Childhood Obesity:
behavioral aberration or biochemical drive?
Reinterpreting the First Law of Thermodynamics

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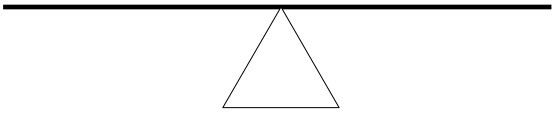
The First Law of Thermodynamics



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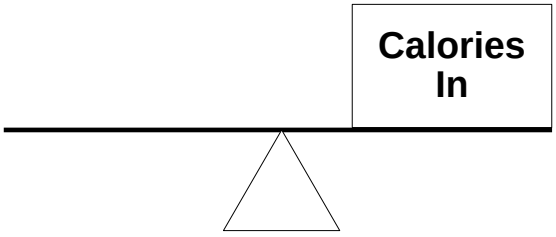

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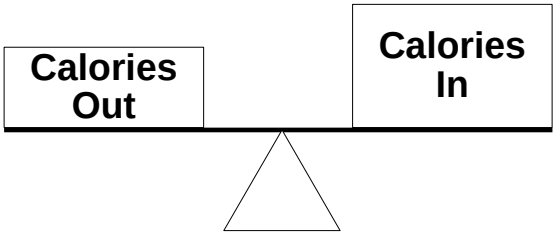

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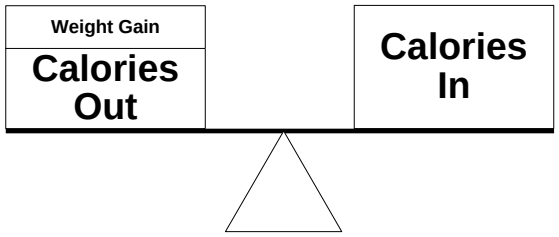

What happened to willpower? I love fat people. Every fat person says it's not their fault, that they have gland trouble. You know which gland? The saliva gland. They can't push away from the table.

Jesse Ventura (I), Former Governor of Minnesota. *Playboy*, November 1999;46:55.

Obesity as a Philosophical Paradigm

1. Obesity is a behavior

Obesity as a Philosophical Paradigm

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No child chooses to obese.

The quality of life of an obese child is equivalent to those on cancer chemotherapy.

(Schwimmer et al. JAMA 289:1813-1819, 2003)

Obesity as a Philosophical Paradigm

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(Schwimmer et al. JAMA 289:1813-1819, 2003)

We even have an epidemic of obese 6-month olds.

(Kim et al. Obesity 15:1107, 2006)

Behavior

Stedman's Medical Dictionary

Def. A stereotyped motor response to a physiological stimulus

Behavior

Stedman's Medical Dictionary

Def. A stereotyped motor response to a physiological stimulus

What are the biochemical underpinnings of gluttony and sloth?

Obesity as a Philosophical Paradigm

1. Obesity is a behavior
2. Obesity is a disease

Obesity as a Philosophical Paradigm

1. Obesity is a behavior
2. Obesity is a disease
3. Obesity is a phenotype

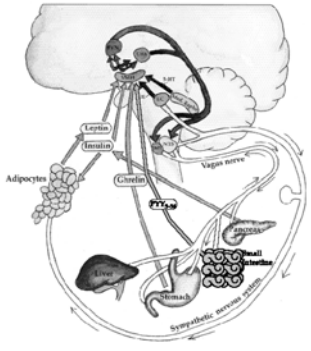
Why do people eat?

- **The homeostatic (hunger) pathway**
- **The hedonic (reward) pathway (won't discuss)**
- **The stress pathway (won't discuss)**

The homeostatic (hunger) pathway:

- **Leptin resistance and the role of insulin**
- **Controlled by the hypothalamus**

The neuroendocrinology of energy balance



Dexfenfluramine

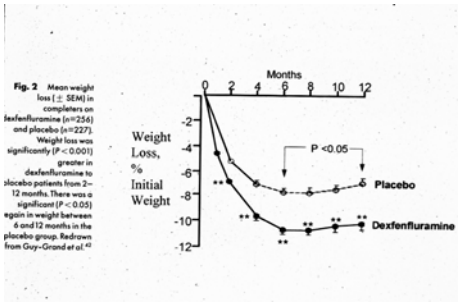
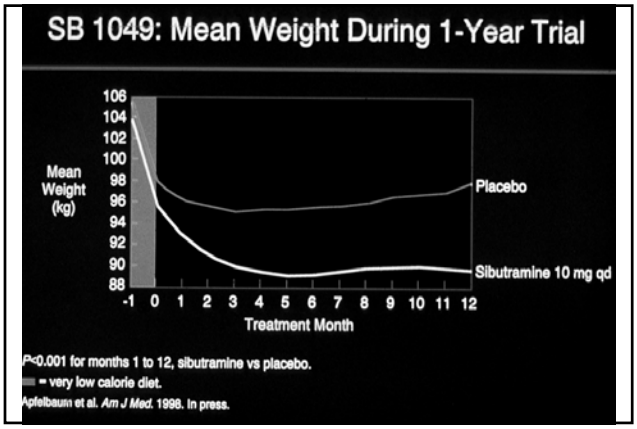
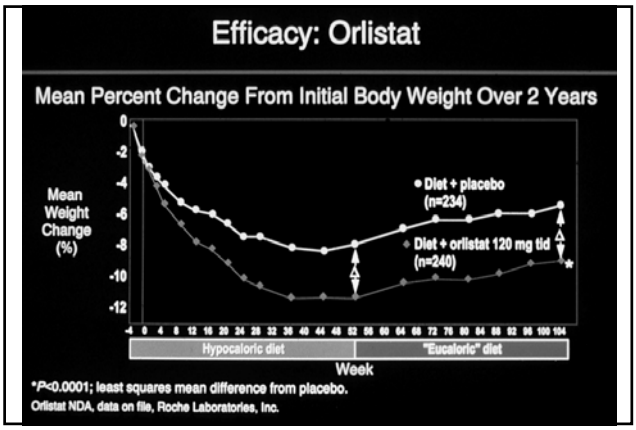


Fig. 2 Mean weight loss (± SEM) in completers on dexfenfluramine (n=256) and placebo (n=227). Weight loss was significantly ($P < 0.001$) greater in dexfenfluramine to placebo patients from 2–12 months. There was a significant ($P < 0.05$) regain in weight between 6 and 12 months in the placebo group. Redrawn from Guy-Grand et al.[42]





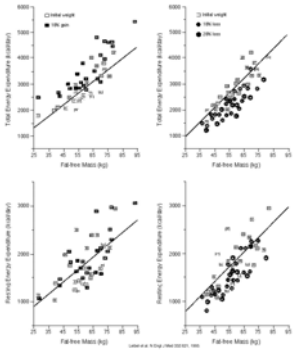
Why the negative plateau with weight loss?

Because of decreased energy expenditure, to offset the decreased caloric intake

T)

This is a manifestation of leptin resistance!

Weight loss lowers REE/FFM by 20%



Leibel et al. N Engl J Med 332:621, 1995

Autonomic Function during the Starvation Response

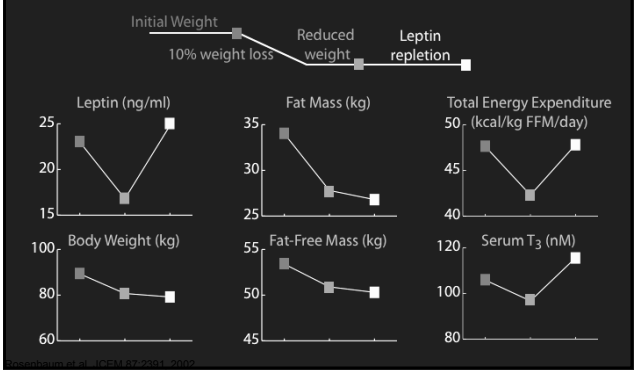
In response to declining leptin:

- Reduced sympathetic activity
- decreased lipolysis
- decreased gluconeogenesis
- decreased energy expenditure

- Increased vagal activity
- reduced myocardial oxygen consumption
- increased adipocyte insulin sensitivity
- increased insulin secretion
- increased energy storage

Aronne et al. Am J Phys 269:R222, 1995

Leptin reverses metabolic effects of caloric deprivation

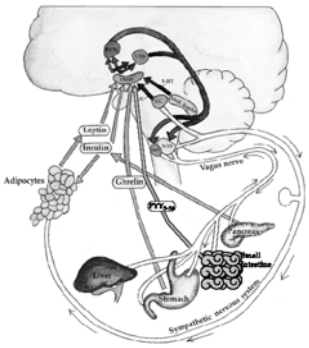


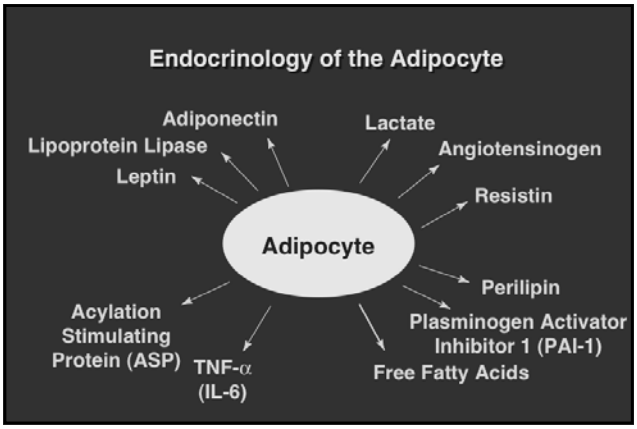
Goldstein et al. NEJM 327:1851, 2002

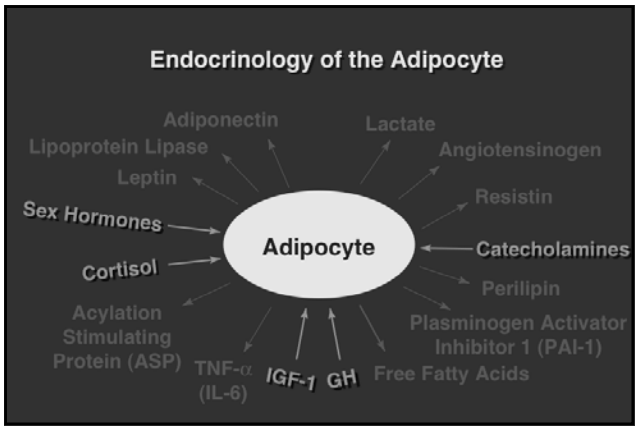
Leptin and Leptin Resistance

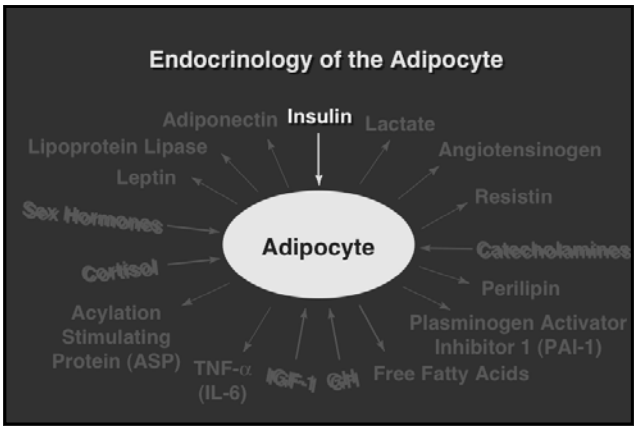
- Leptin levels are a function of adipocyte energy stores
- Leptin tells your brain how thin you are, not how fat you are
- The brain perceives leptin deficiency as a state of starvation
- Leptin deficiency causes energy expenditure to decrease, and thyroid levels to decline, while leptin repletion corrects them
- Caloric restriction leads leptin decline before weight loss, and promotes drive to resume caloric intake
- Obese subjects are hyperleptinemic and "leptin resistant"
- If we could fix leptin resistance, there wouldn't be obesity

The neuroendocrinology of energy balance









Effects of Insulin on the Adipocyte

- Stimulates Glut4 mRNA and protein
- Stimulates Acetyl-CoA Carboxylase
- Stimulates Fatty Acid Synthase
- Stimulates Lipoprotein Lipase

Models/Hypotheses of Hypothalamic Obesity

Damaged Ventromedial Nucleus
↓
Hyperphagia
↓
Obesity
↓
Insulin Secretion
↓
IGF-I Receptor
↓
Growth

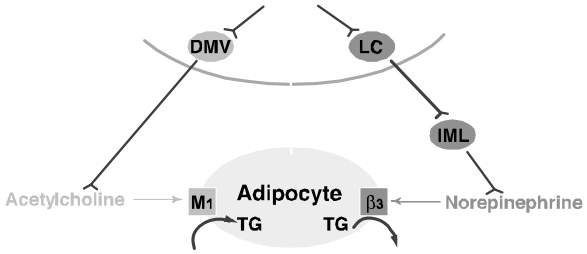
Adapted from
Sklar. *Pediatr Neurosurg.* 1994;21:120-123.

Damaged Ventromedial Nucleus
↓
Vagal Firing Rate
↓
Insulin Secretion
↓
Glucose Utilization
↓
Hyperphagia
↓
Obesity

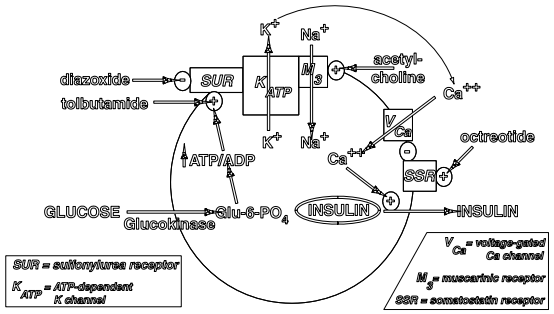
Adapted from
Bray and Gallagher. *Medicine*. 1975;54:301-330.

Hypothalamic Obesity

Autonomic Innervation of the Adipocyte



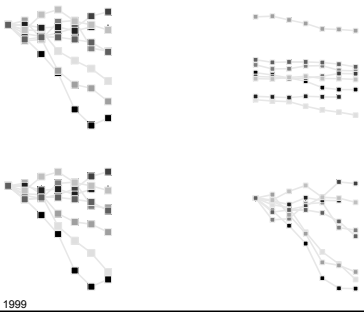
Regulation of β-Cell Insulin Secretion



Hypothalamic Obesity Pilot Study— Purpose

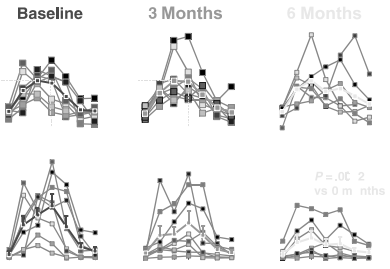
1. To assess the insulin secretory dynamics of patients with hypothalamic obesity
2. To assess the efficacy of octreotide in reducing basal and glucose-stimulated insulin release in patients with hypothalamic obesity
3. To assess the efficacy of octreotide in promoting weight loss in patients with hypothalamic obesity

Hypothalamic Obesity Pilot Study— Weight and BMI Change



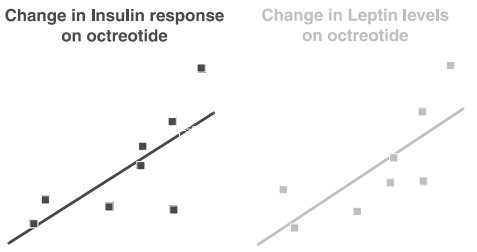
Lustig et al. J Pediatr 138:162, 1999

Hypothalamic Obesity Pilot Study— Effects on Glucose and Insulin Responses



Lustig et al. J Pediatr 138:162, 1999

Hypothalamic Obesity Pilot Study— Weight Loss Versus:



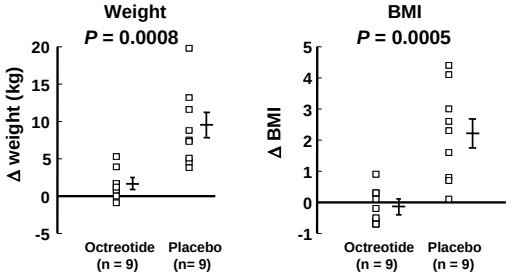
Lustig et al. J Pediatr 138:162, 1999

Octreotide treatment of hypothalamic obesity Demographics

- Double-blinded, 6 month placebo-controlled trial of octreotide
- 20 subjects with pediatric hypothalamic obesity
  - ages 8-18; 11M, 9F
    - 2 from St. Jude
    - 18 from other institutions
  - 13 with craniopharyngioma
  - 4 with hypothalamic astrocytoma, optic pathway glioma
  - 1 with suprasellar germinoma
  - 2 with ALL, S/P cranial XRT and chemotherapy
- Weight 96.8 ± 5.7 kg, BMI 36.3 ± 1.3 kg/m2, annualized weight gain 15.9 ± 2.9 kg

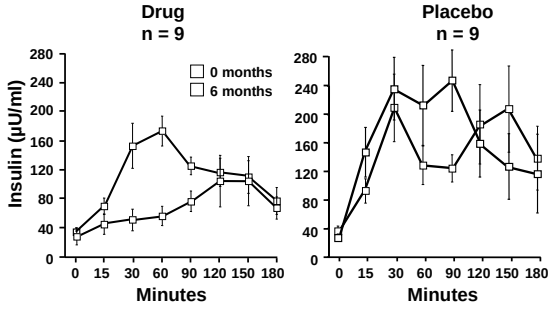
Lustig et al. JCEM 88:2586, 2003

Octreotide treatment of hypothalamic obesity 1st Window (6 Months)



Lustig et al. JCEM 88:2586, 2003

Octreotide treatment of hypothalamic obesity Insulin dynamics during OGTT (1st Window)



Lustig et al. JCEM 88:2586, 2003

Pediatric Cancer Quality of Life PCQL-32, Version 1

32-item proctored questionnaire
Patient and parent reports on:
- **Cognitive** functioning
- **Physical** functioning
- **Psychological** functioning
- **Social** functioning

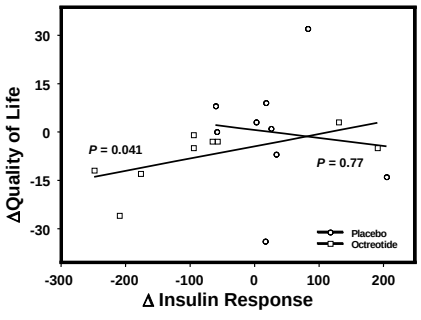
Validated for ages 8-18 yr

Octreotide Treatment of Hypothalamic Obesity PCQL-32 (6 months – 0 months)

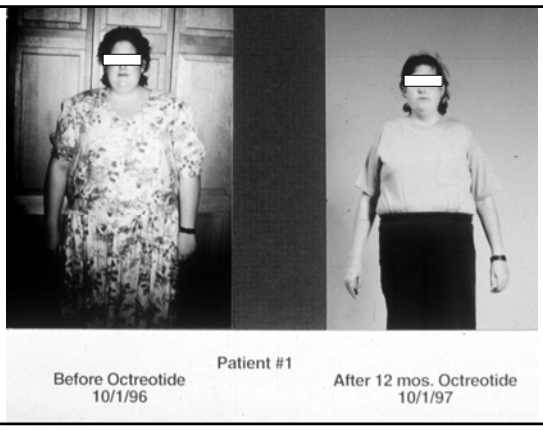
Functioning	Placebo		Octreotide		Intergroup	
	Child	Parent	Child	Parent	Child	Parent
Cognitive	0.33 NS	0.33 NS	0.22 NS	-1.33 NS	0.11 NS	1.67 NS
Physical	0.33 NS	0.78 NS	-1.44 NS	-2.22 *P*=0.05	1.78 NS	3.00 *P* =0.03
Psychological	0.11 NS	-0.11 NS	-1.89 *P* =0.09	-2.11 *P* =0.03	2.00 NS	2.00 NS
Social	0.22 NS	-1.22 NS	-1.89 *P* =0.09	-1.56 *P* =0.04	2.11 NS	0.33 NS

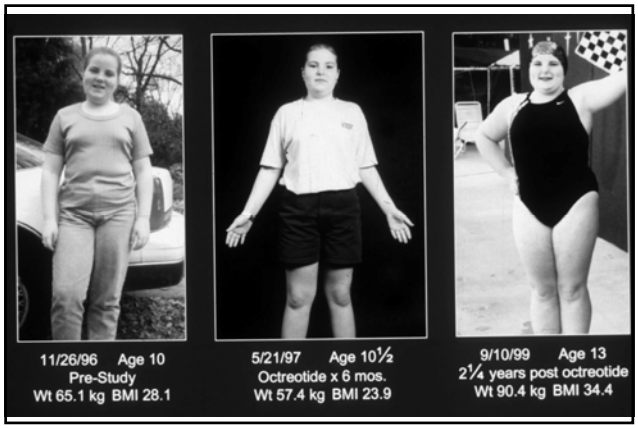
Lustig et al. JCEM 88:2586, 2003

PCQL-32 Parent Report Correlation between ΔQuality of Life and Δ Insulin Response (6 Months – 0 Months)

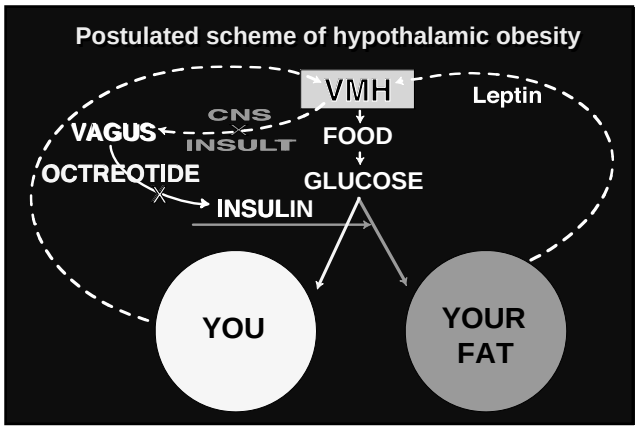


Lustig et al. JCEM 88:2586, 2003





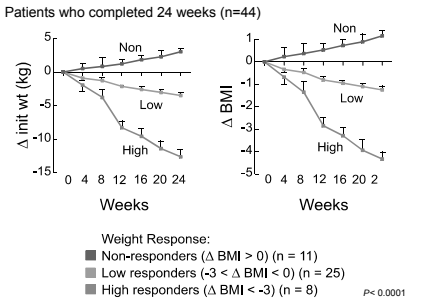
Octreotide x 1 yr



Pilot Study of Octreotide for Adult Obesity Hypotheses:

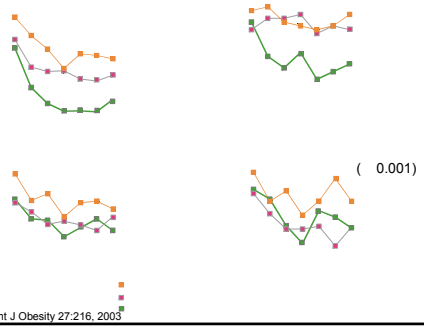
- Insulin hypersecretion occurs in a subset of obese adults
- Insulin suppression using octreotide will
  - Slow or reverse adipogenesis
  - Promote weight loss

Octreotide-LAR 40 mg IM q 28d
Effects on Weight and BMI Stratified By Response



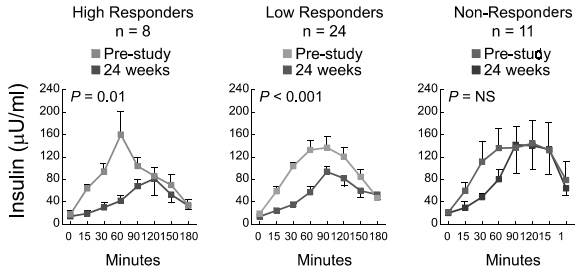
Velasquez-Mieyer et al. Int J Obesity 27:216, 2003

Octreotide-LAR 40 mg IM q28d
Effects on Specific Nutrient Daily Intake



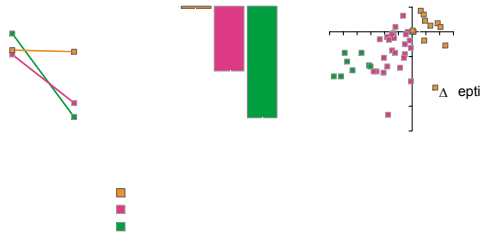
Velasquez-Mieyer et al. Int J Obesity 27:216, 2003

Octreotide-LAR 40 mg IM q 28d
Insulin Dynamics During OGTT



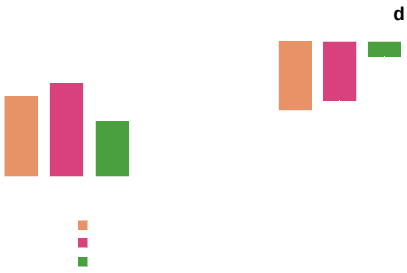
Velasquez-Mieyer et al. Int J Obesity 27:216, 2003

Octreotide-LAR 40 mg IM q 28d
Changes in Plasma Leptin



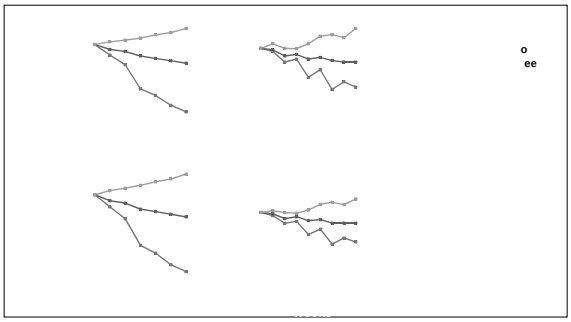
Lustig et al. Int J Obesity 28:1342, 2004

Octreotide-LAR 40 mg IM q28d
Changes in Resting Energy Expenditure (REE)



Lustig et al. Int J Obesity 28:1342, 2004

Octreotide-LAR 40 mg IM q 21d: 6 month extension
Effects on Weight and BMI stratified by initial response

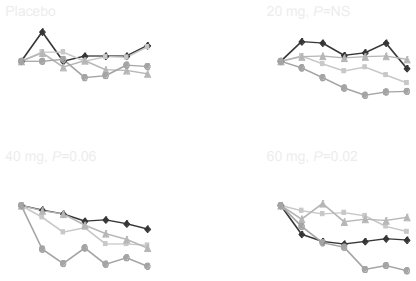


Randomized dose-finding trial of octreotide-LAR in adult obesity due to insulin hypersecretion

- Randomized, double-blind, placebo-controlled, dose-finding trial of octreotide-LAR in adult obesity due to insulin hypersecretion (as measured by baseline CIR > 1.0)
- 19 centers nationwide
- Inclusion criteria:
  - Age 18–65
  - BMI > 30
  - CIR > 1.0 on screening OGTT
- Exclusion criteria:
  - Diabetes mellitus
  - Previous voluntary weight loss
  - Use of weight loss medications
  - Use of any autonomically active or psychoactive medications
  - Gallstones, hepatic disease, renal disease

Lustig et al. Int J Obesity 30:331, 2006

Role of Race and CIR in Prediction of Response to Octreotide-LAR



Caucasians, CIR > 1.43N Treatment Group Comparison, P=0.046

Lustig et al. Int J Obesity 30:331, 2006

Octreotide-LAR x 6 months

Improvement of leptin sensitivity

- Forced weight loss (Rosenbaum)
- Drug-induced reduction in insulin (Lustig)

Improvement of leptin sensitivity

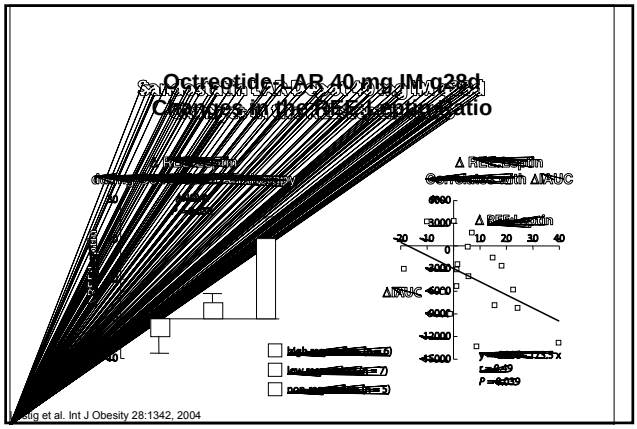
- Forced weight loss (Rosenbaum)
- Drug-induced reduction in insulin (Lustig)

What's the similarity?

The drop in insulin

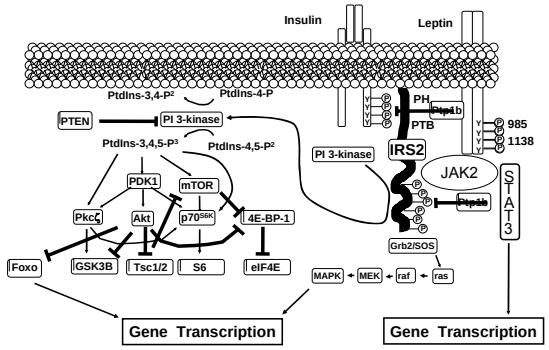
Measuring Leptin Sensitivity
The REE:Leptin Ratio

- There is no simple biochemical measure of leptin sensitivity in humans
- Leptin resistance is a HIGH leptin state
- If your leptin level drops below your body's leptin threshhold (e.g. weight loss), your REE starts to decline (as your brain thinks you are starving, and alters your energy efficiency)
- The most leptin sensitive subjects have the *HIGHEST* REE at the *LOWEST* leptin
- Conversely, the most leptin resistant subjects would,of necessity, increase their circulating leptin level (by increasing their adiposity), in order to stay above their leptin threshhold, so their REE could remain optimal
- Therefore, changes in the REE:Leptin ratio would appear to be a rational surrogate measure of changes in leptin sensitivity (at least within the same subject)



Lustig et al. Int J Obesity 28:1342, 2004

Overlap between hypothalamic insulin and leptin signaling



Isganaitis and Lustig, Arterioscl Thromb Vasc. Biol. 25:2451, 2005

Insulin is an endogenous leptin antagonist (?)

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Does this make sense teleologically?

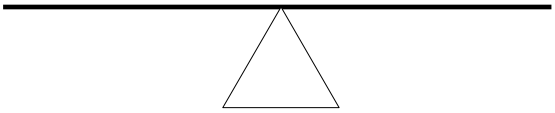
Insulin is an endogenous leptin antagonist (?)

Does this make sense teleologically?

Insulin gives the human the ability to modulate weight gain acutely, by allowing insulin resistance to induce leptin resistance:

1. Puberty
2. Pregnancy

Restating The First Law of Thermodynamics



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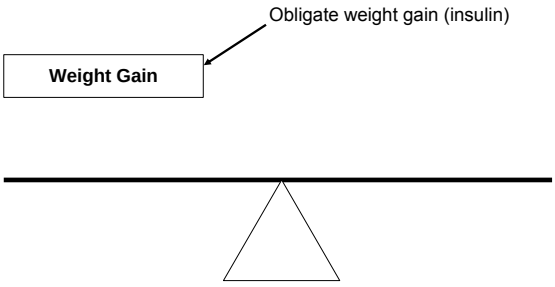

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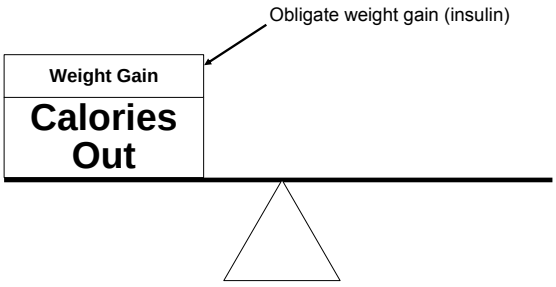

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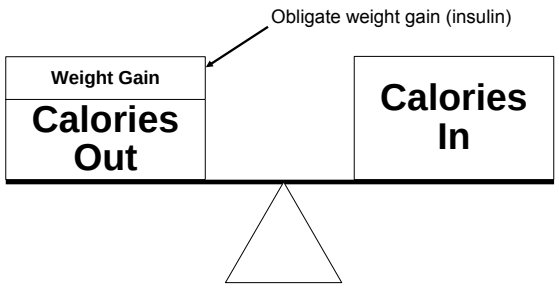
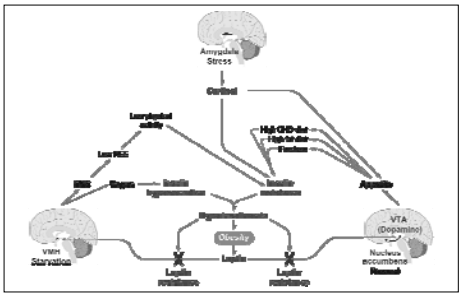


The "limbic triangle"



Mietus-Snyder and Lustig, Ann Rev Med 59:147, 2008

Childhood Obesity—Behavior or Biochemistry? Reinterpreting the First Law of Thermodynamics

- Childhood obesity is on the rise
- Hyperinsulinemia and leptin resistance are both hallmarks of obesity
- Energy expenditure decreases in response to declining leptin, invoking the "starvation response", and causing weight plateaus or reversals
- Reduction in insulin improves leptin resistance and promotes weight loss
- Insulin appears to be an "endogenous leptin antagonist"
- Our diet is insulinogenic; we have to "get the insulin down"
- Our food alters our hormones which alter our food

Collaborators

St. Jude Children's Research Hospital

U.T. Memphis —Ped. Endocrine

UCSF

Novartis Pharmaceuticals, Inc.