Physiological basis for “Metabolic Obesity” & “Hedonic Obesity”

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Complex interactions underlying polygenic obesity

- Physical activity
- Nutrition
- Viruses
- Social Status
- Food Abundance
- Technological Progress
- Pollution
- Peer pressure
- Hormones
- Psychology

Mutch D & Clement K, Plos Genetics 2006
Trends in obesity prevalence among adults aged 20 and over (age-adjusted) and youth aged 2–19 years: United States, 1999–2000 through 2013–2014
Is obesity a reversible condition?
- What’s the pathophysiological basis?

How is obesity developed?
- How should it be treated?
- Metabolic obesity
- Hedonic obesity
Metabolic regulation of energy fluxes – mechanism of compensatory changes

Cumulative nitrogen balance in young man with a minor febrile illness (typical sand fly fever)
Hypothalamic neural circuit for body weight set-point

- Lipostatic signals: Leptin/insulin
- POMC/CART
- NPY/AGRP
- Mc4R and other secondary neurons
  - Energy expenditure
  - Food intake
  - Body weight adiposity

Arrows indicate positive (+) and negative (-) interactions.
Congenital leptin deficiency: before and after leptin treatment

3yr old weighing 42 kg

7yr old weighing 32 kg

I Sadaf Farooqi, and Stephen O'Rahilly J Endocrinol 2014;223:T63-T70
Congenital POMC deficiency: phenotypic triad of red hair, hypocortisolism, and childhood obesity

The culprit of the obesity epidemic is our obesigenic environment

www.newsmax.com
Common forms of obesity is polygenic in etiology... in humans and in animals.
Homeostatic regulation

Temporarily elevated body weight

Metabolic signal to reduce food intake

“Adaptive changes”

Energy expenditure

Set-point body weight

Metabolic signal to increase food intake

“Adaptive changes”

Temporarily reduced body weight
Temporarily elevated body weight

Temporarily reduced body weight

Set-point body weight

Metabolic signal to reduce food intake

Metabolic signal to increase food intake

“Adaptive changes”

Energy expenditure

Elevation of set-point

Homeostatic regulation

“Metabolic obesity”

New Set-point body weight
Re-set of body weight set-point

- Lipostatic signals
- Leptin/insulin
- POMC/CART
- NPY/AGRP
- Mc4R and other secondary neurons

Energy expenditure
Food intake

Body weight adiposity

Leptin resistance
Reactive gliosis, aging/inflammation

< - set of body weight set-point >
Now... Hedonic obesity
“Hedonic obesity”

Elevated body weight kept above the set-point

Hedonic signal to sustain “overeating” despite metabolic abundance

Temporarily elevated body weight

Metabolic signal to reduce food intake

“Adaptive changes”

Energy expenditure

Set-point body weight

Metabolic signal to increase food intake

“Adaptive changes”

Energy expenditure

Temporarily reduced body weight

Homeostatic regulation
Overeating - Food addiction?
Two discernible neural circuits

Miguel Alonso-Alonso, et al
DOI: http://dx.doi.org/10.1093/nutrit/nuv002
Hedonic regulation of food intake

The brain’s corticolimbic structures

Prefrontal Cortex – Orbitofrontal Cortex

Dorsal Striatum

Thalamus

Lateral Hypothalamus

Amygdala

Hippocampus

Nucleus Accumbens

NAc (ventral striatum)

Mesolimbic dopaminergic transmission

Ventral Tegmental Area

VTA

Hindbrain

NTS

Sensory Input
Hedonic obesity is sustained by persistent overeating in the presence of 24-hour available “cafeteria food” in Wistar rats.
Food Addiction: Its Prevalence and Significant Association with Obesity in the General Population

Pardis Pedram1, Danny Wadden1, Peyvand Amini1, Wayne Gulliver1, Edward Randell2, Farrell Cahill1, Sudesh Vasdev1, Alan Goodridge1, Jacqueline C. Carter3, Guangju Zhai4, Yunqi Ji1, Guang Sun1*

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Homeostatic regulation

Elevated body weight kept above the set-point

Temporarily elevated body weight

Metabolic signal to reduce food intake

“Adaptive changes”

Energy expenditure

Temporarily reduced body weight

Metabolic signal to increase food intake

“Adaptive changes”

Energy expenditure

Set-point weight

Extra weight sustained by never-failed consistent overeating

Hedonic weight

“Hedonic obesity”

Hedonic signal to sustain “overeating” despite metabolic abundance

Set-point body weight

Hedonic obesity
How to Distinguish Metabolic Obesity and Hedonic Obesity
Pre-obese weight at set-point:

Hedonic obesity

Metabolic obesity

EE-MM regression line

Energy expenditure (EE)

Metabolic mass (MM)
Focus on future treatment of obesity:

**Hedonic obesity:** tailored behavioral therapy and/or medical intervention to achieve reward modification/balance

**Metabolic obesity:** medical/surgical intervention to alter body weight set-point
Bariatric surgery seems to be effective for both metabolic obesity and hedonic obesity

www.meltingmama.net

**Bypass and the brain**

For reasons not well understood, gastric bypass surgery often changes how the brain responds to food and seems to reduce hedonic eating.

1. The small intestine is attached to a new opening made in the stomach.

2. The two parts of the small intestine are connected so that the unused part of the stomach can drain.

3. Leptin and glucose levels tend to drop, ending diabetes for many people. Scans also show that bypass patients have more dopamine circulating in their brains, which may help control appetite.
Conclusion:

**Metabolic obesity**
1. elevated body weight set-point
2. energy expenditure well within normal range
3. treatment to lower set-point

**Hedonic obesity**
1. persistent overeating overriding metabolic signals
2. energy expenditure above normal limits for unit metabolic mass
3. tailored therapy to modify hedonic neural circuit and achieve a desirable reward balance

Yu et al. Obes Rev. 2015 Mar;16(3):234-47
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