reduce its effects on feeding.
- Mice lacking MRAP-2 become obese at a young age.
- 4 human beings with MRAP-2 variants are obese.

Majzoub et al. Science. 2013 Jul 19;341:275-8. doi: 10.1126/science.1233000

The *FTO* (Fused Toe) Genotype Is Associated with Obesity & Diabetes

- 3 large genome wide scans identified *FTO* as a predictor of increased BMI in children and adults
- Located on chromosome 16, it is expressed in brain, pancreas, fat & adrenal gland
- Expression in arcuate nucleus is regulated by fasting and feeding
- *FTO* encodes an enzyme with 2-oxoglutarate-dependent nucleic acid methylase activity

Frayling et al. Science 2007;316:889; Fredriksson et al Endocrinology. 2008;149:2062-71;
Gerken et al. Science 318;2008:1469-72.

Obesity Is Associated with Inflammatory Hypothalamic Injury

"....Consumption of a HFD rapidly induces neuronal injury in a brain area critical for energy homeostasis in mice."

"In human beings there is MRI evidence for gliosis in the hypothalamus....."

Fattening Foods Cause Dropout of POMC Neurons and Glial Ensheathment of ARC Neurons. This May Explain Why It's So Hard To Lose Weight?

Thaler et al. J Clin Invest. 2012 Jan 3;122:153-62.

Our Pleasure System Favors Overeating by Some People

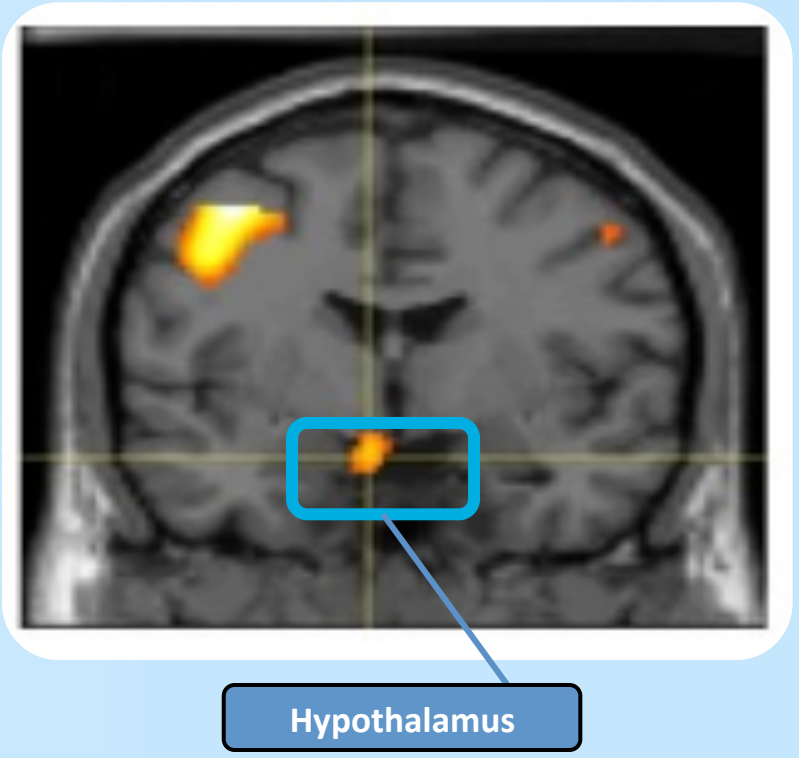
- Stimulation of the ventral tegmental area of the brain releases dopamine into the rostral nucleus accumbens which produces “pleasurable” sensations.
- This circuitry is activated by addictive drugs, alcohol, nicotine, and food.
- Obese people have smaller activation of the pleasure center when they taste food – but more response of this center with the anticipation of food, that is, they crave food more – but like it less.

Linden DJ. The Compass of Pleasure. 2011;NY:Penguin Books.

Food Lights Up the Brain in a PET Scan

PET scan of the brain & hypothalamus

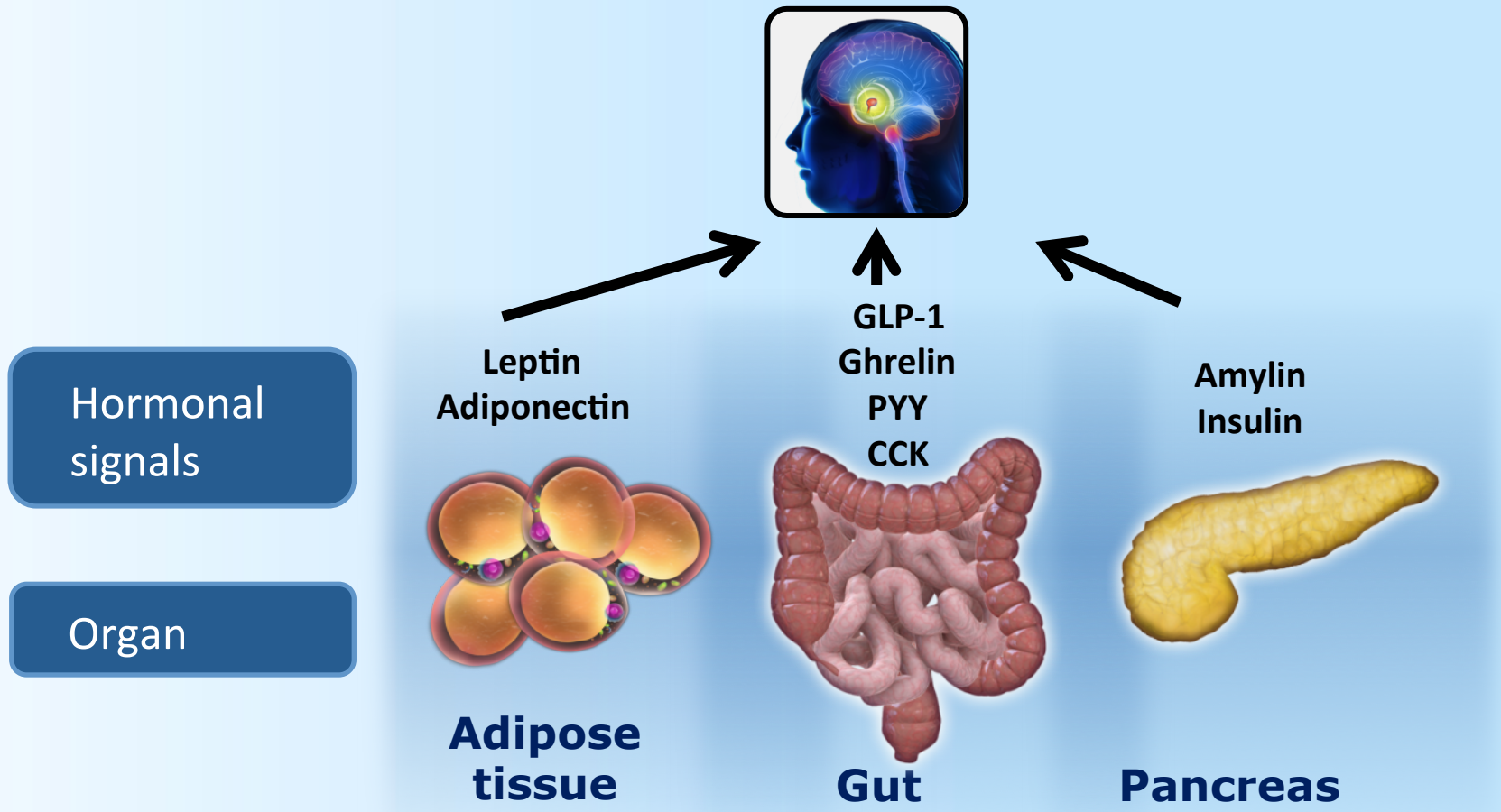
- The hypothalamus and brain are activated by pleasurable response
- Obese people have smaller activation of the pleasure center when they taste food – but more response of this center with the anticipation of food



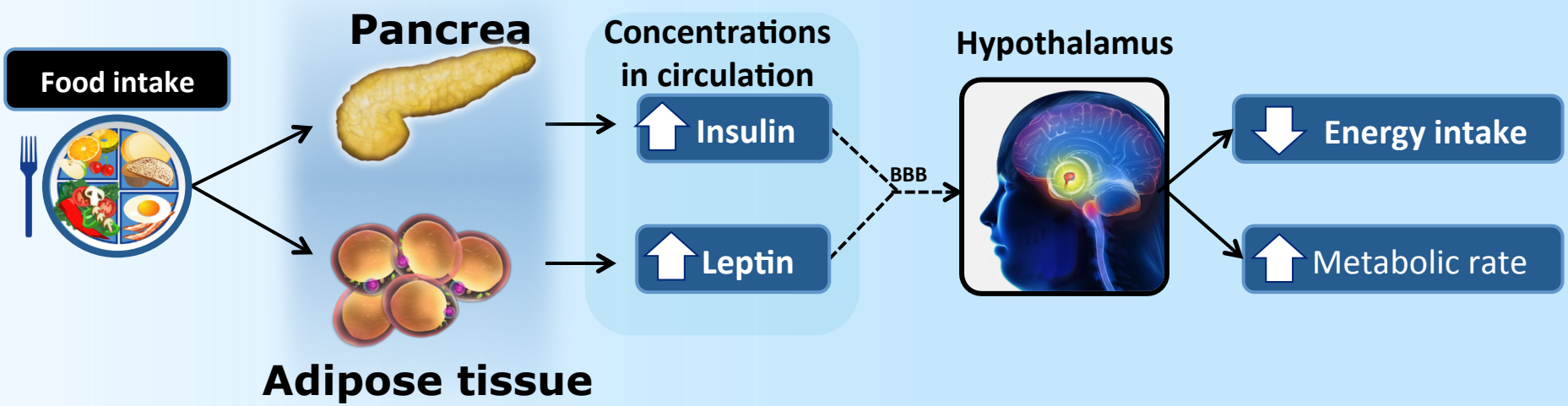
PET, positron emission tomography.

Riediger. Proc Nutr Soc. 2012;71:463-77. Pannacciulli et al. Neuroimage. 2007;35:511–17.

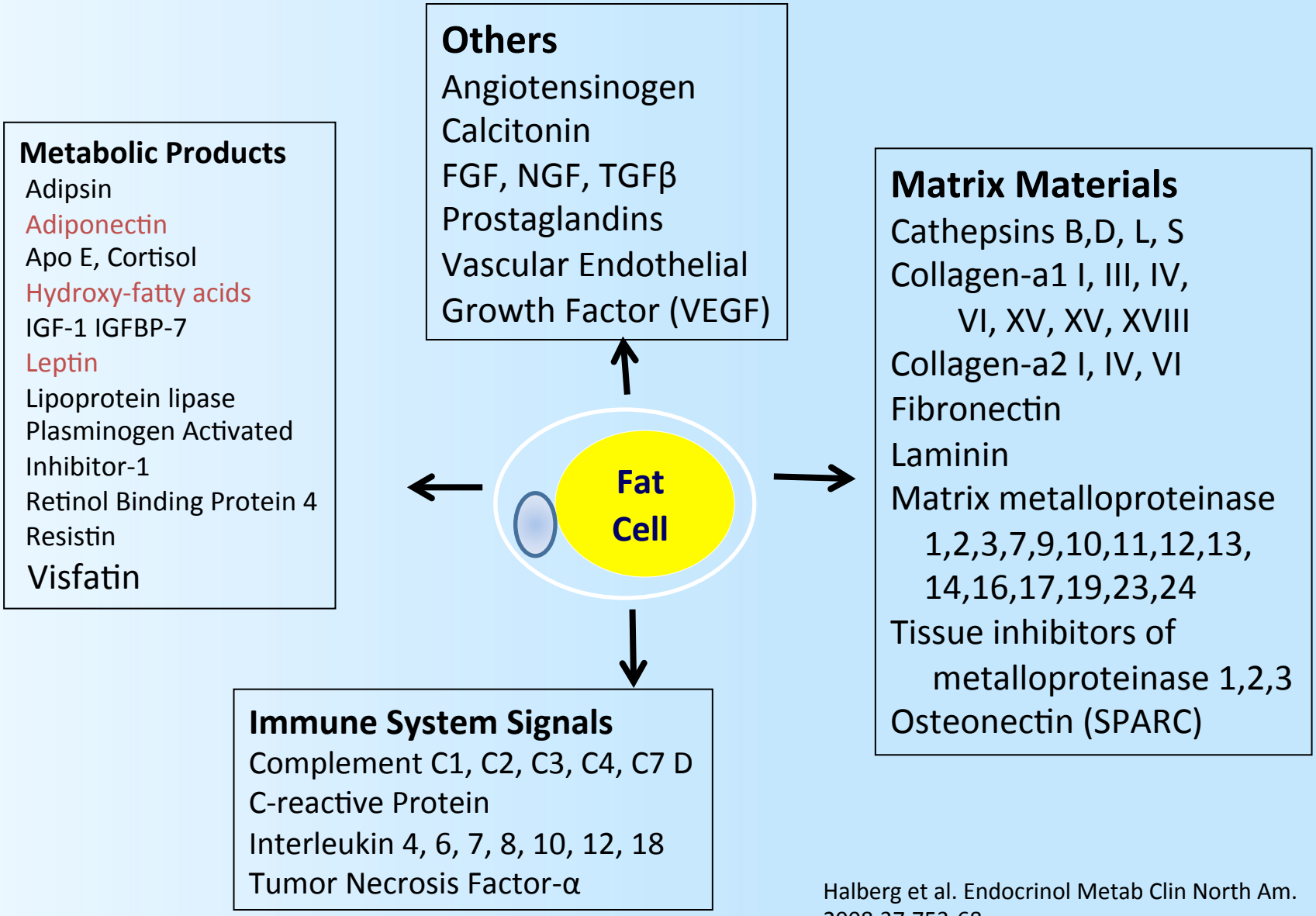
Multiple Hormonal Signals Influence Food Intake



Adiposity Signals in Energy Homeostasis

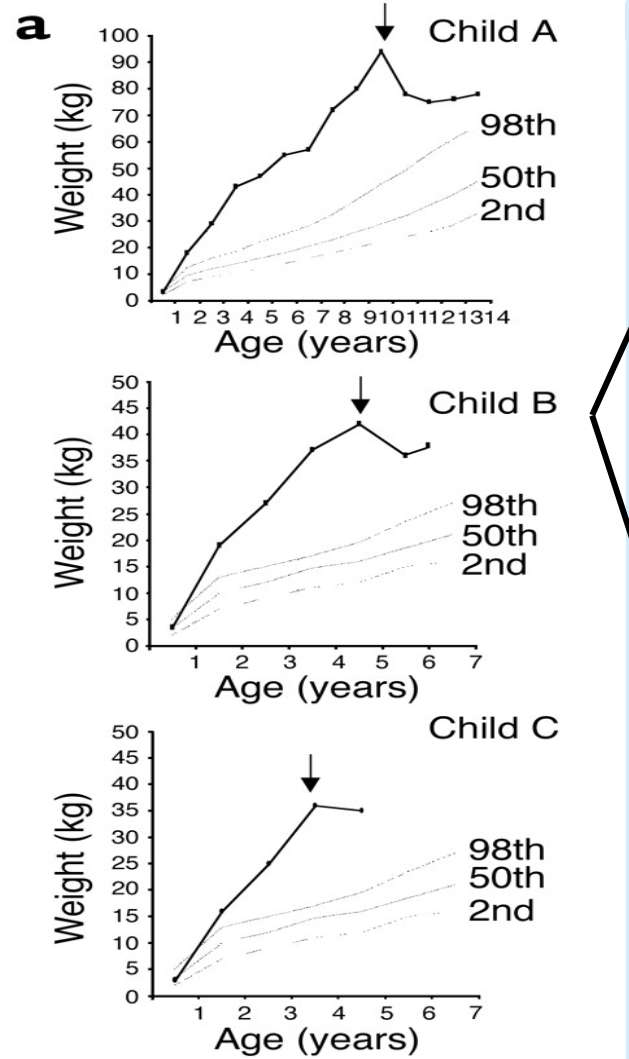


The Fat Cell Is an Endocrine Cell



Halberg et al. Endocrinol Metab Clin North Am. 2008;37:753-68.

Effect of Leptin Treatment in Children with Leptin Deficiency



Farooqi et al. JCI.2002;110:1093-1103.

Hydroxy Fatty Acids Affect Insulin Sensitivity in Fat Cells

- Fat cells store and release fatty acids.
- These fatty acids can also be coupled to other fatty acids with interesting results. One example is Palmitic-acid-9-hydroxy-stearic-acid or 9-PAHSA.
- Levels of this fatty acid (9-PAHSA) correlate highly with insulin sensitivity.
- PAHSA administration in mice improves glucose tolerance and stimulates GLP-1 and insulin secretion.
- PAHSAs reduce inflammation in adipose tissue and may prove a new target in the fight against diabetes and obesity.

Yore et al. Cell. 2014;159:318-32.

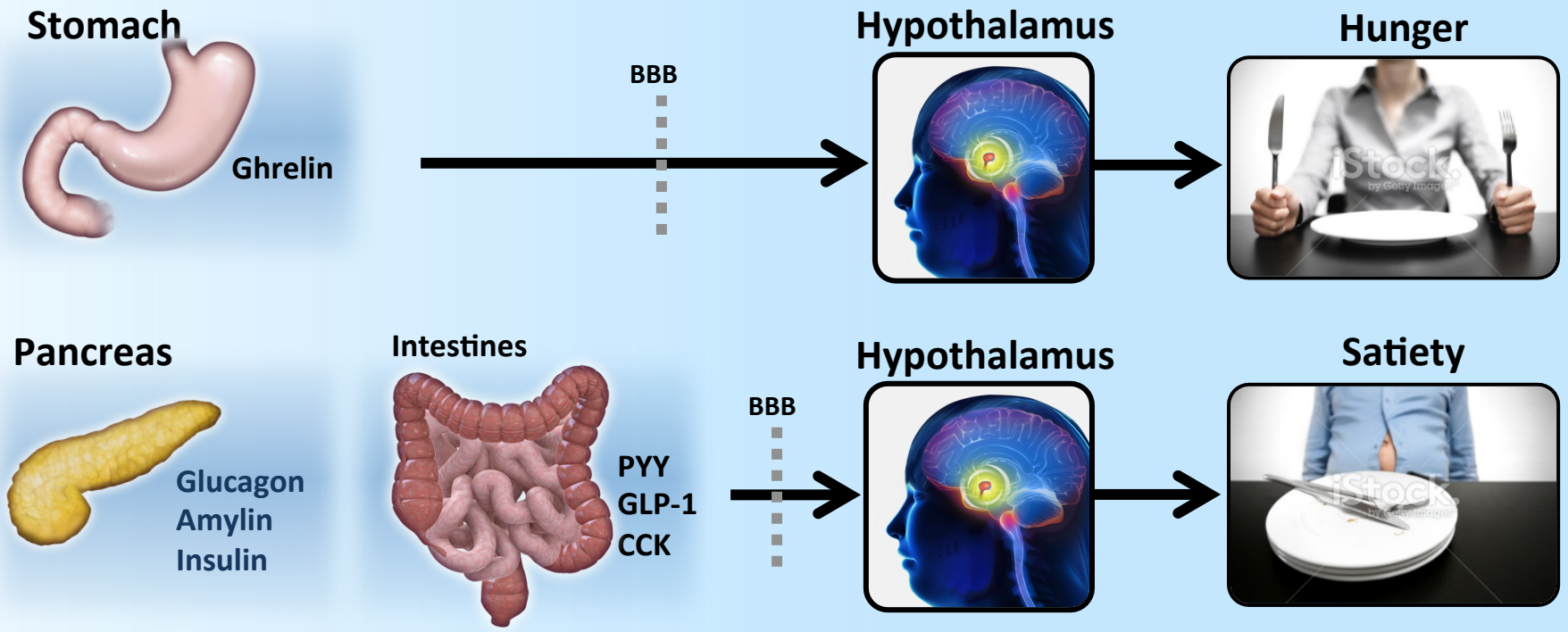
Multiple Hormonal Signals Influence Appetite

Gut hormones	Food intake	Site of secretion
GLP-1	↓	Intestine
PYY	↓	Intestine
OXM	↓	Intestine
CCK	↓	Intestine
PP	↓	Pancreas
Glucagon	↓	Pancreas
Amylin	↓	Pancreas
Ghrelin	↑	Stomach

CCK, cholecystokinin; GLP-1, glucagon-like peptide-1; OXM, oxyntomodulin; PP, pancreatic polypeptide; PYY, peptide YY .

Suzuki K et al. Exp Diabetes Res. 2012;2012:824305.

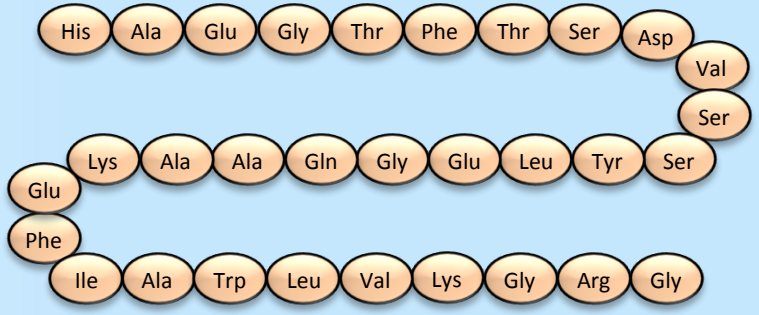
GI Signals Usually Reduce Food Intake, But Can Increase It



GLP-1 Appears to be the Most Important GI Signal to Stop Feeding

- GLP-1 is a 31 amino acid peptide
- Gut hormone—member of incretin family
- Primarily secreted in the small intestine (L-cells) and brain.
- Half life of 1.5-2 min
- Enzymatically degraded by DPP-4 in circulation

Human endogenous GLP-1



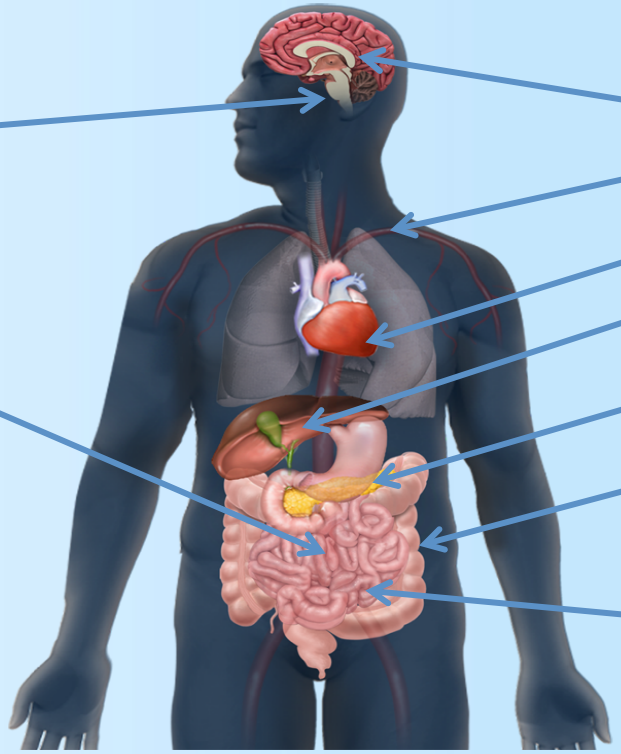
DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1.

Drucker et al. Lancet 2006;368:1696–705.

Tissues That Make GLP-1 a Location of Its Receptors

GLP-1 is secreted by:

- Nucleus tractus solitarus
- L-cells of the gut



GLP-1R is expressed in:

- Brain
- Endothelium
- Myocardium
- Liver
- Pancreas
- Kidney
- Gastrointestinal tract

Merchenthaler et al. J Comp Neurol. 1999;403:261-280; Baggio et al. Gastroenterology. 2007;132:2131-57; Ban et al. Circulation. 2008;117:2340-50; Vrang et al. Prog Neurobiol. 2010;92:442-62; Pyke et al. Endocrinology. 2014;155:1280-90.

GLP-1 Effects on the Gastrointestinal and Central Nervous Systems

Gastric emptying

Acid secretion

Satiety

Energy intake

Satiety signals

Fullness

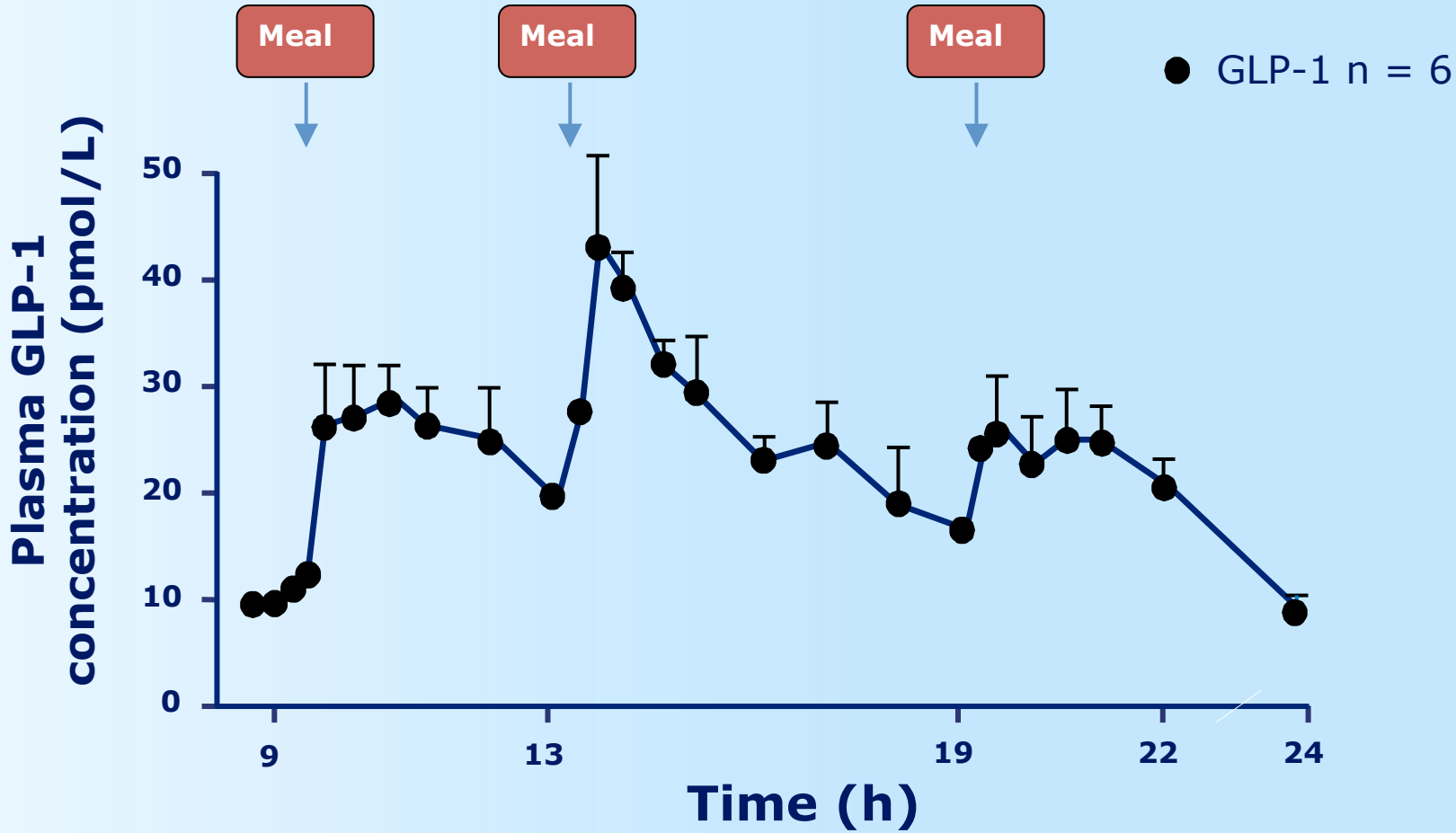
Hunger

Food consumption

GLP-1, glucagon-like peptide-1.

Holst. Physiol Rev. 2007;87:1409-39.

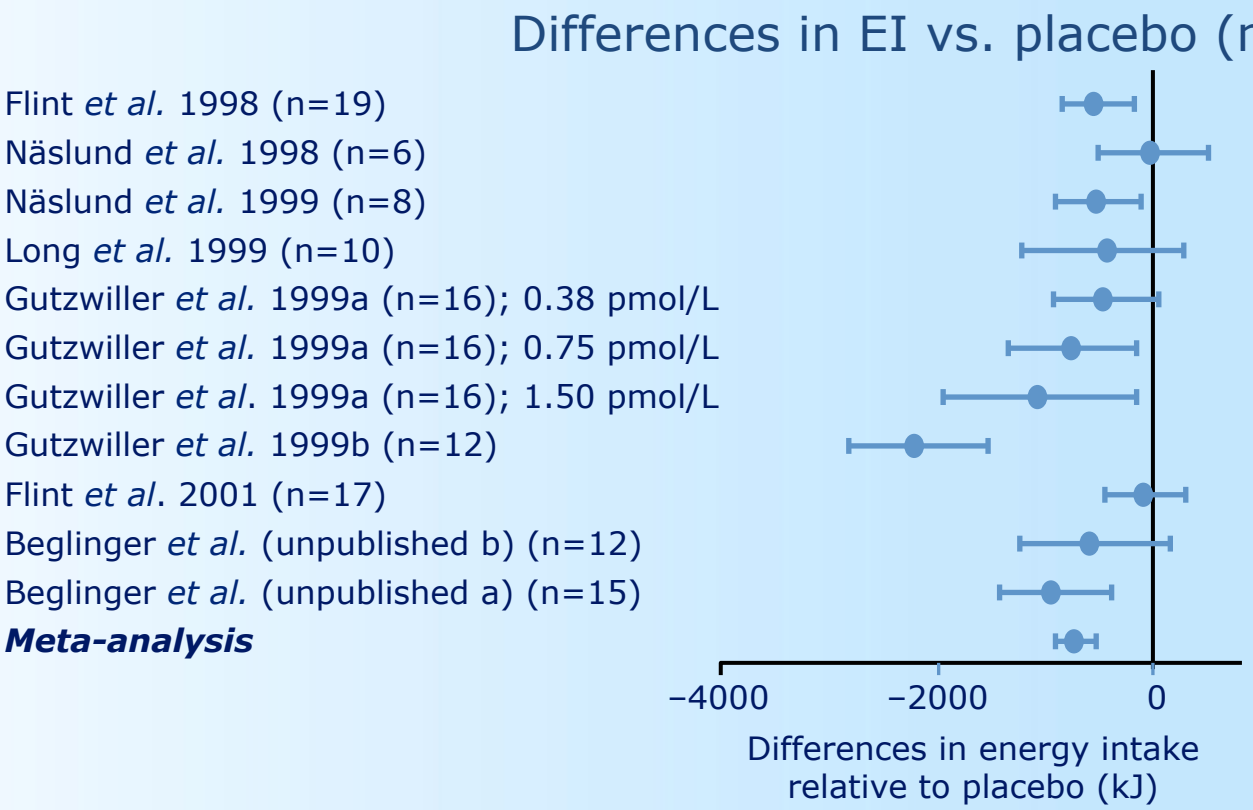
Glucagon Is Secreted in Response to Meals



GLP-1, glucagon-like peptide-1.

Orskov et al. Scand J Gastroenterol 1996;31:665–70.

GLP-1 reduces energy intake in humans



Mean reduction in *ad libitum* energy intake of 727 kJ (*P* <.001) or 11.7% (*P* <.001), compared with control infusion

Data are mean and 95% CI.

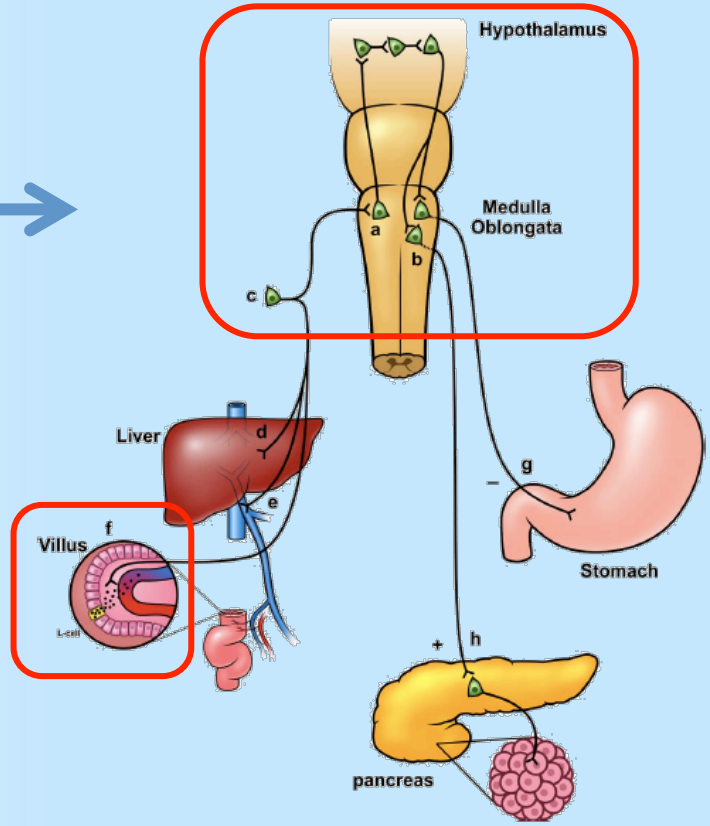
EI, energy intake; GLP-1, glucagon-like peptide-1.

Verdich et al. J Clin Endocrinol Metab 2001;86:4382–9.

Neural pathway of GLP-1

- GLP-1 receptors are widely distributed in the brain

- GLP-1 secretion is stimulated by nutrients in the gut lumen and activates sensory afferent neurons, which may in turn activate neurons of NTS



GLP-1, glucagon-like peptide-1; NTS, nucleus tractus solitarius.

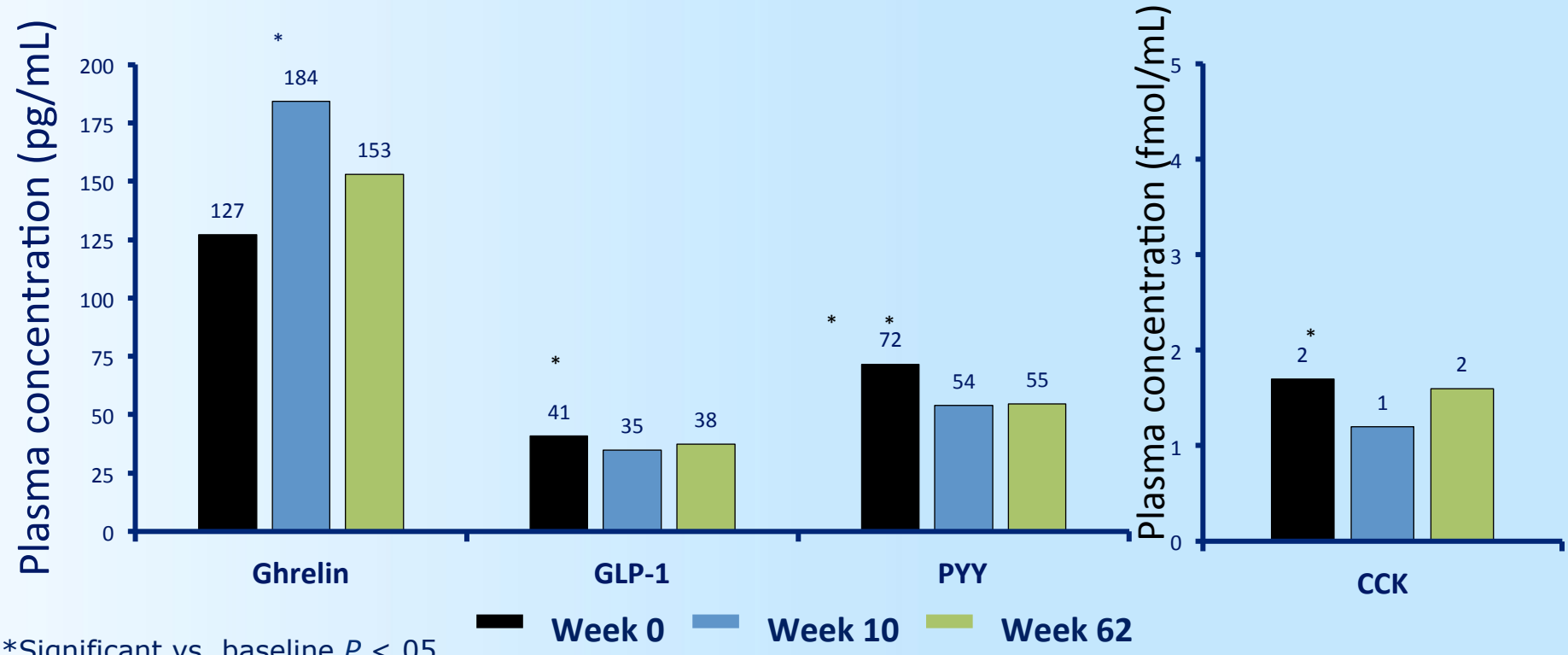
Holst JJ. Int J Obes. 2013;37:1161–68; Holst JJ. Physiol Rev. 2007;87:1409-39.

So Why Does the Homeostatic System Fail and Obesity Develop?

- Genetics and genetic variability:
- Environmental factors:
  - Hedonic or pleasurable responses overwhelm the homeostatic controls
  - Compensatory hormonal and metabolic changes to weight loss drive weight regain

Fasting Gut Hormonal Changes to Weight Loss

Hunger hormones increase — satiety hormones decrease



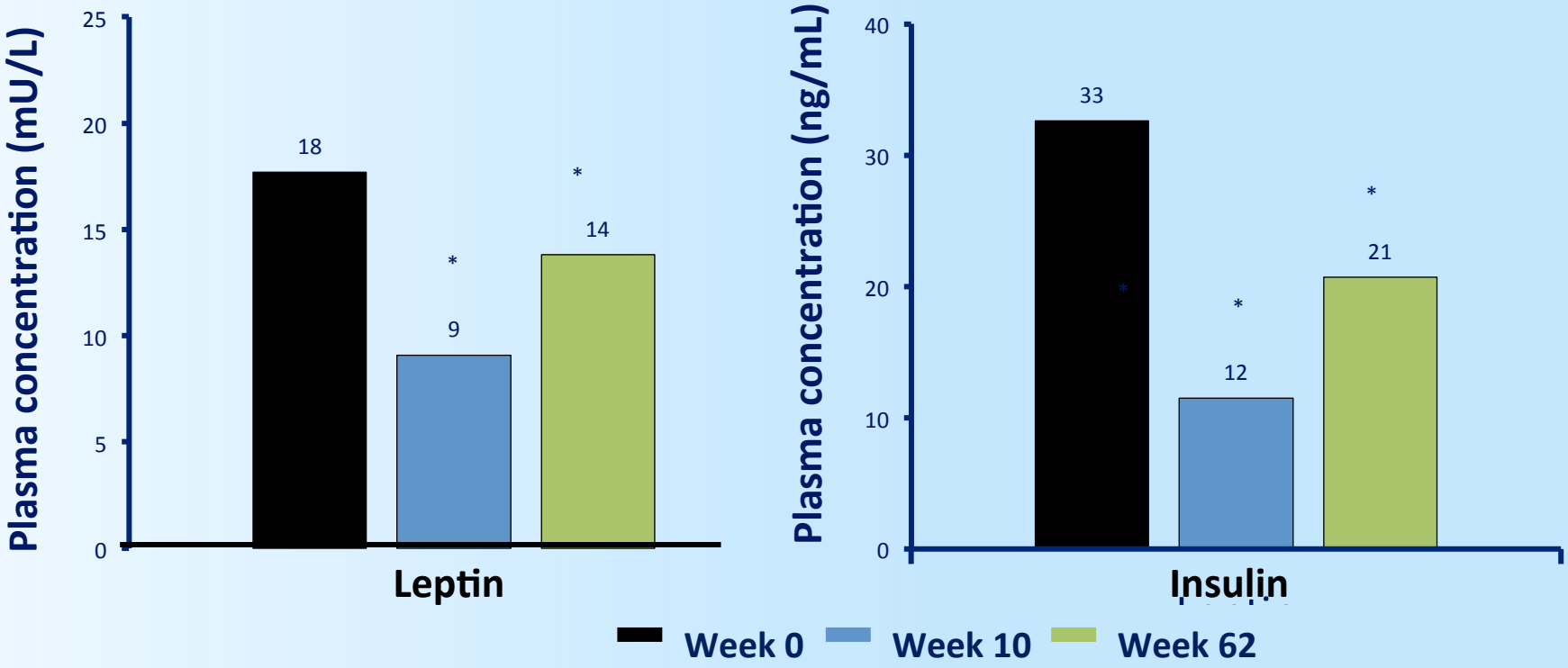
*Significant vs. baseline $P < .05$.

CCK, cholecystokinin; GLP-1, glucagon-like peptide-1; PYY, peptide YY.

Sumithran et al. N Engl J Med 2011;365:1597–604.

Fasting Adipose Hormonal Changes to Weight Loss

Decrease in adiposity hormones insulin and leptin



*Significant vs. baseline $P \leq .02$.

Sumithran et al. N Engl J Med. 2011;365:1597–604.

Metabolic Adaptations to Weight Loss Favor Weight Regain

- ↑ Ghrelin, ↓ Leptin, PYY → ↑ Hunger
- ↓ Energy Expenditure
- No increase in fat oxidation
- ↓ T3, T4 levels (cold intolerance, hair loss, dry skin)
- ↓ Sympathetic nervous system (bradycardia)

Gut Microbiota and Obesity

- Gut microbes contribute to
  1. Energy homeostasis
  2. Gut permeability in obesity and T2D
  3. Low grade inflammation
- Prebiotics are power tools for prevention
- 99% of gut microbiota are from 2 phyla – Bacteroidetes and Firmicutes
- Akkermansia muciniphila is a new and potentially important gut bacterium

Summary

- Body weight is a regulated system
- Hedonic rewards from the pleasure of food may override the inhibitory system
- MRAP-2, FTO and Inflammatory changes in brain are a few of mechanisms for modulation of body fat
- GLP-1, Oxyntomodulin, PYY3-36 and Ghrelin are important signals to inhibit or initiate feeding
- Fat is an endocrine tissue – fat cells make leptin and adiponectin, two important products, as well as esters of hydroxy-fatty acids
- Gut microbiome affects feed efficiency and disease

Treatment for Obesity

"The human body is composed
Of head and limbs and torso
Kept slim by gents
At great expense
By ladies even more so."

-Ogden Nash

That's All Folks!

Advances in Therapeutic Interventions for Weight Loss: What Is the Evidence and Where Are We Going?

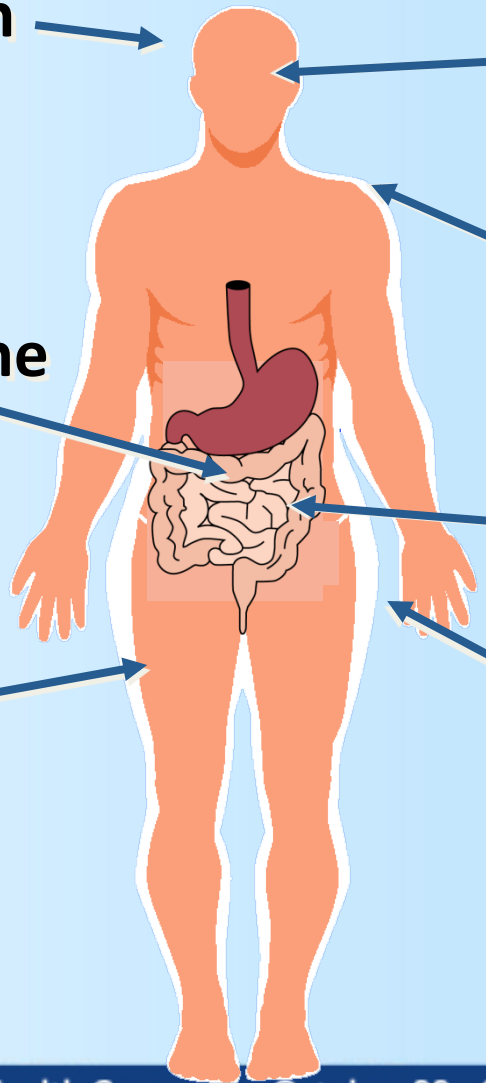
Michael D. Jensen, M.D.

Professor of Medicine

Mayo Clinic College of Medicine

Rochester, MN USA

Potential Sites for Intervention



Appetite regulation

Increase physical activity

Increase BAT

Mimic gut hormone effects

Increase GI or urinary losses

Uncouple mitochondria

Mimic adipose tissue effects

BAT=brown adipose tissue

Case Study

44-year-old man – depression, allergies, seizure disorder, and regular marijuana user. Which compounds might affect his appetite?

1) Bupropion

2) Cannabis

3) Diphenhydramine

4) Topiramate

Appetite Regulation via Small Molecule Pathways

- **Serotonin –** lorcaserin (selective serotonin 5-HT2C agonist)
- **Norepinephrine –** phentermine
- **Dopamine –** no specific compounds
- **Cannabinoids –** rimonabant,* etc.
- **Histamine –** Histamine receptors (H1, H2, H3) in the hypothalamus influence food intake; H1 receptors decrease food intake

***Rimonabant withdrawn from European market in 2009; not approved in US.**

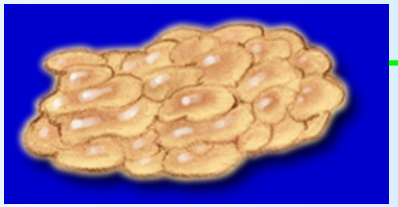
Small Molecule Effects on Appetite – Complex/Uncertain Mechanisms

- **Topiramate/zonisamide** – glutamate pathway?
- **Bupropion** – antidepressant; inhibitor of norepinephrine, dopamine reuptake, enhanced noradrenergic transmission/ stimulate POMC neurons?

POMC=pro-opiomelanocortin

Appetite Regulation

White adipose tissue



Leptin

Vagus nerve → Nucleus of solitary tract

Noradrenergic
Endocannabinoid
Histamine and
Serotonin systems

Paraventricular nucleus

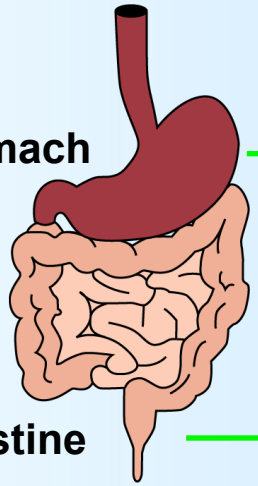
Lateral hypothalamus

Cerebral cortex

Sympathetic nervous system

Brainstem nuclei

Stomach



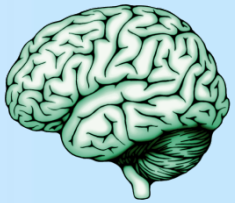
Ghrelin
obestatin

NPY/AGRP

GLP-1

CCK

Intestine



PYY_{3-36}

oxyntomodulin

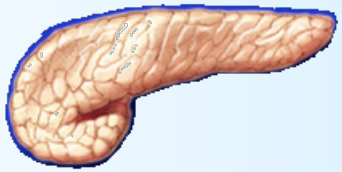
POMC

↓ Feeding

↑ Metabolic rate?

↓ Gastric emptying

Pancreas



Insulin
amylin

Hypothalamic arcuate nucleus neurons

NPY/AGRP=neuropeptide Y/agouti-related peptide; CCK=cholecystokinin; PYY_{3-36}=peptide Y 3-36

Adapted from Neary et al. Clin Endocrinol. 2004;60:153-60.

CNS Appetite Pathway Results

- **5 HT/serotonin**
  - **Fenfluramine –** pulmonary hypertension and heart valve damage
  - **Lorcaserin –** modest (3%> placebo) weight loss
- **Norepinephrine –** amphetamine-like compounds, sibutramine
- **Cannabinoids –** rimonabant* - depression

CNS=central nervous system

***Rimonabant withdrawn from European market in 2009; not approved in US.**

Appetite Regulation via Combined Small Molecule Pathways

- **Topiramate and phentermine –** fewer cognitive side effects than topiramate alone; 1-yr weight loss 8%>placebo
- **Bupropion** stimulates hypothalamic POMC neurons, reducing food intake **+ naltrexone** to block opioid receptor-mediated POMC auto-inhibition, synergistically augmenting POMC effects; 1-yr weight loss 5%>placebo

Compounds That Modulate Multiple CNS Monoamine Pathways

- **Phentermine –** releases both dopamine and norepinephrine; approved for short-term use and prescribers may be monitored by state boards
- **Tesofensine*** **–** inhibitor of norepinephrine, dopamine, and serotonin reuptake; may indirectly stimulate the cholinergic system
  - High adverse event drop-out rates, activates sympathetic system

*Investigational

Current Medications

Table 1. Drugs With US Food and Drug Administration–Approved Indication for Obesity

Generic Drug (Proprietary Name[s] Dose Frequency/d)	Mechanism of Action	Wholesale Price/mo, $[a]	1-y Weight Change Relative to Placebo, Mean (95% CI), kg[b]	Common Adverse Effects
Short-term approval[c]				
Phentermine 15-37.5 mg (Adipex-P, Fastin, Oby-Cap, Ionamin, Others; 1×)[d]	Noradrenergic causing appetite suppression	6-45	Not included	Insomnia, elevation in heart rate, dry mouth, taste alterations, dizziness, tremors, headache, diarrhea, constipation, vomiting, gastrointestinal distress, anxiety, and restlessness[e]
Diethylpropion 25 mg or 75 mg, SR (Tenuate, Tenuate Dospan, Tepanil; low dose, 3×; SR dose, 1×)[d]	Noradrenergic causing appetite suppression	47-120	Not included	Same as phentermine[e]
Phendimetrazine 17.5-70 mg or 105 mg, SR (Bontril; lower doses, 2-3×; SR dose, 1×)[f]	Noradrenergic causing appetite suppression	6-20	Not included	Same as phentermine[e]
Benzphetamine 25-50 mg (Didrex; 1-3×)[f]	Noradrenergic causing appetite suppression	20-50	Not included	Same as phentermine[e]
Long-term approval[c]				
Orlistat 60 mg (Alli) or 120 mg (Xenical; 3× within 1 h of a fat-containing meal)[g]	Lipase inhibitor causing excretion of approximately 30% of ingested triglycerides in stool	60 mg, 45 120 mg, 207	60 mg, −2.5 kg (−1.5 to −3.5) 120 mg, −3.4 kg (−3.2 to −3.6)	Oily spotting, flatus with discharge, fecal urgency, fatty oily stool, increased defecation, fecal incontinence[h]
Lorcaserin 10 mg (Belviq; 2×)[d]	Highly selective serotonergic 5-HT2C receptor agonist causing appetite suppression	240	−3.2 kg (−2.7 to −3.8)	Headache, dizziness, fatigue, nausea, dry mouth, cough, and constipation; and in patients with type 2 diabetes, back pain, cough, and hypoglycemia[h]
Phentermine plus topiramate-ER (Qsymia; 3.75 mg/23 mg for 2 weeks, increased to 7.5 mg/46 mg, escalating to a max of 15 mg/92 mg; 1×)[d]	Noradrenergic + GABA-receptor activator, kainite /AMPA glutamate receptor inhibitor causing appetite suppression	140-195	7.5 mg/46 mg, −6.7 kg (−5.9 to −7.5) 15 mg/92 mg, −8.9 kg (−8.3 to −9.4)	Paresthesias dizziness, taste alterations, insomnia, constipation, dry mouth, elevation in heart rate, memory or cognitive changes[h]

Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; ER, extended release; GABA, γ-aminobutyric acid.

[a] Reference prices[9] as of March 8, 2013.

[b] Weight change data are relative to placebo using intent-to-treat analyses for each medication at 1 year. No studies for older noradrenergic agents met inclusion criteria for length of treatment, sample size, and attrition.

[c] Food and Drug Administration–approved for short-term (ie, a few weeks) or long-term use.

[d] Medications listed on Drug Enforcement Administration Schedule IV are associated with a lower risk of abuse than medications on Schedule III.

[e] Common adverse events for noradrenergic agents include those listed as common in Prescription Medications for the Treatment of Obesity[10] because adverse event frequency is not available in drug package inserts for these agents.

[f] Drug Enforcement Administration Schedule III medication.

[g] Orlistat is a non-Drug Enforcement Administration–scheduled drug.

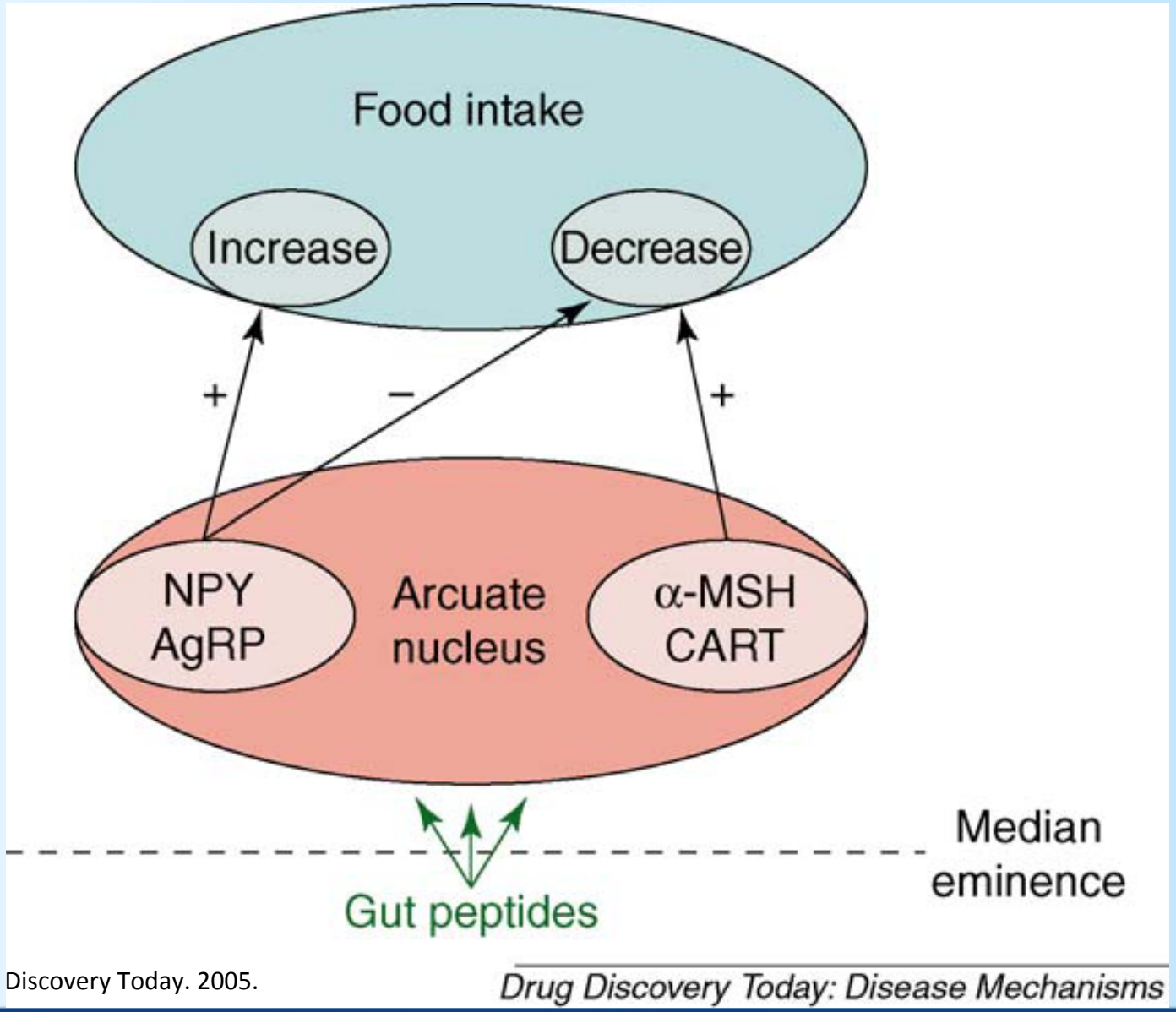
[h] For orlistat, lorcaserin, and phentermine plus topiramate-ER, common adverse events are those listed in the drug package inserts[11-13] that are reported to occur more frequently than placebo and with more than 5% prevalence. See full prescribing information for all adverse effects, cautions, and contraindications.

Yanovski & Yanovski. JAMA. 2014;311:74-86.

Summary

- The small molecule approach to appetite regulation is littered with failed compounds
- Unanticipated side effects are the #1 cause of failure/withdrawal
- Efficacy of the approved compounds is modest by standards of patient expectations, but getting better

Hypothalamic Targets



α-MSH=alpha melanocyte-stimulating hormone; CART=cocaine-and-amphetamine-regulated transcript

Chaudhri et al. Drug Discovery Today. 2005.

Attempts to Modulate CNS Peptide Pathways

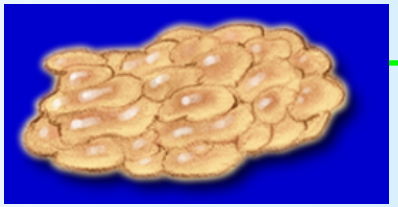
- NPY antagonism (Y_5-receptor blockade) – 2 early compounds induced statistically (not clinically) significant weight loss.
- Melanin concentrating hormone (MCH) – MCH1 receptor antagonists – QT interval problems and sleep disturbances
- α-melanocyte stimulating hormone (αMSH) – MC4 agonists (bremelanotide) – sympathetic nervous system activation side effects

Summary

- Targeting more specific pathways has not yet proved successful
- Again, unanticipated side effects are the #1 cause of failure/withdrawal
- Limited efficacy of the NPY antagonist compounds

Appetite Regulation

White adipose tissue



Leptin

Vagus nerve

Nucleus of solitary tract

Noradrenergic
Endocannabinoid
Histamine and
Serotonin systems

Paraventricular nucleus

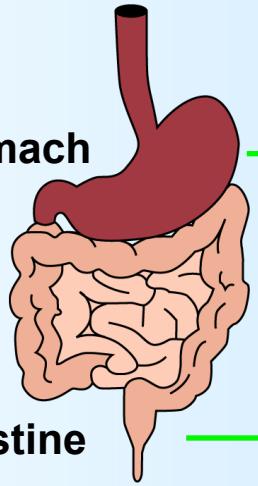
Lateral hypothalamus

Cerebral cortex

Sympathetic nervous system

Brainstem nuclei

Stomach



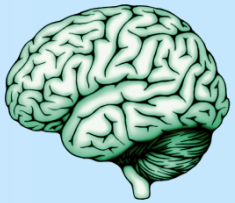
Ghrelin
obestatin

NPY/AGRP

GLP-1

CCK

Intestine

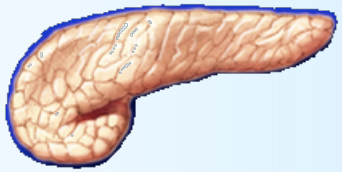


PYY_{3-36}

oxyntomodulin

POMC

Pancreas



Insulin
amylin

Hypothalamic arcuate nucleus neurons

↓ Feeding

↑ Metabolic rate?

↓ Gastric emptying

Adapted from Neary et al. Clin Endocrinol. 2004;60:153-60.

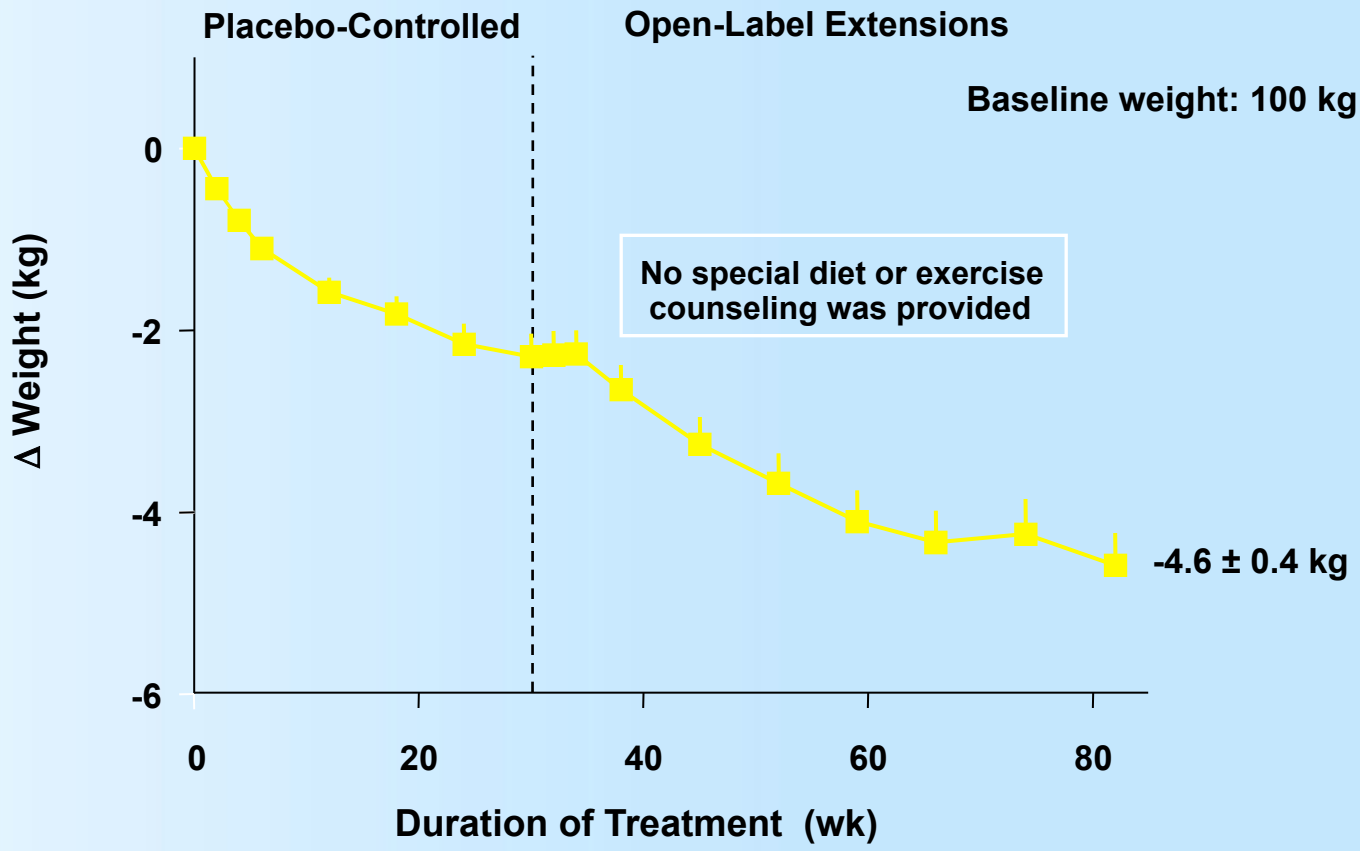
Gut and Adipose Hormone Approaches for Appetite Regulation

- GLP-1 agonists
- PYY_{3-36}
- Oxyntomodulin
- Ghrelin
- Leptin

GLP-1 Actions

- Developed because GLP-1 increases glucose-responsive insulin secretion
- Enhanced satiety – reduction in meal size rather than in meal frequency
- Delayed gastric emptying
- Exenatide and liraglutide are GLP-1 agonists
- Significant weight loss is a side effect of these medications

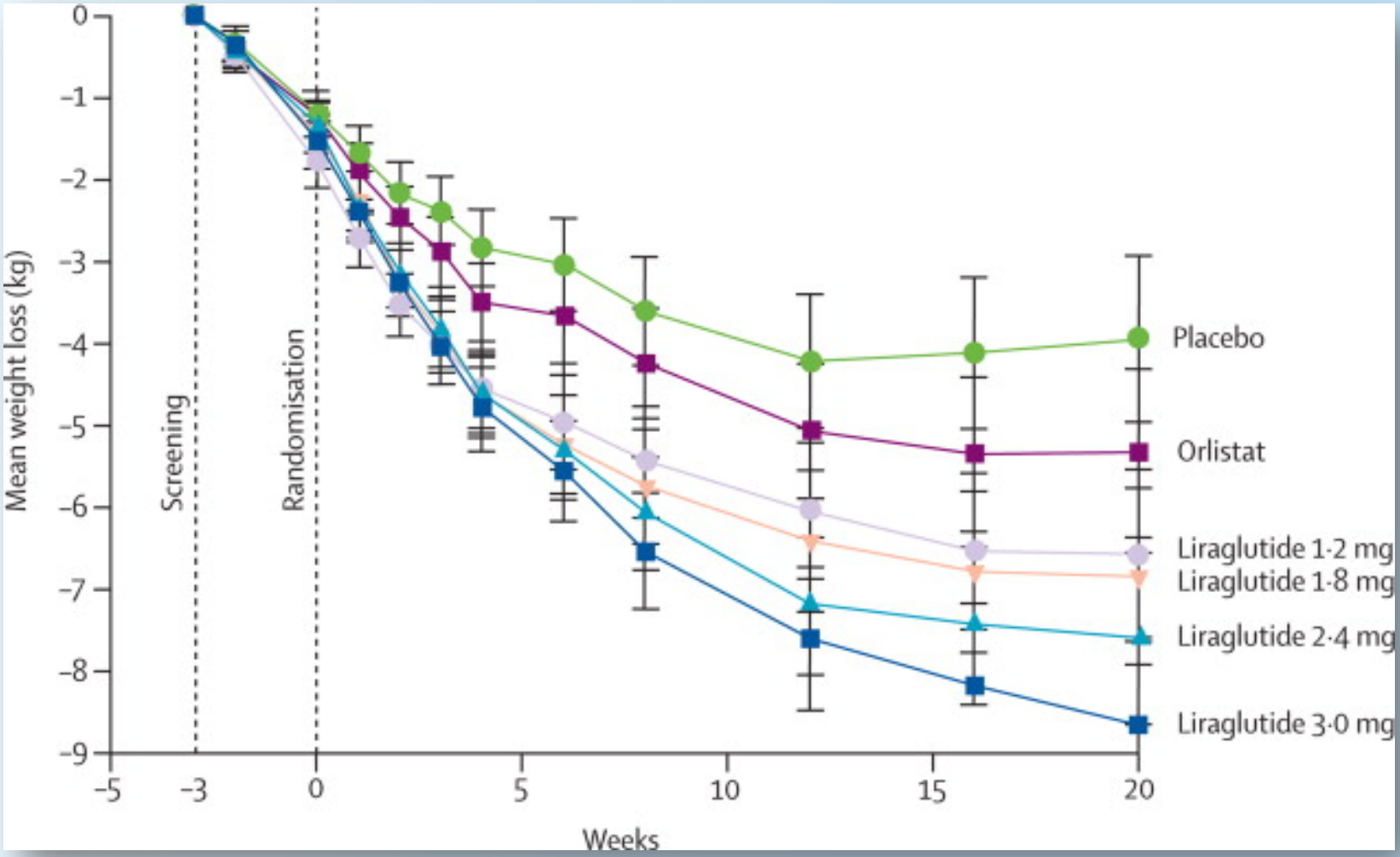
Progressive Weight Reduction Exenatide (GLP-1 receptor agonist)



N = 265; Mean (SE)

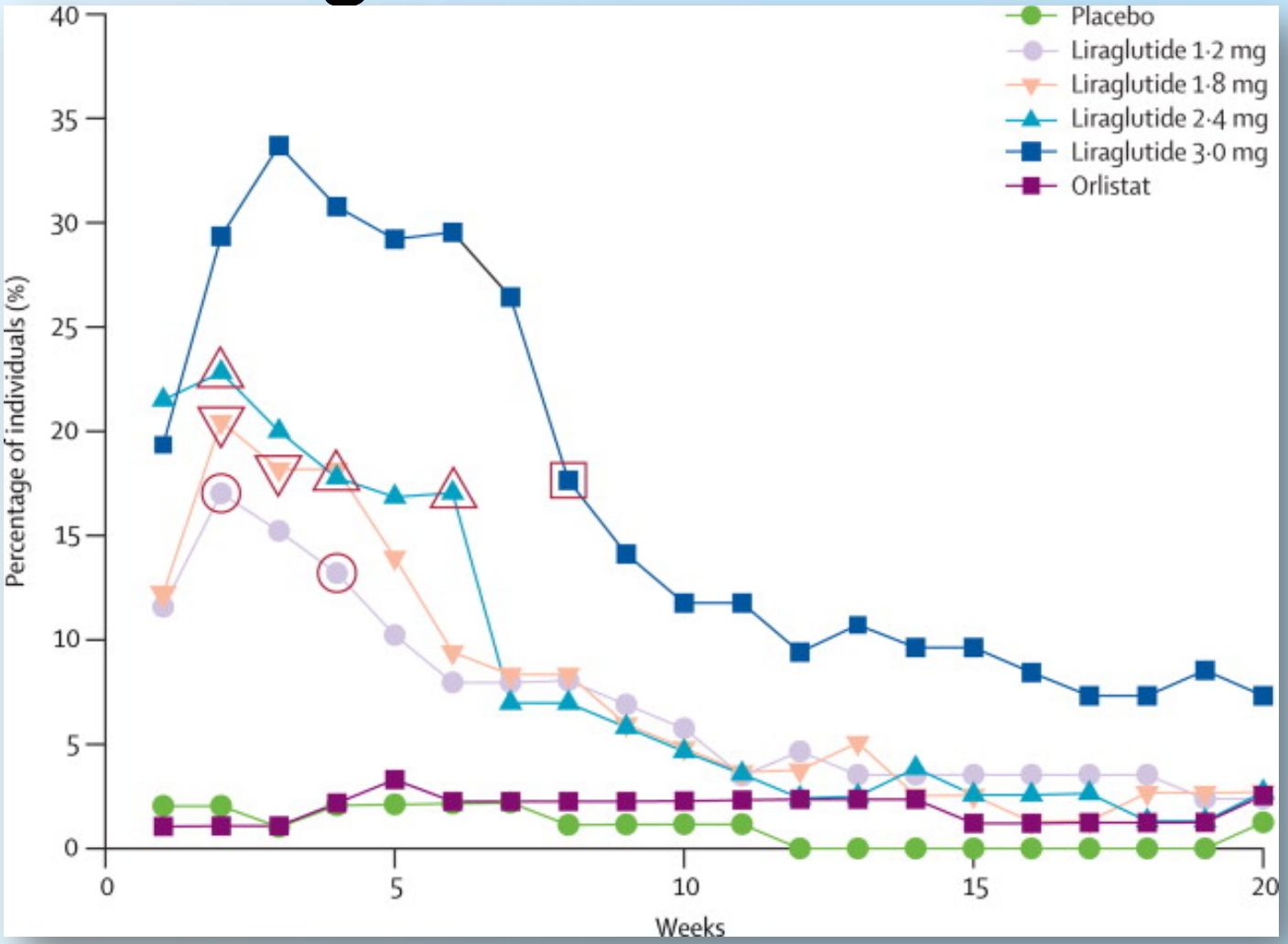
Ratner et al. Diabetes Obes Metab. 2006;8:419-28.

Liraglutide Weight Loss Results



Astrup et al. The Lancet;2009;374:1606 -16.

Liraglutide Side Effects



Percentage of individuals with nausea; each individual who withdrew because of nausea is shown by a red symbol.

Astrup et al. The Lancet;2009;374:1606 -16.

SCALE™ Obesity and Prediabetes trial

- 3,731 participants randomized to treatment with liraglutide 3 mg or placebo in combination with diet and exercise

- Liraglutide 3 mg/d resulted in:
  - body-weight loss of 8% from baseline (vs. 2.6% with placebo, $p<0.0001$)
  - fewer people with obesity and normal blood glucose at baseline progressing to prediabetes (6.9%) at 56 weeks, compared with placebo (19.9%, $p<0.0001$).
  - higher rate of prediabetes reversal compared with placebo (69.7% vs. 32.1%, $p<0.0001$)
  - Significantly greater reductions in BP, improvements in HDL-C, LDL-C, and TG, as well as less use of lipid-lowering and antihypertensive medications

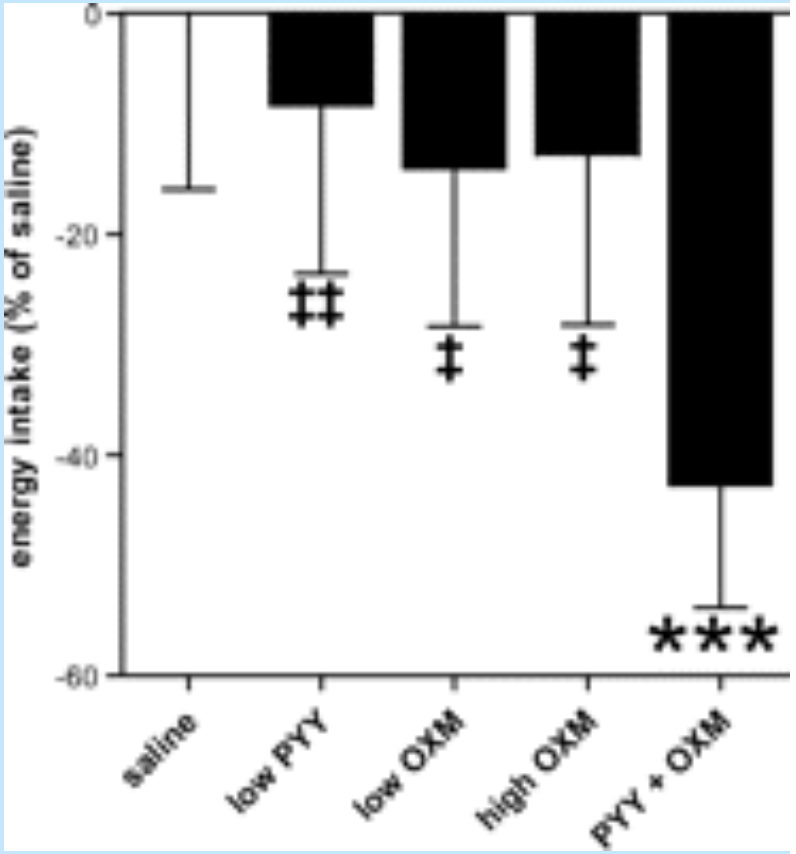
Pi-Sunyer et al.Presented at AACE 23rd Annual Scientific and Clinical Congress. May 14-18, 2014; Las Vegas, NV.

Weight Loss and Obesity Pharmacotherapy

- SCALE trial results not an anomaly
- Most trials find that improvements in glucose, lipid, and blood pressure parameters are in line with those expected from lifestyle weight loss
- Exceptions are medications that:
  - Stimulate sympathetic nervous system (BP doesn't improve as much)
  - Alter lipid metabolism (orlistat lowers LDL more by malabsorption)
  - Anti-diabetics with weight loss effects preferentially lower glucose

PYY_{3-36} and Oxyntomodulin

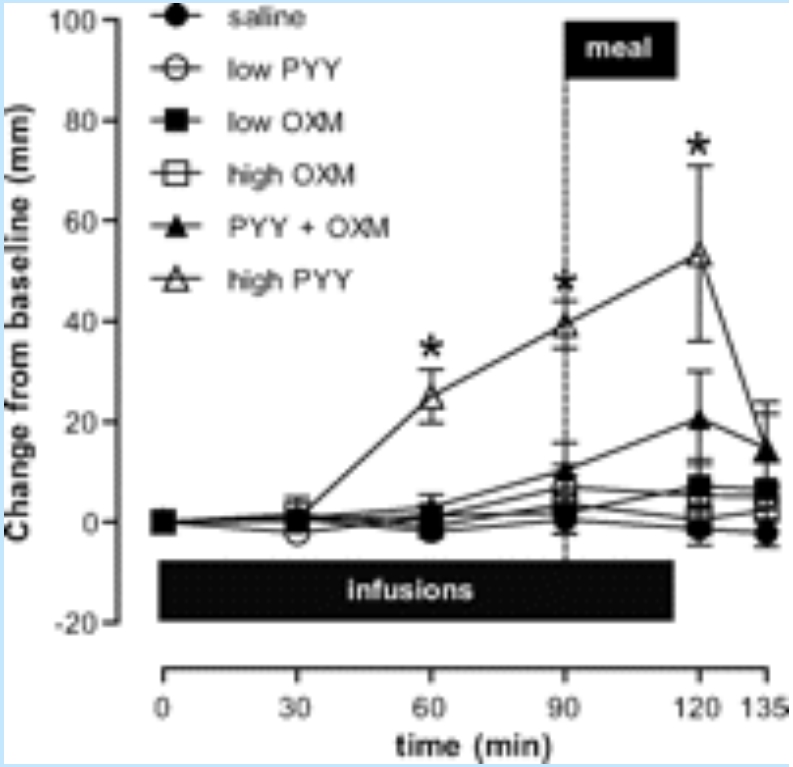
- Oxyntomodulin is a GLP-1 receptor agonist
- These hormones are co-secreted by intestinal L cells in response to meals
- Co-infusion results in substantial reductions in food intake



Field et al Diabetes 2010;59:1635–39.

PYY_{3-36} and Oxyntomodulin

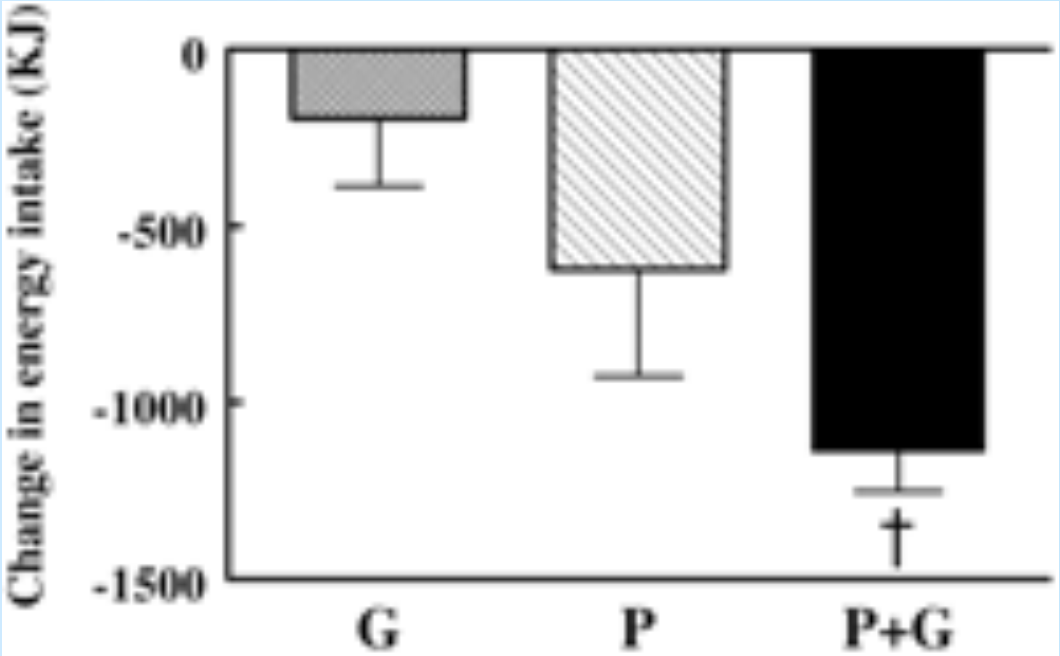
- Higher doses of PYY_{3-36} needed to best reduce food intake
- Also associated with greater ratings of nausea
- When those without nausea excluded the reduction in food intake from combined Rx was ~ 1/3



Field et al Diabetes 2010;59:1635–39.

PYY_{3-36} and GLP-1

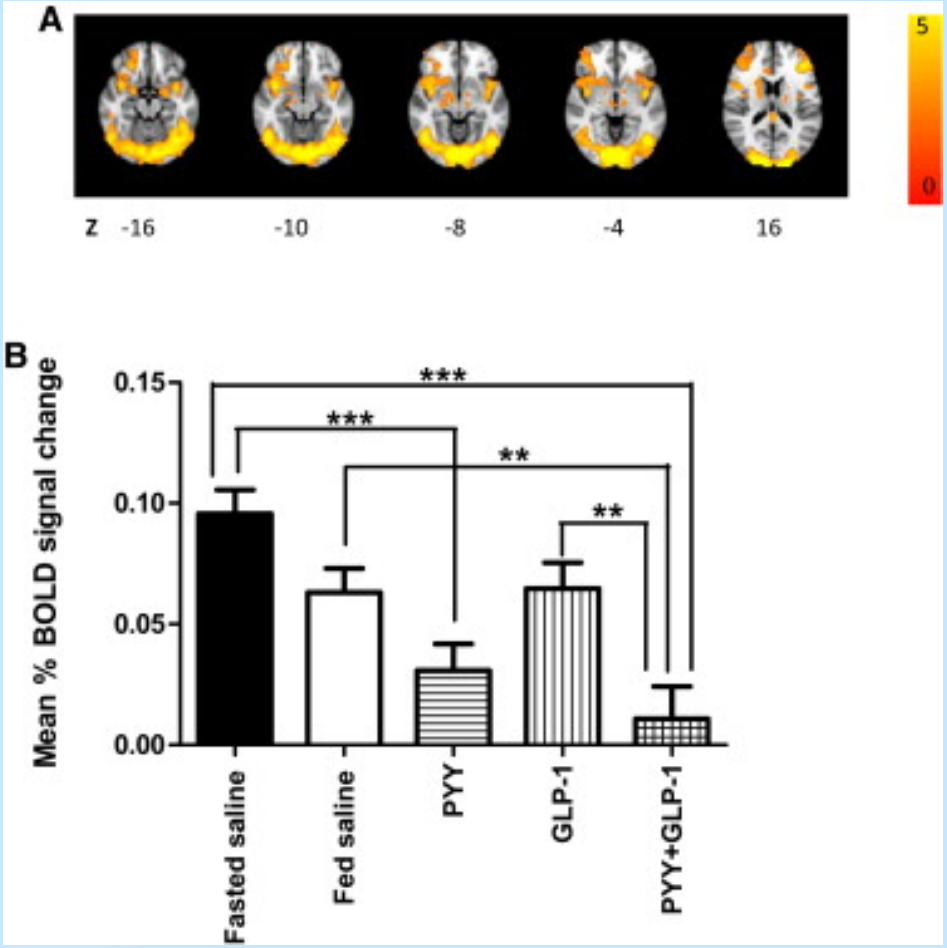
- Similar to finding with PYY_{3-36} and oxyntomodulin, co-infusion of PYY_{3-36} and GLP-1 results in greater reductions in food intake than single infusions of either



Neary et al. Endocrinology 2005;146: 5120–27.

PYY_{3-36} and GLP-1

The changes in activation of brain neural pathways by co-infusion of PYY_{3-36} and GLP-1 are similar to the changes seen with meal ingestion



De Silva et al. Cell Metabolism.Nov 2011.

Amylin Actions

- Co-secreted with insulin
- Enhanced satiety – reduction in meal size rather than in meal frequency
- Delayed gastric emptying
- Pramlintide is an example of an amylin agonist
- Significant weight loss is a side effect of pramlintide

Summary

- Several GI hormones and leptin clearly regulate appetite
- Although they require injection, there seem to be fewer “off target” effects than with other approaches
- Combination therapy appears more effective, but FDA regulations make this a more difficult approach

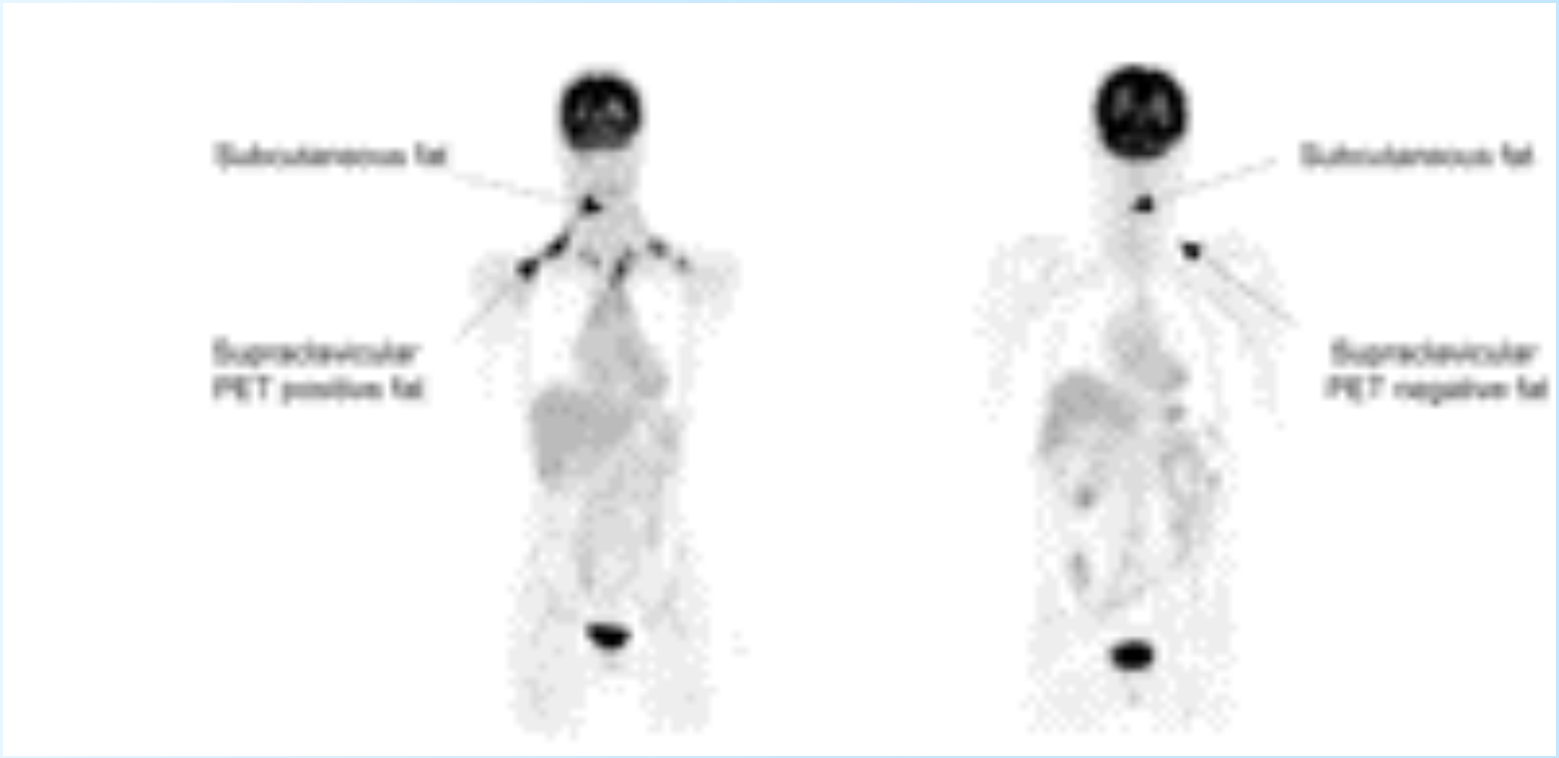
Potential Approaches for Calorie Loss

- **Increase energy expenditure** – passive (increased basal metabolic rate/energy wasting) or promote increased activity
- **Maldigestion –** lipase inhibitor orlistat
- **Urinary glucose losses –** SGLT-2 inhibitors for patients with diabetes

Increasing Energy Expenditure

- **Non-selective attempts at uncoupling mitochondria – β_3 agonists – cardiotoxic**
- **Brown fat?** Previously thought to be restricted to infants
- **CNS activation of spontaneous physical activity –** orexin A, brain-derived neurotrophic factor and neuromedin (all animal studies)

Brown Fat in Adults



- Modest amounts detectable by PET scan under select conditions
- Thermogenic potential limited – amount; duration of activity
- Gene therapy approaches to increase BAT decades away from approval

Summary

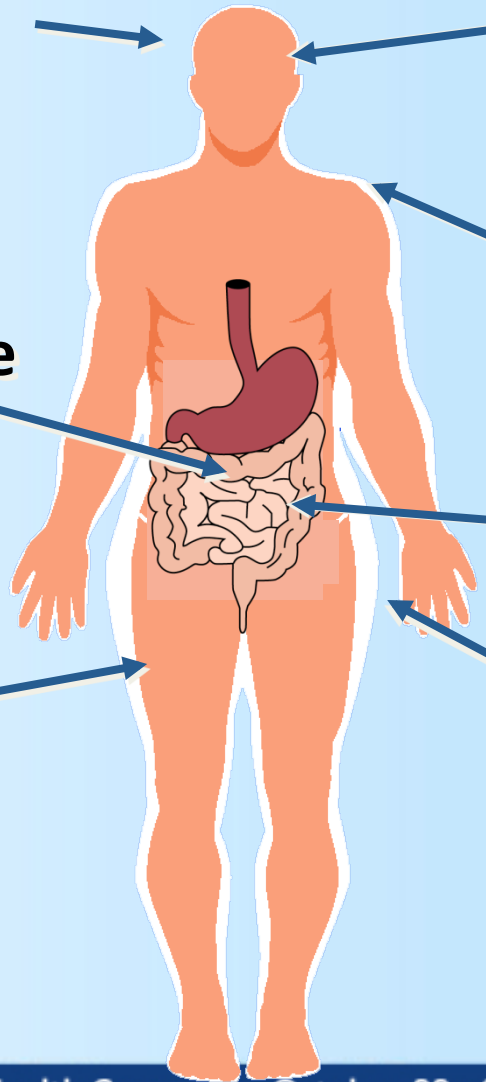
- Potentially attractive target
- Uncoupling approach seems a poor idea for skeletal muscle
- Toxicity a major concern
- Gene therapy approaches to increase BAT being investigated – high risk

Potential Approaches for Weight Loss

Greater loss of nutrients – malabsorption vs. "diversion" of nutrients

- Our old friend orlistat – safe, modestly effective, side effects can be problematic, OTC in the U.S.
- SGLT-2 inhibitors and urinary glucose losses

Potential Sites for Intervention



Appetite regulation

Increase physical activity

Increase BAT

Mimic gut hormone effects

Increase GI or urinary losses

Uncouple mitochondria

Mimic adipose tissue effects

Expert Strategies to Optimize the Management of the Obese Patient and Reduce Cardiometabolic Risk: Case Study and Panel Discussion

Robert H. Eckel, MD
Jamy D. Ard, MD
George A. Bray, MD
Michael D. Jensen, MD

Cardiometabolic Health Congress • October 22 - 25, 2014 • Boston, MA

Case Study

- A 60 year old man was referred for low HDL-C and an EBCT coronary calcification score of 545 with a normal stress thallium ETT.
  He had a long history of obesity, hypertension and also c/o erectile dysfunction.
- He was adopted, denied tobacco use and drank alcohol infrequently.
- He ate 3-4 servings of F&V and 2-3 of whole grains daily, and fish 2x/wk. Only Rx was lisinopril.
- BMI was 33.5 kg/m^2, waist circumference 104 cm, pulse 96 and BP 142/72.
- The fasting plasma glucose was 115 mg/dL and HbA1c 6.3%.
  Cholesterol was 190, TG 330, HDL-C 28 and calculated LDL-C 96 mg/dL.
  Testosterone was 303 ng/dL, hsCRP 3.4 mg/dL and apo B 115 mg/dL.

Case Study

A 10% weight reduction and 3 months of weight stabilization in this case should result in this set of co-morbidities:

A. ↓ HbA1c, ↓ systolic BP, ↓TG, ↓ LDL-C
B. ↓ HbA1c, ↓ systolic BP, ↓TG, ⇔ LDL-C
C. ↓ HbA1c, ⇔ systolic BP, ↓TG, ⇔ LDL-C
D. ⇔ HbA1c, ⇔ systolic BP, ↓TG, ↓ LDL-C

Panel Discussion

ARS Case Study:

44-year-old man – depression, allergies, seizure disorder, and regular marijuana user.

Which compound would not affect his appetite?

1. Bupropion
2. Cannabis
3. Montelukast
4. Diphenhydramine
5. Topiramate

ARS

All of the following gut hormones decrease food intake, except:

1. Cholecystokinin
2. Glucagon-like peptide-1
3. Oxyntomodulin
4. Ghrelin

The *MOST* important consideration in developing a treatment strategy for a patient with obesity is:

1. Current weight and age
2. Body mass index and associated risk factors
3. Obesity stage (overweight, stage I, II, or III)
4. Dietary preferences and ability to exercise

Questions and Answers