

The Biology and Pathophysiology of Obesity



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Disclosures

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Definition and likelihood of successful weight loss maintenance in adults

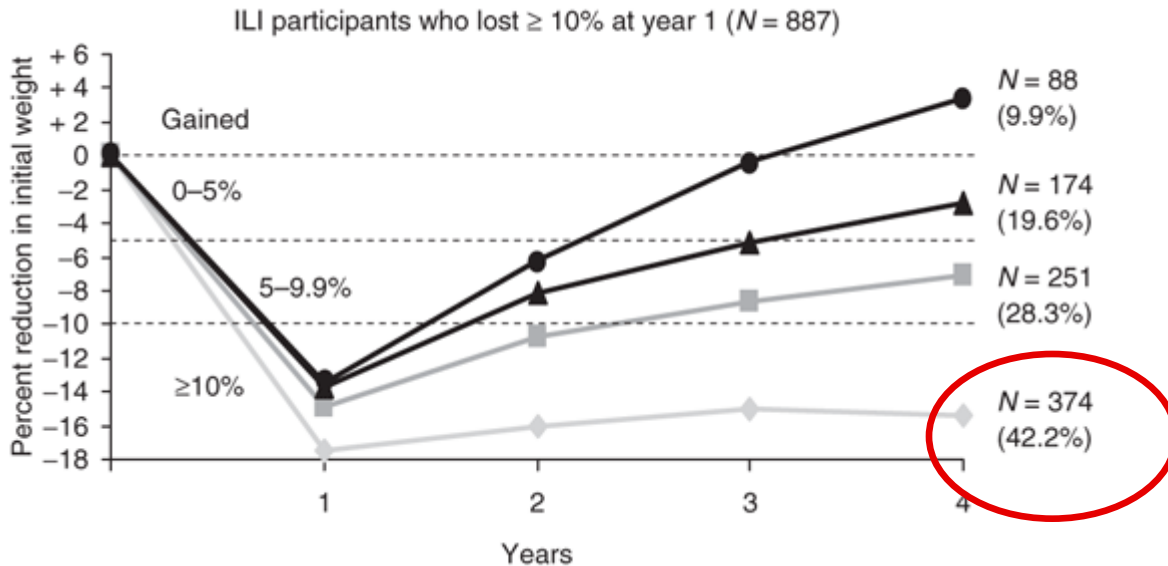
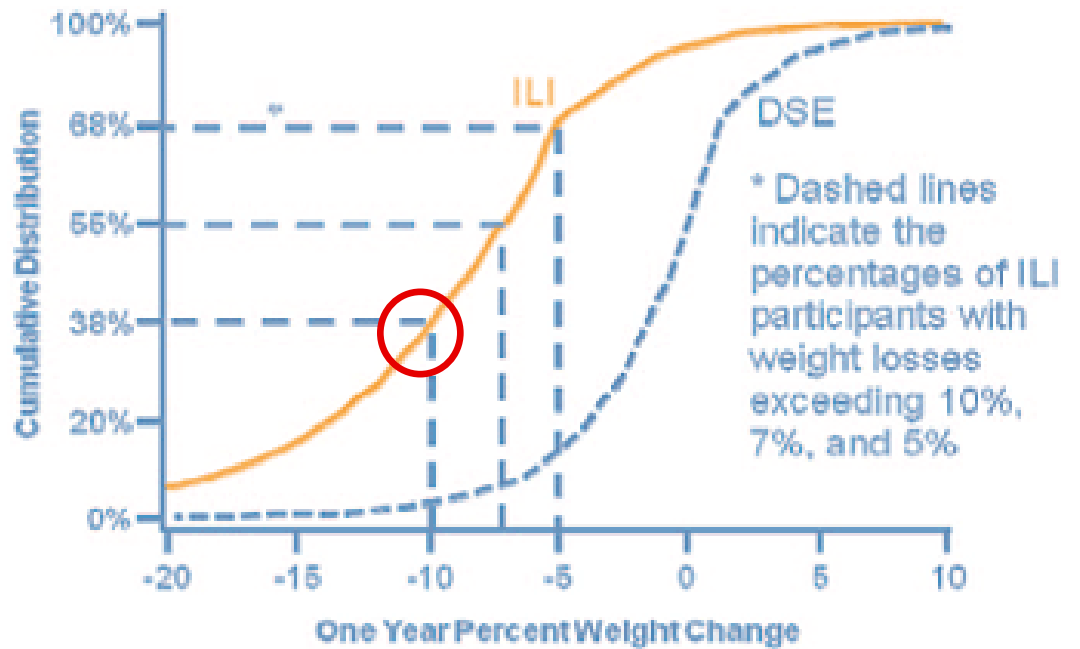
- Successful weight loss maintenance is *“individuals who have intentionally lost at least 10% of their body weight and kept it off at least one year”*

(Wing and Hill, Annu. Rev. Nutr., 23:323, 2001)

- “One out of every 6 adults who has ever been overweight or obese has accomplished long term weight loss maintenance of at least 10%”.

(Kraschnewski et al, Int. J. Obes., 34:1644, 2010)

The Look AHEAD Trial



38% lose 10% of whom 42% keep it off.

Net success = 16%

Points

- Body weight is “regulated” such that obesity and the difficulty in sustaining weight loss are biological diseases.
- Obesity is a disease that continues to manifest itself as a hypometabolic and hyperphagic state long after it has been supposedly “cured” by weight loss.
- It is not correct that lean people have trouble keeping weight off because they have “slow metabolism” while obese people have trouble because they lack willpower.
- Understanding of this biology provides insights into the next steps in obesity prevention and treatment via personalized medicine.

Evidence that body weight is regulated

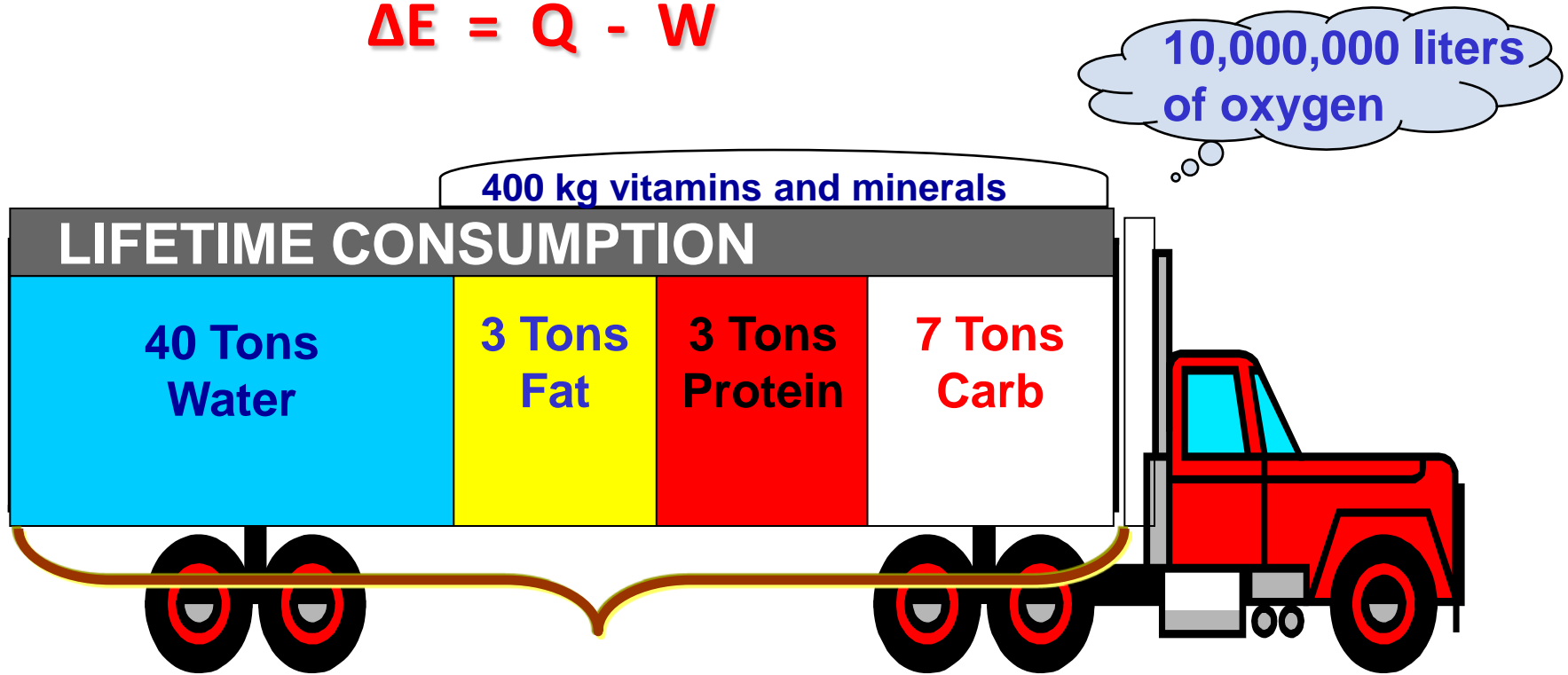
- Heritability of body fatness equals that of height.
- ~75%-85% of those who are successful at losing weight will regain it within 2 years.
- Those successful at keeping weight off report:
 - They need to maintain dietary restriction (eat less than matched individuals at usual weight).
 - They need to maintain regular exercise (exercise more than matched individuals at usual weight)
- There is a remarkable long term constancy of body weight in adults

Study of Successful Weight Loss Maintainers: The National Weight Control Registry

- Subjects: Mostly Caucasian women with an average weight loss of ~70 lbs. sustained for about 6 years.
- Compared to weight-matched but non-reduced individuals:
 - Diet: About 250 calories/day less
 - Exercise: About 45 minutes/day (200 calories/day more)
 - TV: Average < 10 hrs/week vs. 28 hours.
 - Brain response to food: higher dietary restraint.

Regulation of Energy Stores:

$$\Delta E = Q - W$$



< 1 kg carbohydrate
3.4 kg minerals
10.2 kg protein
8.8 kg fat
48 kg water

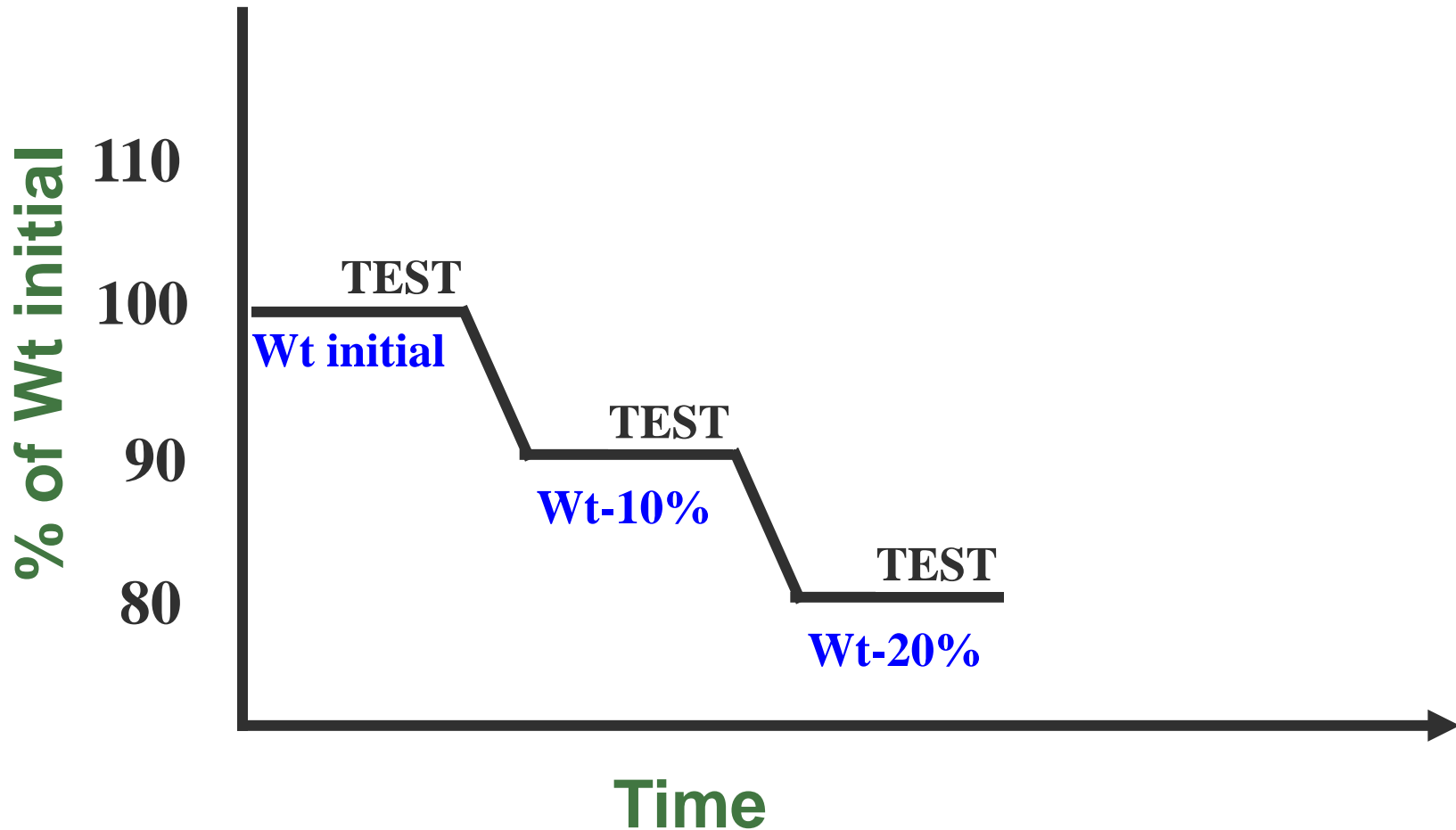


70 Kg Man

CO₂, Waste,
Heat, Work

Protocol: Over 150 subjects

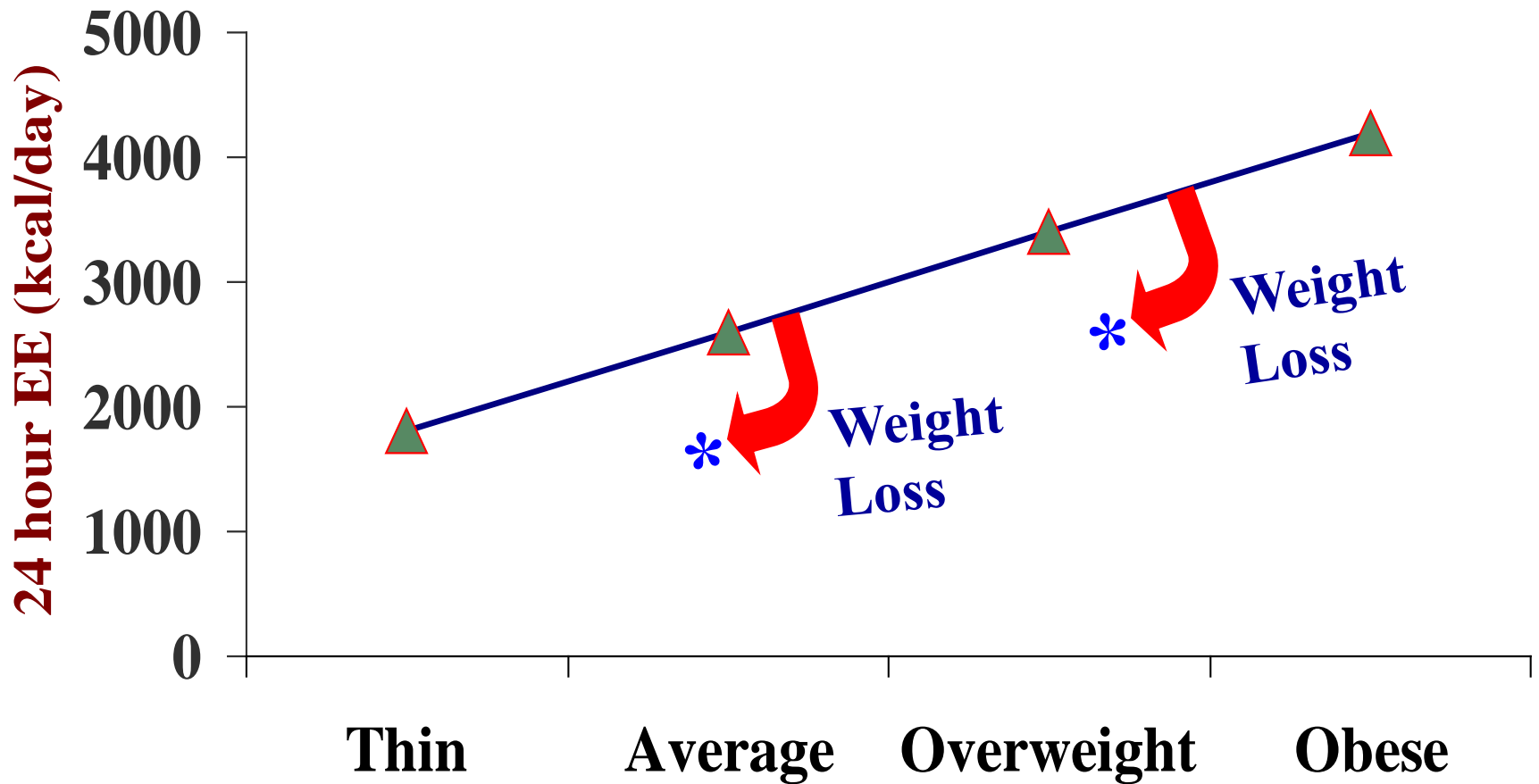
- In-patients on a liquid formula diet for 6-26 months.
- Each weight plateau or loss period: 6-8 weeks.



Rigorous Testing

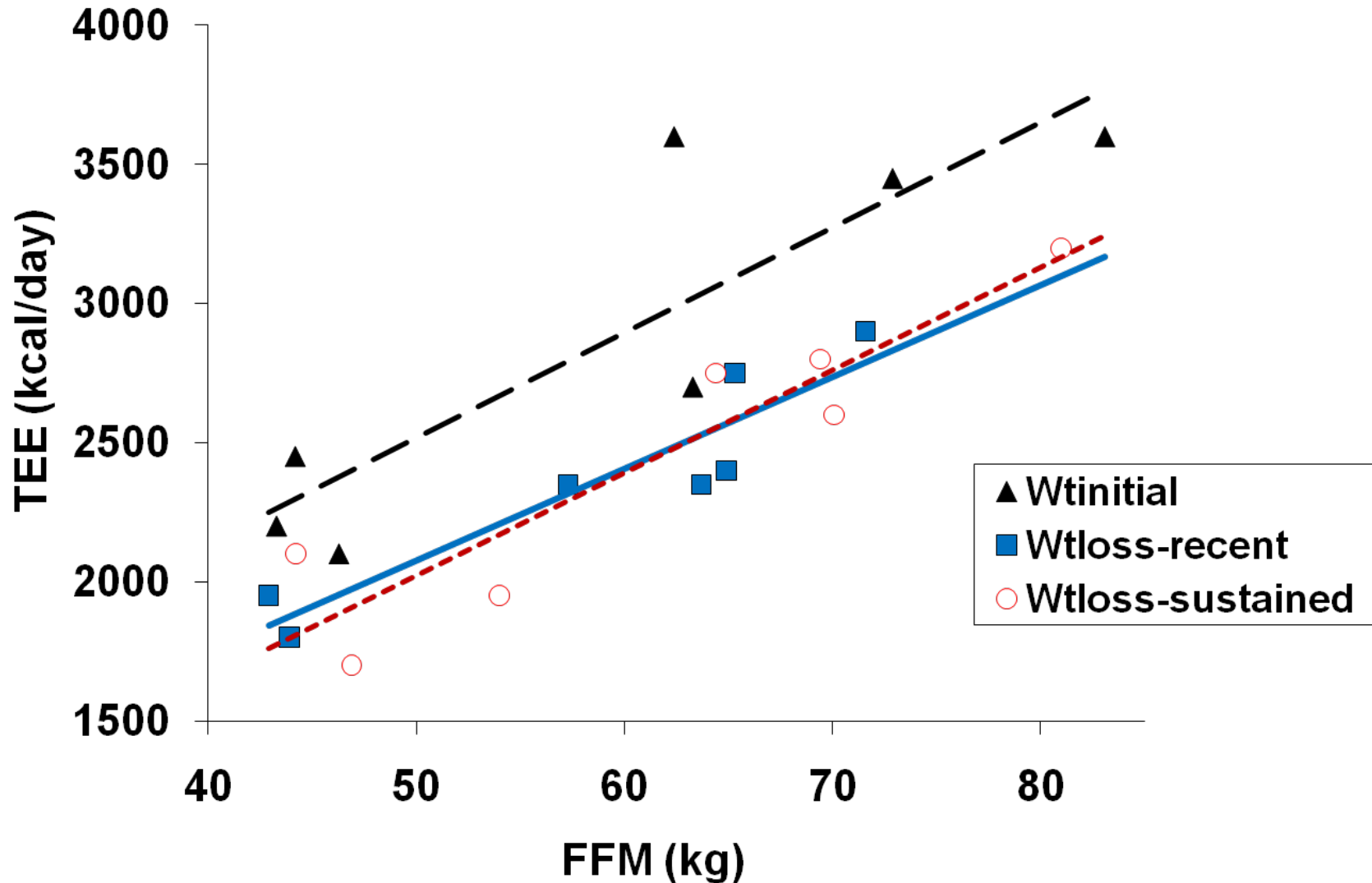
- **Body Composition:**
 - DXA, MRI
- **Energy Expenditure:**
 - Caloric titration/DLW, calorimetry, accelerometer
- **Energy Intake**
 - Behavioral Studies
 - Functional MRI
- **Skeletal muscle:**
 - Ergometry (whole body), NMR (single fiber), vastus lateralis biopsy (biochemistry and molecular physiology)
- **Autonomics:**
 - Urine catecholamines, pharmacological ANS blockade
- **Neuroendocrine function:**
 - Thyroid, cortisol, leptin, hypoglycemia, OGTT

How many calories needed to maintain weight?



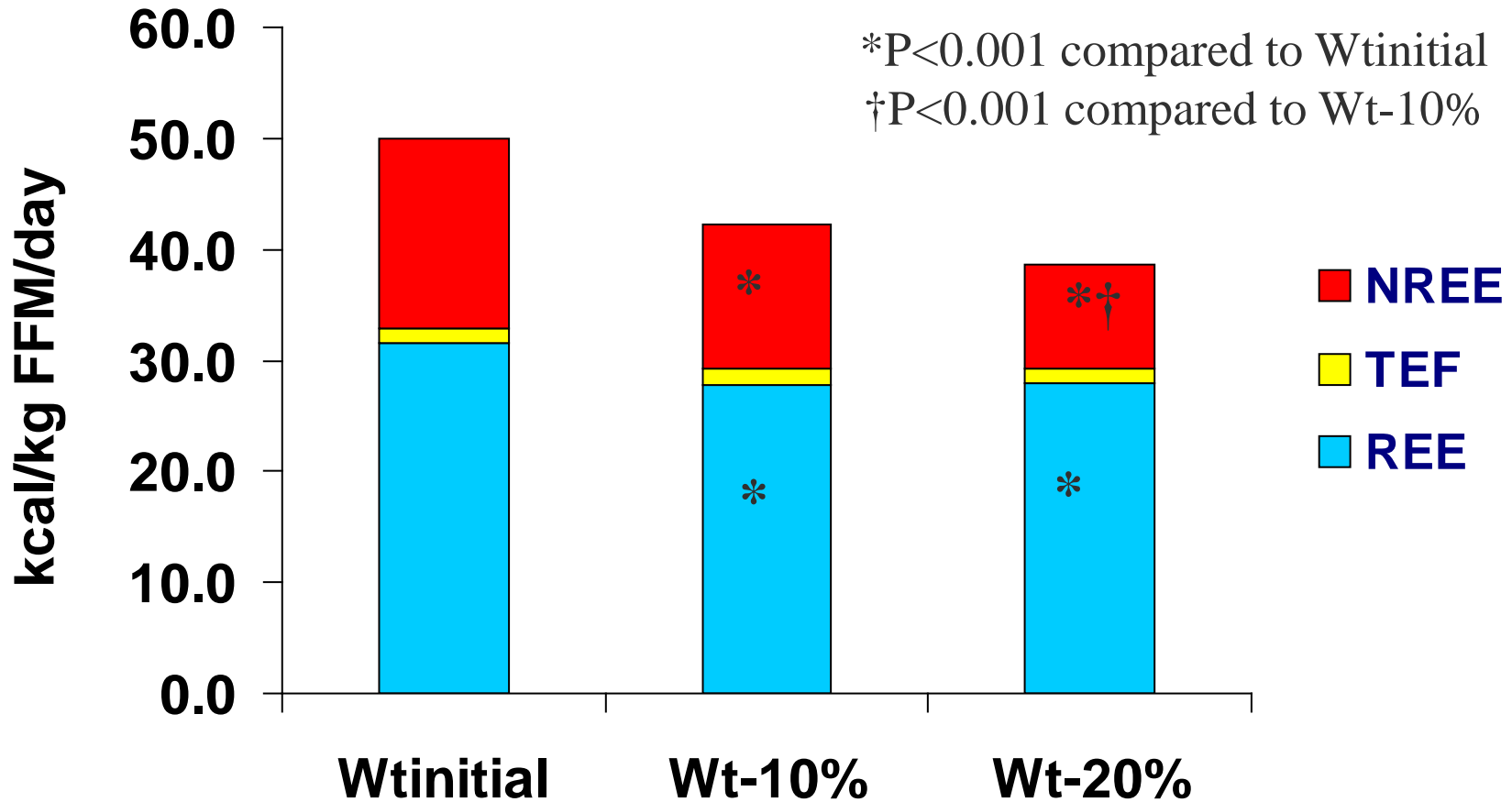
Leibel et al, 1995, NEJM, 335:521; Rosenbaum and Leibel, 2010, IJO, 34:S47;
Wing and Hill, 2001, Ann Rev Nutr, 21:323

The hypometabolic state in individuals maintaining a reduced weight does not abate with time



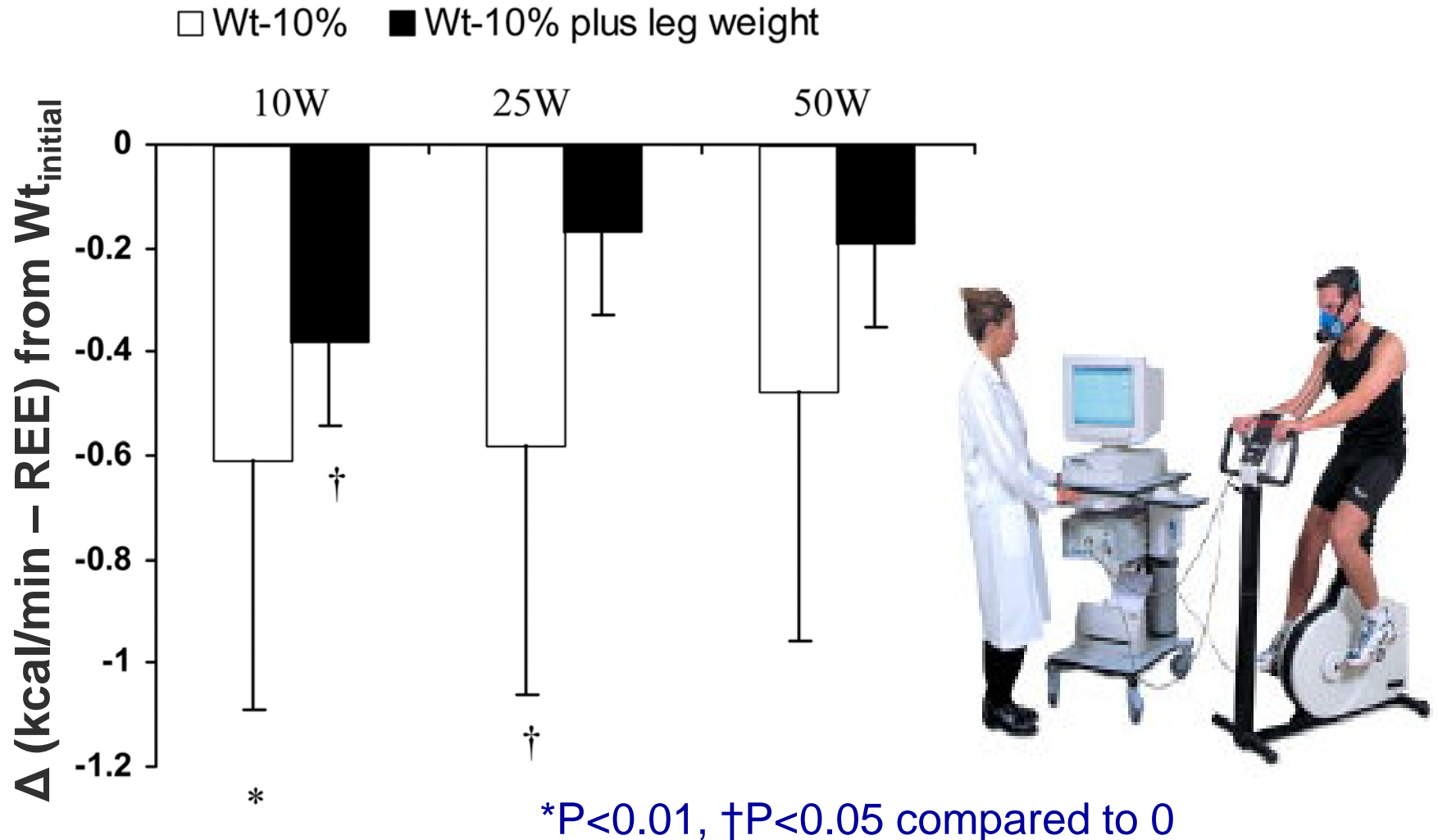
Rosenbaum et al, AJCN, 88:906, 2008.

Predominance of NREE changes after weight loss suggests skeletal muscle is the primary effector organ.

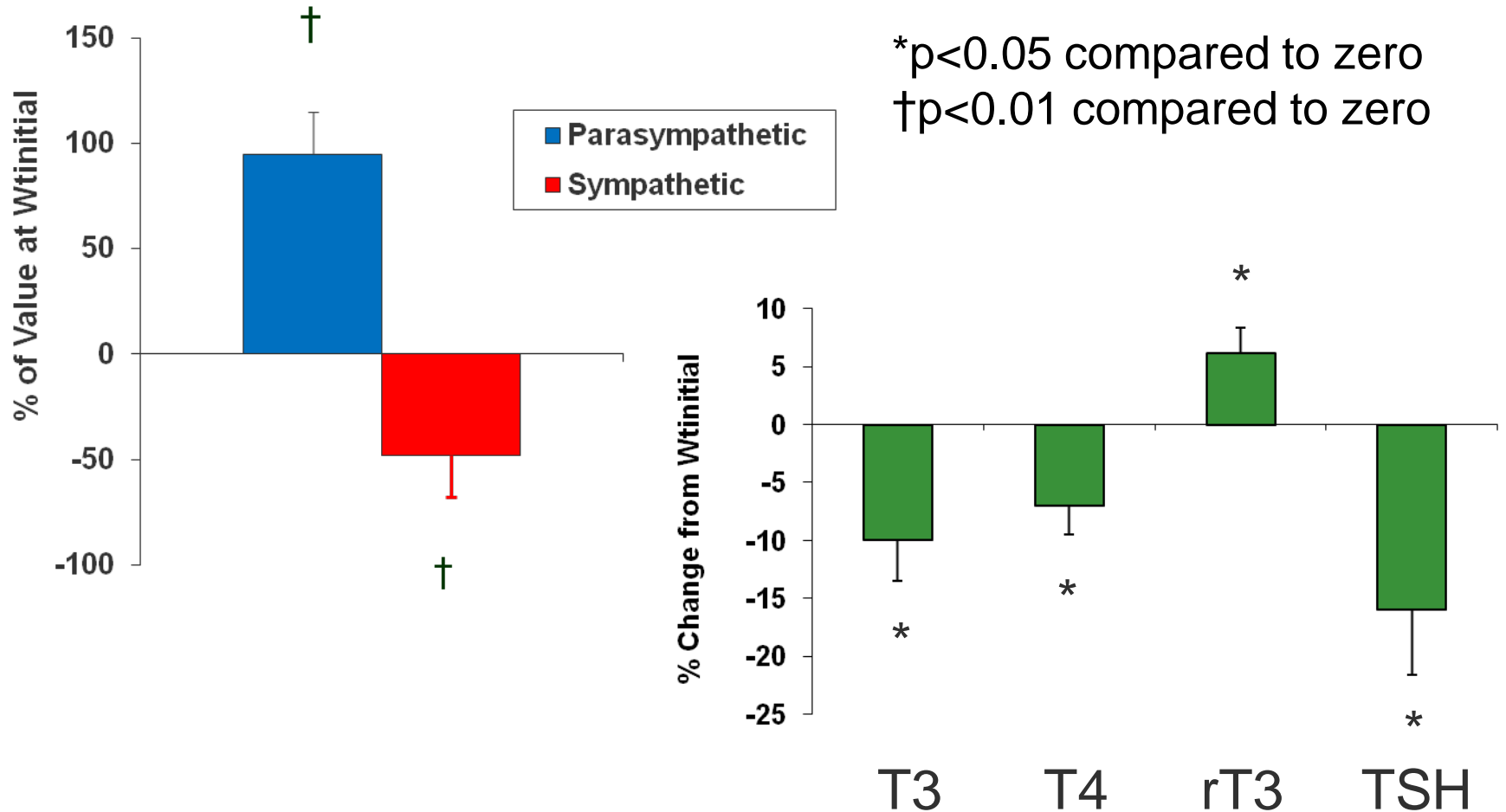


Kulkarni and Shetty, Ann. Hum. Biol., 19:421, 1992; Leibel et al, NEJM 332:521, 1995; Kern et al, JCEM, 84:4185, 1999; Rosenbaum et al, AJP, 285:5183, 2003

Physiology: Decreased energy expenditure per unit of work after 10% weight loss



Autonomics and Neuroendocrine



Aronne et al, 1995, AJP, 38: R222; Rosenbaum et al, 2000, AJCN, 71:1421;
Rosenbaum et al, 2010, IJO, 34:S47

Energy Intake

- At usual body weight, energy intake and output are coupled to maintain weight.
- If this coupling persisted after weight loss, it would be easy to keep it off.
- Behavioral and fMRI studies indicate that this is not the case.

Brain responses to food before vs. after weight loss (Columbia Visual Foods Task)

Reduced weight greater than initial weight

- Emotional and Cognitive Response to Food
- Executive Decision Making Functions

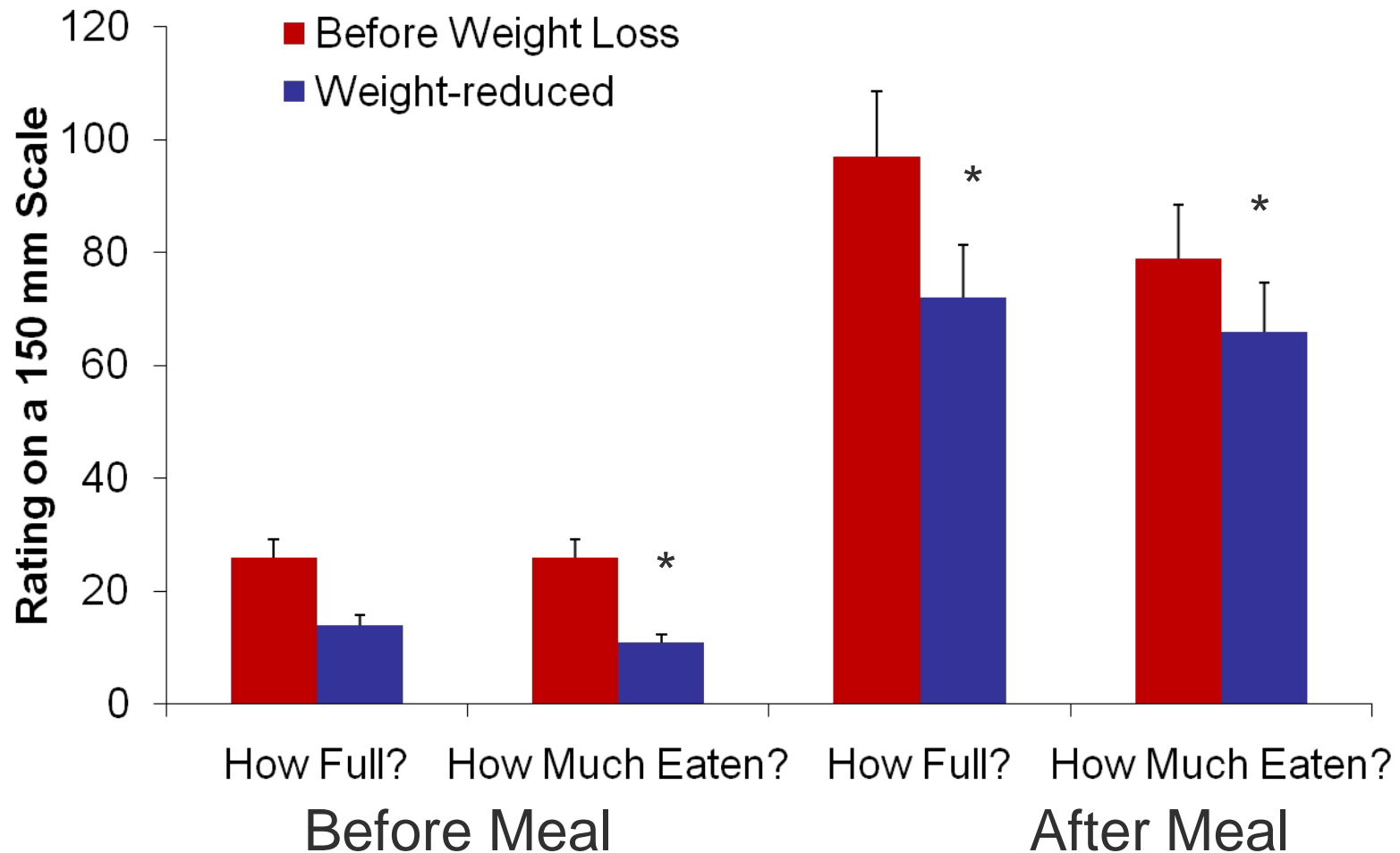
Suggests that you want it more and you debate it less.

Initial weight greater than reduced weight

- Knowledge Representation
- Emotional/Cognitive Planning and Control
- Hypothalamus

Suggests that you are less aware of what you've eaten and have less restraint.

Behavior Matches fMRI: Decreased perception of fullness and amount eaten after weight loss



The weight-reduced state is the perfect storm for weight regain and is distinctly different from dynamic weight loss.

Autonomics

- ↓ SNS tone
- ↑ PNS tone

Neuroendocrine

- ↓ T3, T4, TSH, leptin, ↑ rT3

Muscle

- ↑ efficiency

Energy Expenditure:

- 300-400 kcal/day < predicted
- ↓ Physical activity EE

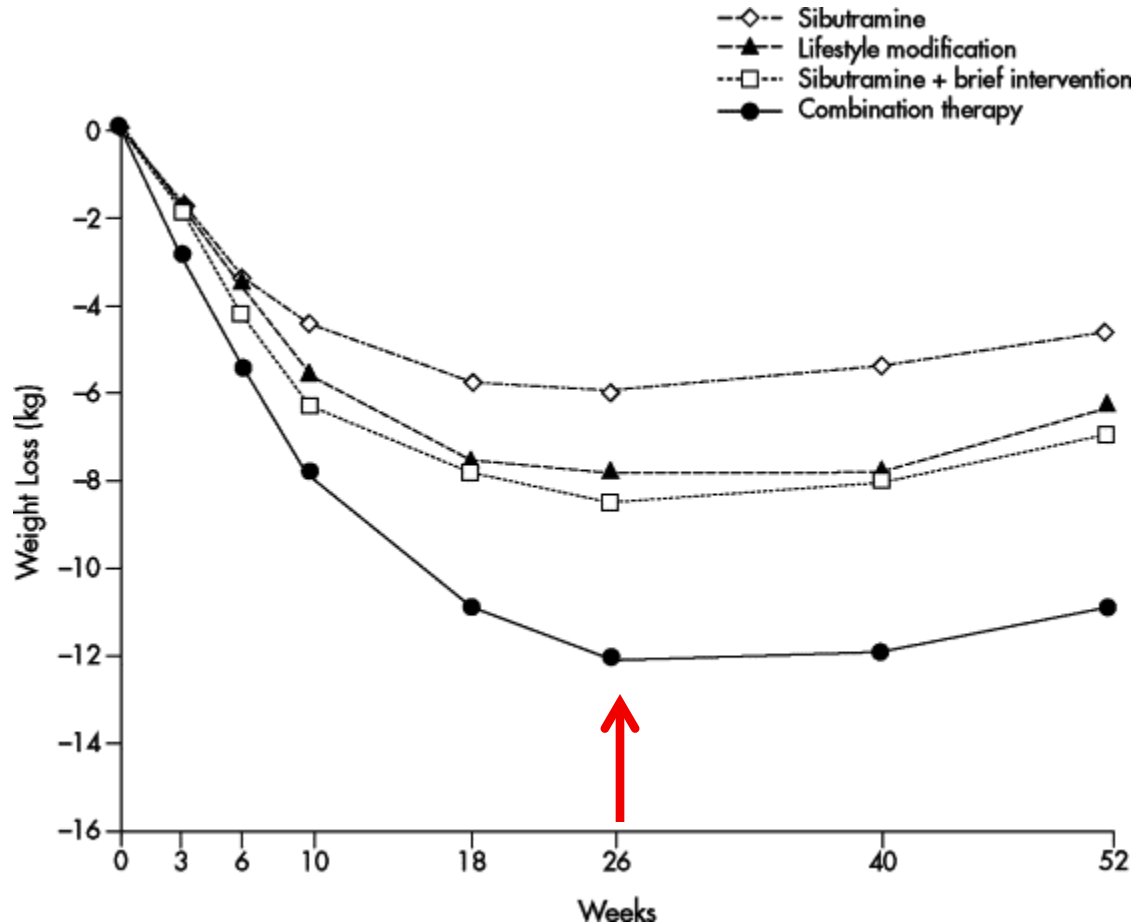
Energy Intake

- ↑ food reward
- Delayed satiation
- ↓ perception of amount eaten

Questions

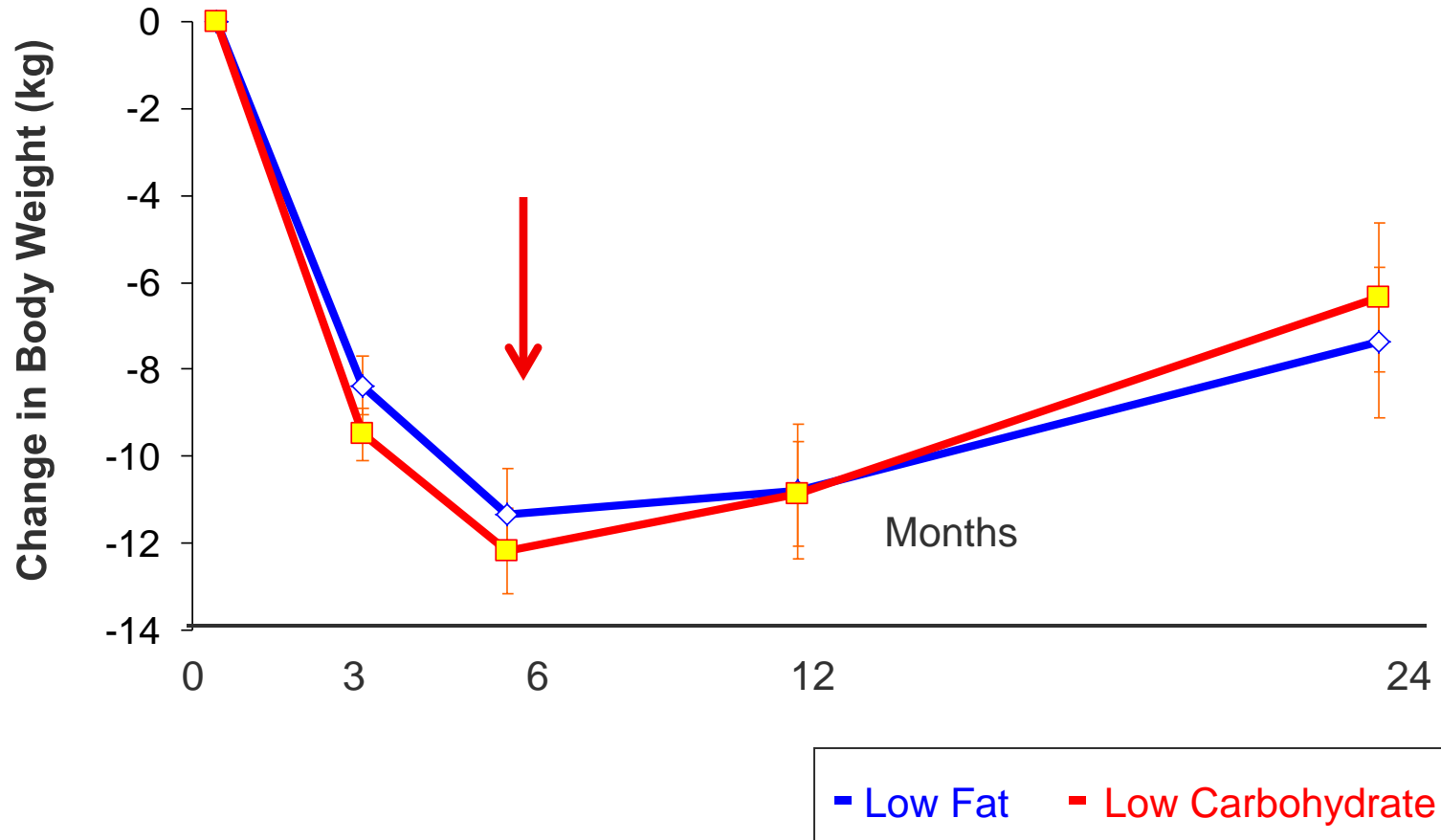
- Most weight loss interventions work for about 6-9 months followed by reduced weight maintenance or weight regain.
 - Is there a way to extend that time period?
- Only about 35-40% of individuals lose more than 10% of their weight and only 40% of those who have lost weight keep it of: **net success rate 15%**
 - Attempts to sustain decreased intake?
 - Attempt to reverse changes in muscle (increase energy expenditure) ?
 - **Attempts to reverse both?**

Pharmacotherapy and lifestyle

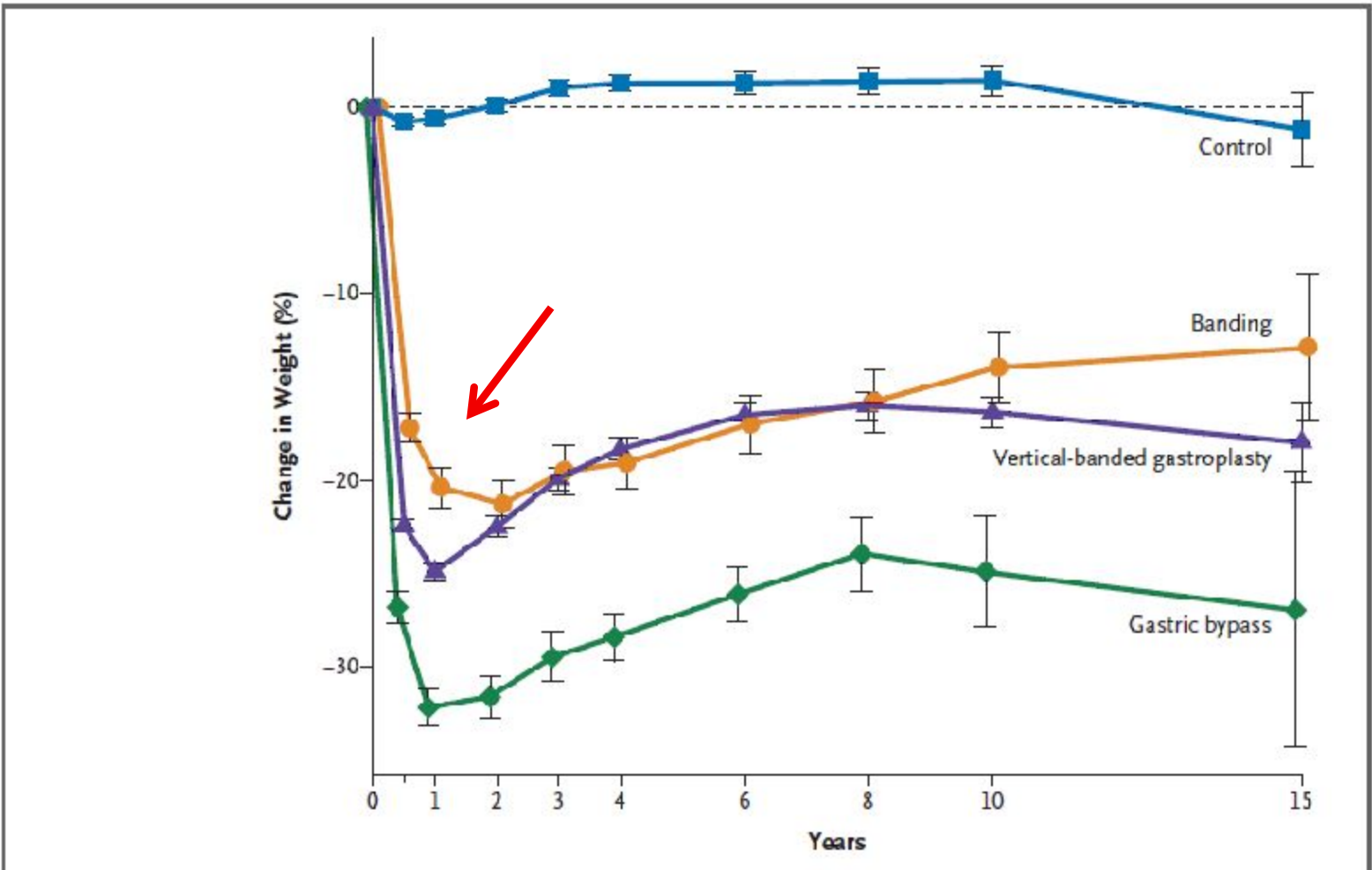


Wadden et al, NEJM, 2005, 325: 2111

Diet Composition and Weight Loss

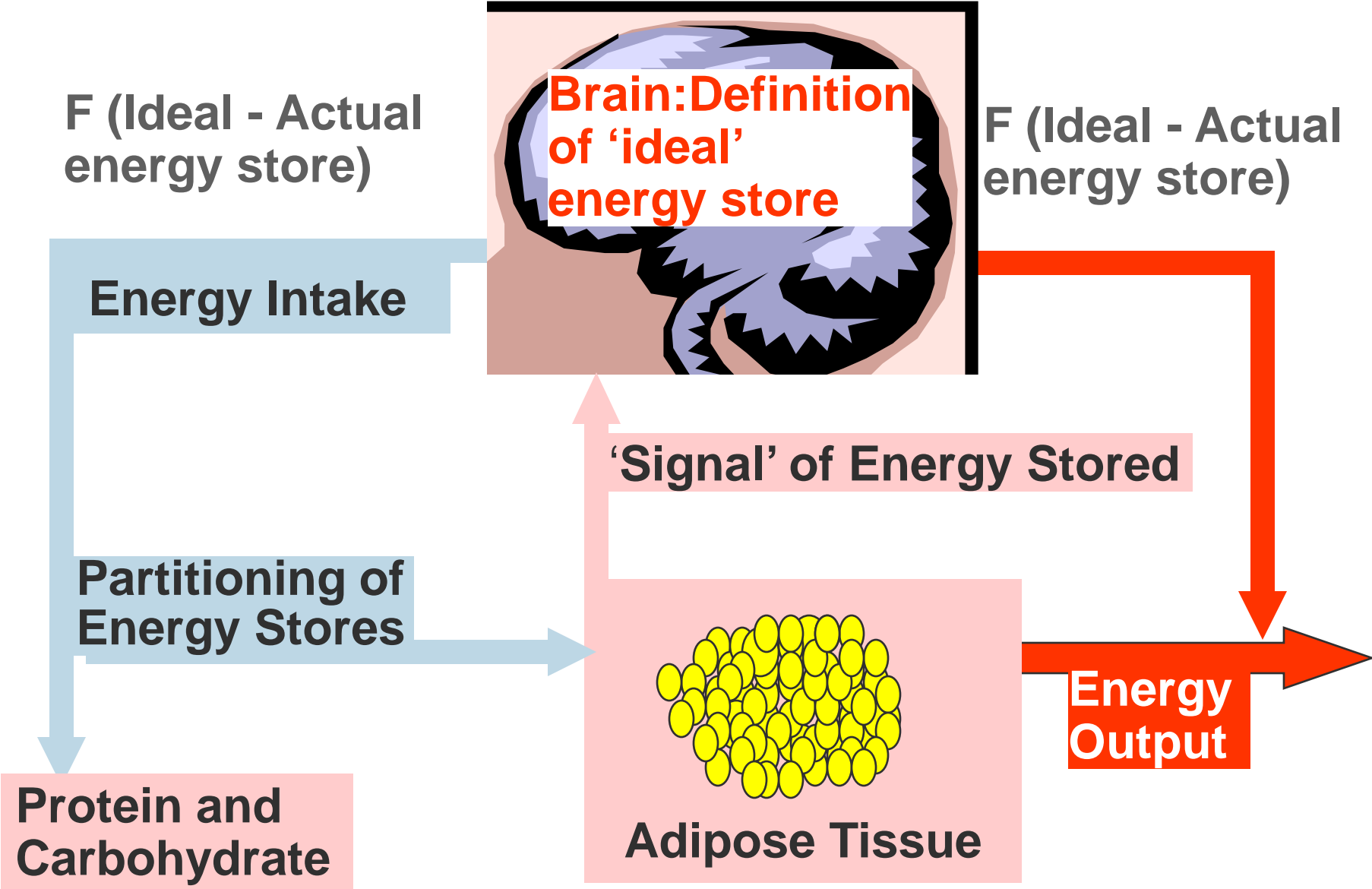


Surgical



Sjostrom et al, 2007, NEJM, 357:741

Model for Body Weight Regulation



The Leptin-Threshold Model: Body Fatness, not Thinness is Defended

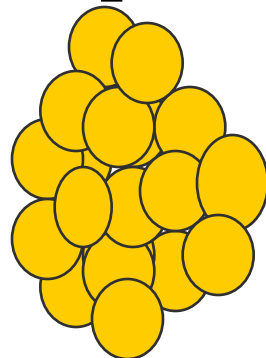
Leptin Sufficient

Satiated
Eumetabolic
Fertile
Euthyroid

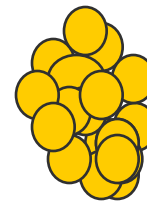
Leptin



Individualized Leptin Threshold



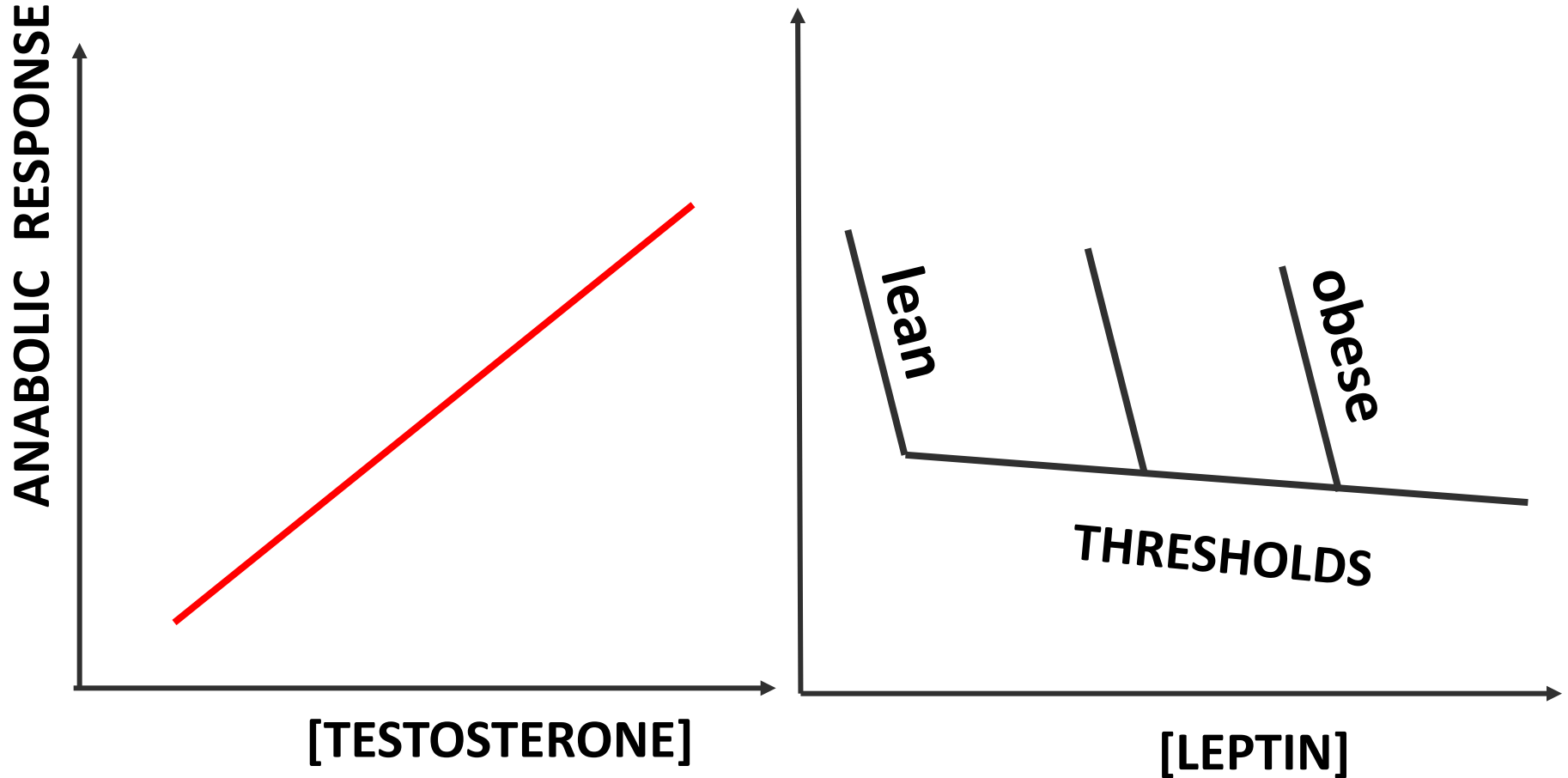
Leptin



Leptin Deficient

Hyperphagic
Hypometabolic
Infertile
Hypothyroid

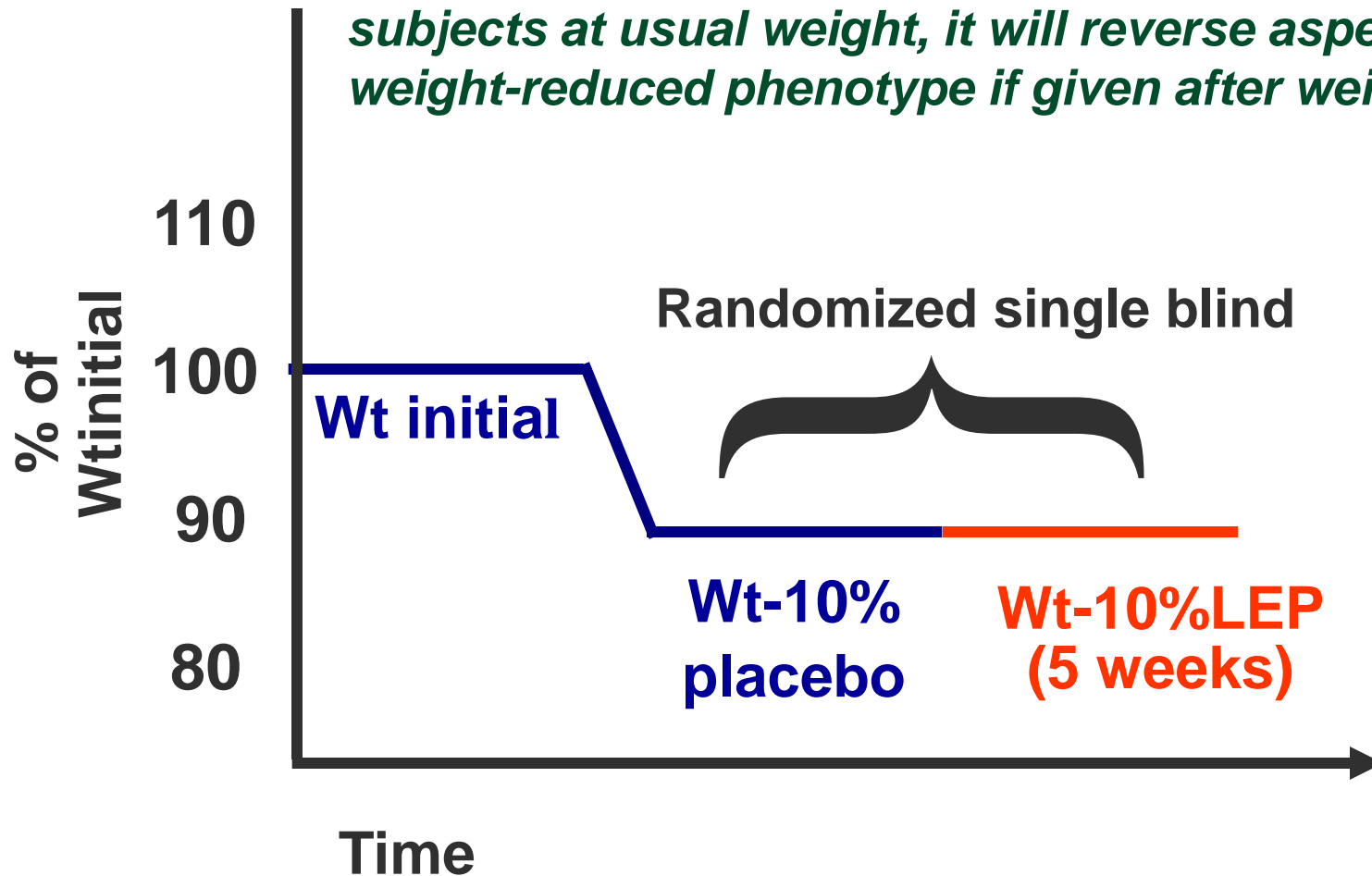
SYMMETRIC AND ASYMMETRIC ENDOCRINE PHYSIOLOGY



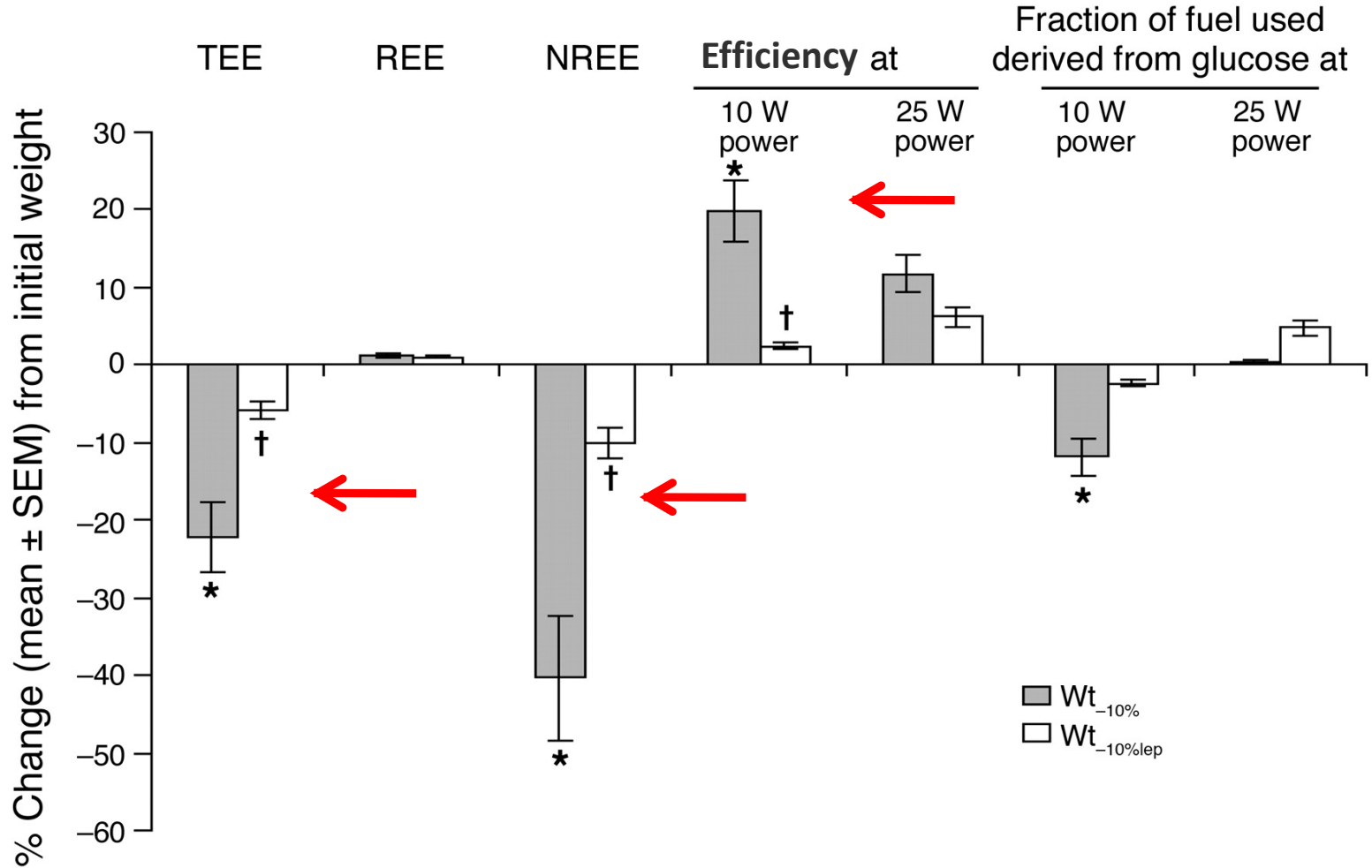
Schematic of Protocol

Hypothesis:

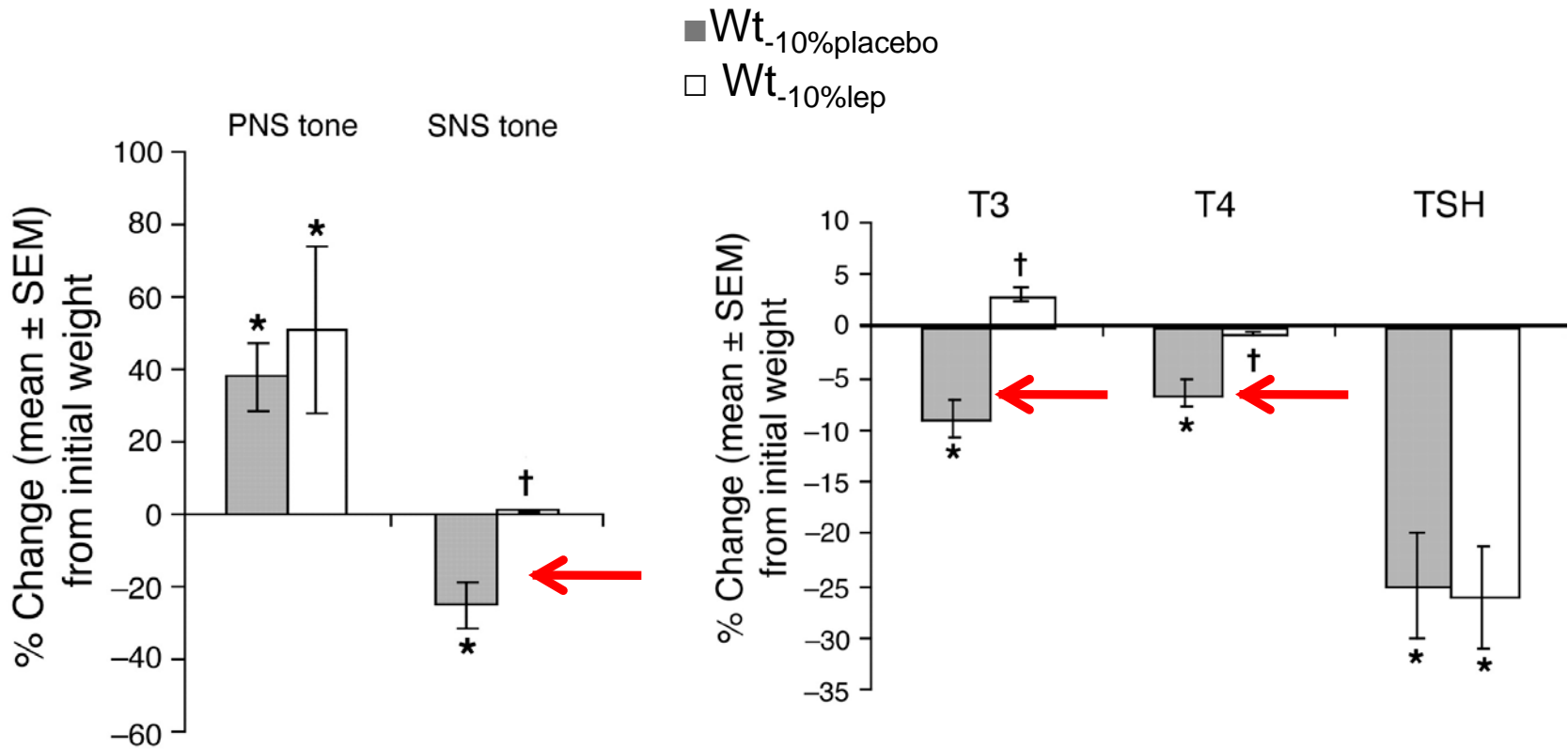
Though leptin administration has little effect on subjects at usual weight, it will reverse aspects of the weight-reduced phenotype if given after weight loss.



Results: Energy expenditure and skeletal muscle



Autonomic and Neuroendocrine Weight Loss and Leptin Effects

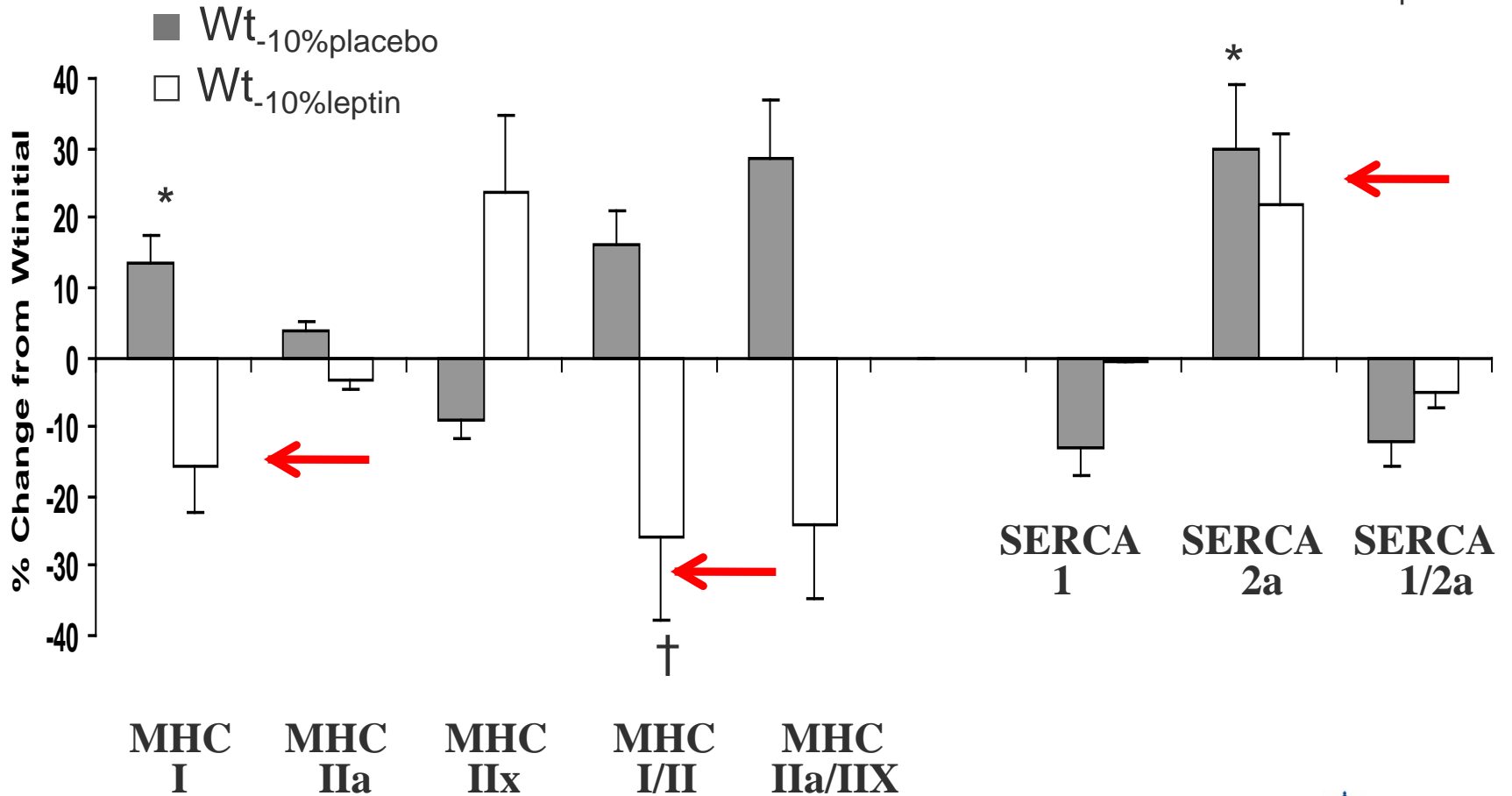


* $P < 0.05$ versus zero
 † $P < 0.05$ versus Wt_{-10%}placebo

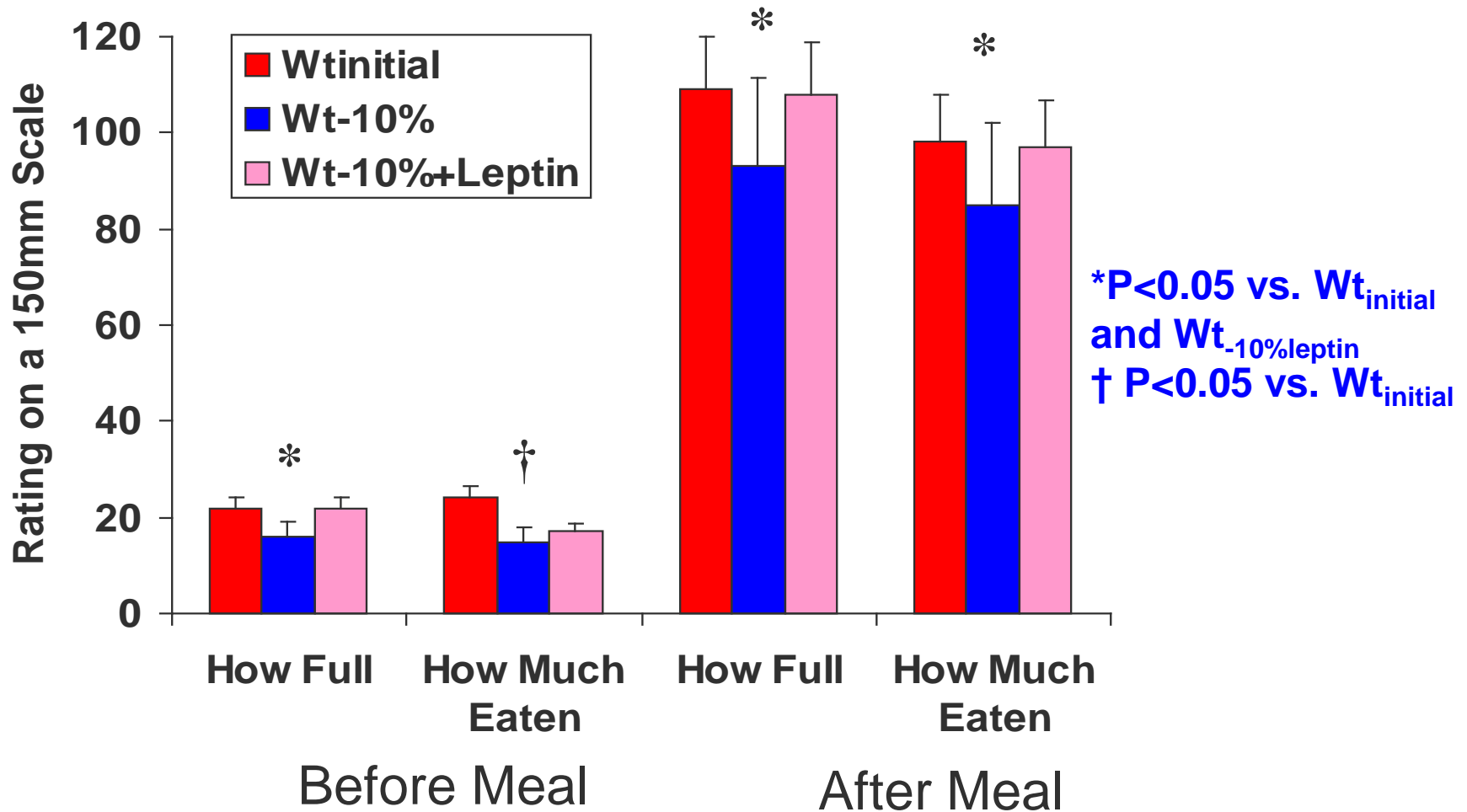
Leptin, myosin MHC and SERCA isoforms

* P<0.05 compared to 0

† P<0.05 compared to 0 and to Wt_{-10%}placebo



Eating Behavior



Brain responses to food in leptin deficient (weight reduced) vs. Leptin sufficient (usual weight or leptin-repleted) states

More active after weight loss w/o leptin

More active when leptin sufficient

Structure	Net Function (effect)	Structure	Net Function (effect)
Brainstem	↑ Signal processing (food recognition)	Hypothalamus	↓ integration of leptin/humoral signaling (satiety recognition)
Globus pallidus	↑ Food reward		
Insula	↑ Food reward expectation	Amygdala	↓ response to sensory cues (feelings of fullness)
Ventral striatum	↑ Food reward and motivation	Cingulate	↓ self-control and error recognition (dietary restraint)
Lingual and superior temporal gyri	↑ affective response to high and low caloric density foods	Inferior parietal lobule	↓ response based on experience (action based on previous knowledge)
Net Effect after weight loss	↑ Food Reward	Net Effect after weight loss	↓ Food Restraint

Leptin Effects on Weight-reduced Phenotypes:

Energy Expenditure:

- 300-400 kcal/day < predicted
- ↓ Physical activity EE

• Energy Intake

- Delayed satiation
- ↓ perception of amount eaten
- ↑ response to food
- ↓ restraint in response to food

***Not “reversed” following leptin repletion in weight-reduced subjects**

Autonomics

- ↓ SNS tone
- ↑ PNS tone*

Neuroendocrine

- ↓ T3, T4, leptin, ↑ rT3
- ↓ TSH*

Muscle

- ↑ efficiency and MHC1
- ↓ glucose utilization and PFK/COX
- ↑ SERCA2*

Why this should not be depressing

- It's biology – not a lack of willpower.
- The response is heterogeneous and potentially predictable.
- Ongoing studies seeing the weight-reduced state as a distinct physiological entity from weight loss or gain.
 - Thyroid, combination medications, etc.
 - Exercise
 - Predictors of subsequent risk in children

The following should happen within 10 years:

- Prospective identification of the best weight loss and weight maintenance therapies for an individual.
- Development of better pharmacological/behavioral interventions to reduce opposition to sustained weight loss.
- Better understanding of obesity prevention in childhood.

Conclusion

- **How should we view the difficulty in keeping weight off?**
Potent biology not impotent psychology – respect and encourage improved health.
- **What should patients know trying to keep weight off?**
Obesity is a disease that continues to manifest itself long after it is supposedly “cured” by weight loss in the form of potent metabolic and behavioral resistance.
- **What might work?**
A new class of weight-maintenance interventions or predictors of optimal therapeutic interventions.
- **What do we need to?**
More personalized preventive and therapeutic medicine and weight maintenance versus weight loss treatments.

People: All our volunteers and...

Columbia University

Rudolph L. Leibel

Dympna Gallagher

Ellen Murphy

Sanobar Parkar

Elisabeth Shamoon

Katherine Pavlovich

Yomery Espinal

Elinor Naor

Rochelle Goldsmith

Laurel Mayer

Judy Korner

Sharon Wardlaw

Harry Kissileff

Joy Hirsch

Steve Heymsfield

Fernando Arias-Mendoza

Richard Smiley

Martica Heaner

ICCR Nurses and

Nutrition Staff

Rockefeller University

Jules Hirsch

Cindy Seidman

David Markel

Rachel Kolb

Karen Segal

University of Pennsylvania

Krista Vandeborne

Marty Eastlack

Jack Leigh

Laval University

Denis Joannis

Jean-Aimé Simoneau

Weill-Cornell

Louis Aronne

Alfons Pomp

Greg Dakin



UC Irvine

Kenneth M. Baldwin

Fadia Haddad

Shlomit Aizik

NYU

George Fielding

Christine Ren-Fielding

SportsClub LA

Frank Maggi

Chris Oehl

Lakeesha Robinson

Nikki Williams